ANGEWANDTE CHEMIE
International Edition
VOLUME 11 · NUMBER 1
JANUARY 1972
PAGES 1–72

Signal Transducers: *Terra Incognita* of Molecular Biology[**]

By Max Delbrück [*]

In this article four cases of signal transduction in biology are discussed, ranging from a case which we do understand in molecular detail (genetic induction) through two cases where the fog may be beginning to clear (vertebrate vision and bacterial chemotaxis) to a case where we are still struggling to define the participants of the play (the avoidance response of the fungus Phycomyces).—Although most of the facts presented are not brand new, the juxtaposition of them is perhaps unconventional and may be of interest at least by way of outlining an area of research of some promise. No doubt modern concepts and technologies of chemical and physical research will play a great role in this borderline area between a variety of fields, presenting great challenges to the ingenuity and versatility of the experimenter.

1. The Lactose Operon

E. coli cells respond to the presence of lactose in the medium within seconds with an increase in the rate of production of the enzyme β-galactosidase which can cleave this disaccharide to glucose and galactose.

The signal is lactose, the ultimate response is the production of the enzyme. In this case the control of the synthesis of the protein takes place at the DNA level: The signal causes increased transcription of the gene which codes for the enzyme. The synthesis of the appropriate m-RNA is *induced* by the substrate. How does the signal manage to give this effect? It acts by removing a physical obstacle to the transcription, the repressor (Fig. 1). An astounding trick and, surprisingly, one that can be quite clearly understood in physical and chemical terms. For once, in biology, the advance of our understanding of a problem has not led us to a confrontation with more baffling problems.

Let us have a closer look at this repressor, the transducer of a chemical signal from the environment into DNA transcription.

The lactose repressor[1] is a protein, a tetramer consisting of four identical subunits, MW 35000 each. It binds to the

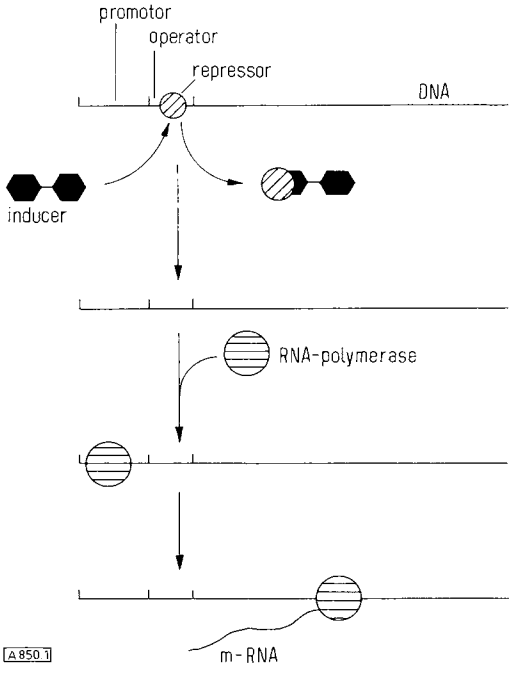


Fig. 1. Derepression of the lactose operon. The lactose operon, a piece of the DNA of the bacterium *E. coli*, codes for three proteins. Before the information coded in the DNA can be read, *i.e.* before it can be transcribed by the RNA polymerase into messenger RNA, an obstacle has to be removed, the repressor. The repressor sits on the operator region of the operon. The polymerase can initiate transcription only at the promoter, to the left of the operator, but cannot do so if its path is blocked by the repressor. The inducer, lactose, combines with the repressor and causes it to dissociate from the DNA. Transcription can then proceed.

[*] Prof. Max Delbrück
Division of Biology
California Institute of Technology
Pasadena, California 91109 (USA)

[**] Festvortrag, General Meeting of the GDCh, Karlsruhe, September 15, 1971.

operator region of the lactose operon. The lac operon is a piece of DNA of the chromosome of *E. coli*, about 5000 base pairs. It codes for three proteins, of which the enzyme β-galactosidase is one. The operator region is a very short piece (12—15 base pairs) of DNA at one end of the operon, the end where transcription starts. The repressor recognizes this short piece of DNA with a very high degree of specificity (Fig. 2). The repressor is about 30 Å in diameter, the

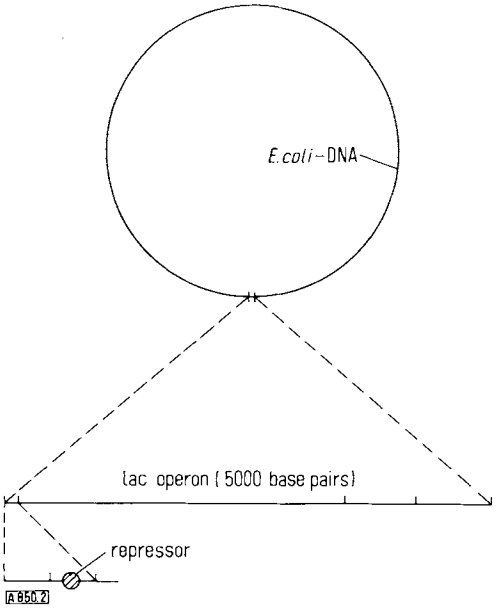
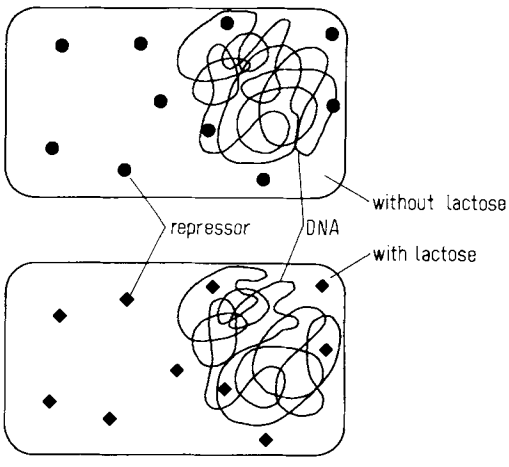


Fig. 2. Scale diagrams of genetic components. In the upper half the circle represents the bacterial chromosome, the tiny segment at the bottom of the circle the lactose operon. In the lower half the lactose operon has been enlarged across the width of the figure. The tiny section at the left end represents the promoter and operator region, respectively.

chromosome 500000 times longer. The binding of the repressor to the operator is very tight indeed, but distinctly finite. The dissociation constant *in vivo* can be estimated and it can be measured in the test tube. *In vivo* it is 10^{-11} M. There are only 10 repressor molecules per cell (a concentration of 10^{-8} M) yet this very small number suffices to keep the operator 99.9% blocked if there is no waste of repressor, *i.e.*, if none is sequestered by unspecific adsorption.

One knows, in fact, not only the dissociation constant, but also its components, the association and dissociation *rate* constants. It takes minutes for the operator-repressor complexes to dissociate. The association rate is *faster* than diffusion controlled. That seems at first paradoxical. How can operator and repressor get together faster than by diffusion? The answer is simple: The repressor finds its target by "reduction of dimensionality"; it adsorbs at first unspecifically on any portion of the DNA, sufficiently tightly not to come off for a while and sufficiently loosely to be able to diffuse along the DNA, by one-dimensional surface diffusion. This is a principle of zero-ing in on a specific target which the cell presumably employs in many situations[2].

The inducer, lactose, also interacts with the repressor (as do many of its analogs). The binding sites on the repressor for lactose and for the operator are distinct; the two ligands do not interfere with each other. The binding of lactose is tight (dissociation constant $\approx 10^{-6}$ M) but not nearly so



	dissociation constant repressor-operator (mol/liter)	blocking of operator (%)
without lactose	10^{-11}	99.9
with lactose	2×10^{-7}	5

A 850.3

Fig. 3. Chemical equilibria involving chromosome, repressor, and inducer. The bacterial cell contains *one* (or two) chromosomes, with *one* lactose operon, with *one* operator region, and about 10 repressor molecules. In the absence of lactose the operator is 99.9% blocked; in the presence of a low concentration of lactose it is blocked only 5% of the time.

tight as that of the operator to the repressor. The main trick of the transduction of the environmental signal consists in the structural modification of the repressor caused by the binding of lactose to the repressor (Fig. 3); the modification is of such nature as to increase the dissociation constant of the repressor to the operator by a factor 20000 from 10^{-11} M to 2×10^{-7} M, just sufficient to shift the equilibrium from nearly total blockage of the operator to nearly total release.

Organisms utilize a vast number of other biochemical control systems on the cellular and subcellular level. The most startling perhaps are the ones of which cyclic AMP forms a link. One of these involves a steroid hormone, the transmembrane enzyme adenyl cyclase, c-AMP as intracellular transducer, protein-kinase, and carbohydrate metabolism[3,4]. Many such control systems are being worked on but the lac-repressor still has the lead in telling us a chain of events without a gap from the environmental signal down to the gene and back to the effect on the environment, fermentation[*]

2. Vision

We turn now to our next example, vertebrate vision. Here the signal is light and the ultimate effect, by definition, is "seeing", *i.e.* a psychic effect, involving consciousness. It thus spans the vast gulf between the external world and consciousness that is as baffling to science now as it was to

[*] The lactose operon is controlled not only by the repressor, as discussed above, but also by a second protein, linking it to catabolism. This second protein binds to the operator DNA and its binding is regulated by c-AMP [5, 6].

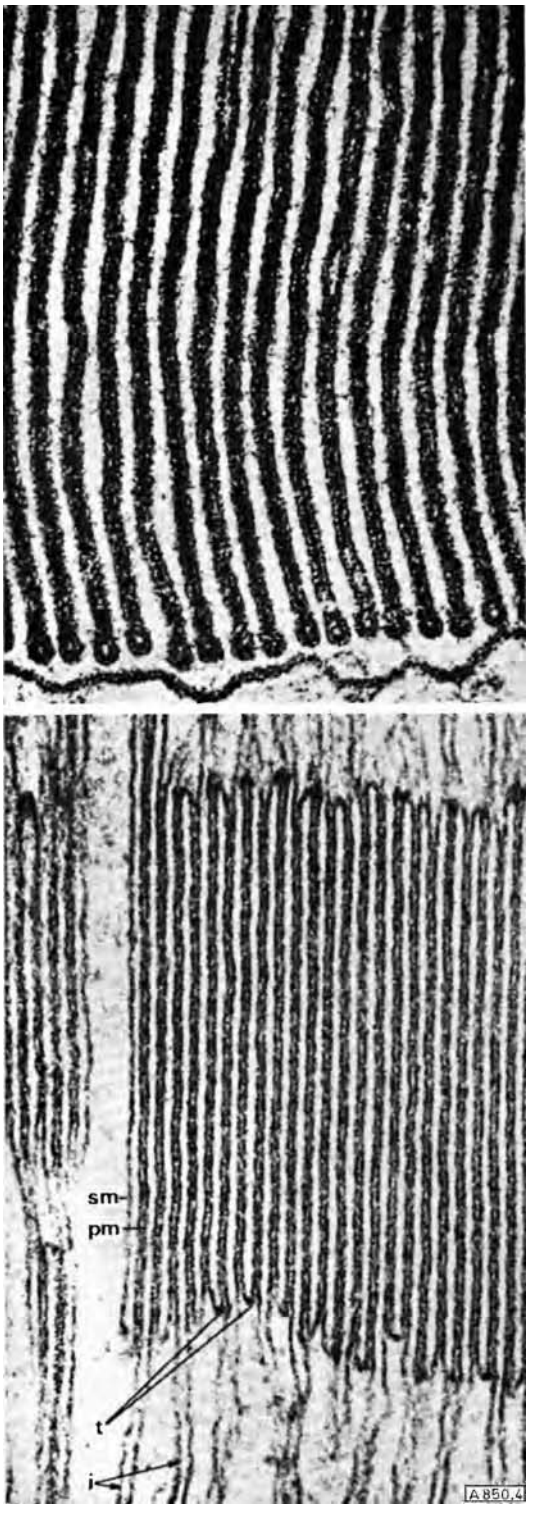


Fig. 4. Detail of retinal rod outer segment (above) and of chloroplast (below). These two specialized regions of specialized cells of vertebrates and higher plants, respectively, are both designed to deal with light: retinal rod for the purpose of vision, the chloroplast for the purpose of photosynthesis. Their ultrastructure, as revealed in electron micrographs of fixed and stained and sectioned preparations, is remarkably similar [24].

Descartes who first codified the language that still fetters us. The time may not be far off, however, when the exigencies of intensive experimental work in the area of psychobiology will lead us to develop a more fitting rational language.

In this discussion I will confine myself to a seemingly minute subproblem. Leaving aside the psyche, the brain, the eye and even most of the retina, let us focus our attention on the receptor cells, specifically those for dim-light vision, the rods. (For a general survey of the structure of receptor cells see *Thurm*, 1969[7].) These remarkable transducers act as quantum counters, converting the absorption of a single light quantum into a signal passed on to the synapse with the next cell, which is a bipolar one. At this synapse the effect produced by a single quantum is amplified sufficiently to cause a discernible signal[12].

The primary action takes place in the outer segment of the rod, a specialized structure containing, within the cytomembrane envelope, what appears to be a stack of several thousand flat membrane sacs, very similar in appearance (in the electron microscope, Fig. 4) to the stacks of sacs in the chloroplasts of higher plants. In both cases the stacks of membrane sacs are specialized for absorbing a large part of the impinging light and to do it with high efficiency. Accordingly, in both cases they are packed with pigments absorbing light of the desirable wavelengths. In the rod the pigment is rhodopsin with $\lambda_{max} = 500$ nm; in the chloroplast it is chlorophyll with two λ_{max} (420 and 680 nm).

The purpose of the absorption of light is radically different in the two cases. In the chloroplast maximal conservation of free energy is the purpose: Nature wants conversion of the free energy of light into free energy of carbohydrate; in the rod energy conservation is not the point; instead we want to "see" the light. The free energy is utilized merely to gate a much larger energy supply provided by general metabolism. In spite of this ultimate difference the constraints on the first step are quite similar: in neither case can we afford low absorbance or a low quantum yield of a primary photochemical reaction.

We used to believe that in the chloroplast there is the additional requirement of bringing together about eight primary photoproducts to reduce one CO_2 molecule and doing it in a reasonably short time even in dim light where the absorption acts are few and far between. We now know that this requirement is solved in part by intermediate chemical storage of energy in ATP and NADPH. However, the machinery for making and using these intermediates is massive, much more massive than a single chlorophyll molecule. It would be wasteful to have such a ponderous machine attached to each chlorophyll molecule. Nature has solved this problem by constructing photosynthetic units, assemblies of several hundred chlorophyll molecules that act as collecting antennas for reaction centers containing a few specialized chlorophyll molecules. To these centers energy is funneled by exciton travel (Fig. 5)[8]. Thus the vast majority of the chlorophyll molecules never undergo a photochemical reaction. Even the specialized ones in the reaction center get only momentarily oxidized. They get reduced so fast (within microseconds) that it has only very recently become possible, by elaborate ESR measurements, to identify this transient radical as a radical of chlorophyll[9].

Does a similar exciton travel towards specialized centers take place in the sacs of the rods? Apparently not, since there is *convincing* evidence that every absorbing rhodopsin molecule is a *potential* reaction center and can undergo a series of chemical changes ending with the detachment of

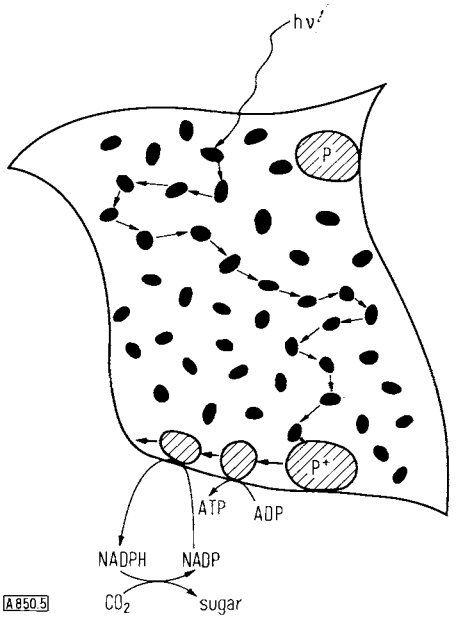


Fig. 5. The photosynthetic unit. The photosynthetic unit consists of several hundred chlorophyll molecules. These serve as "antenna" for a "reaction center" containing several specialized chlorophyll molecules. A light quantum absorbed by any one of the chlorophyll molecules of the antenna travels by exciton migration to the reaction center, where its energy is used for the synthesis of ATP or for the reduction of NADP. These compounds, in turn, bring about the reduction of CO_2 to sugar and the liberation of oxygen. Whether the 10^8 visual pigment molecules of a rod outer segment are organized into a very large number of analogous "antennas", feeding energy by exciton travel into reaction centers at the rim of the organelle is an open question.

the chromophore from its protein carrier. Actually, the experiments that have been performed do not preclude that *at low intensities* exciton migration to specialized reaction centers does occur and constitutes the decisive physiological transducer process. Too little attention has been paid to this possibility.

The chromophore is retinal, a C_{20} polyisoprenic type aldehyde, attached covalently as a Schiff base to the ε-amino group of a lysine in the carrier protein opsin[10, 11]. Absorption of a light quantum leads to a series of chemical changes that have been characterized very incompletely and inadequately by observing spectroscopic changes and lifetimes at various temperatures. The series of steps terminates, at least in the case of isolated rhodopsin, in the isomerization from 11-*cis* to all-*trans*-retinal and the hydrolysis of the Schiff base.

Thus we know at least where the light gets into the act but beyond this point we encounter two major unsolved problems:

1) How is the signal transduced from the photochemical step to the next known event?

2) How is rhodopsin regenerated?

Regarding the first transduction steps very important progress has recently been made[12]. By elaborate and ingenious extracellular potential recordings it has been shown that the rod cell maintains a rather large dark current of about 70 pA, directed outward at the inner segment and here presumably generated by energy coupled active transport of Na^+ ions, and inward through the cytomembrane of the outer segment, adjacent to the rhodopsin-containing sacs, by passive flux through Na^+ specific pores (Fig. 6). After a pulse of light this current decreases transiently, probably due to a reduction in the number of open Na^+ channels in the rod's cytomembrane. Perhaps only one Na^+ channel is closed when one quantum is absorbed. The amplification effected by this closure is enormous. The current transient amounts to a deficit of 10^6 charges passing the cytomembrane. It could be sufficient to effect a voltage change at the synapse lying above the thermal voltage noise. Therefore the voltage change could be adequate for further signal processing, provided the synapse constitutes an ideal detector.

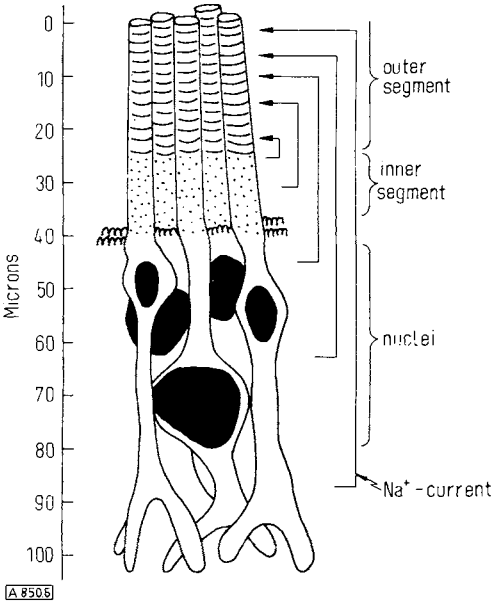


Fig. 6. Distribution of extracellular electrical current in the vicinity of retinal rods [12]. In the dark, current enters the cells along the outer segment and leaves it in other portions of the cell; presumably this current is driven by energy generated in the mitochondria. In light, there is superimposed a smaller current in the opposite direction which may cut down the net current from its value in the dark by 50%. This current is carried by Na^+ ions, through pores in the cell membrane of the outer segment which are specific for Na^+. A fraction of these pores are apparently closed when light is absorbed by the visual pigment in the outer segment, thus raising the impedance of the membrane of the outer segment. The mechanism of this transduction of the signal from the visual pigment to the cell membrane is unknown.

So far, so good. But there is still a big gap in our knowledge of this transduction chain. How does the signal get from the rhodopsin which absorbs the quantum to the cytomembrane where a Na^+ gate gets closed? Geometrically the gap is about 1 μ = 10000 Å, very large on the molecular scale. What transducing mechanism bridges this gap? The guesses that have been put forward proceed from the assumption that the absorbing rhodopsin molecule undergoes a photochemical reaction. However, none of these schemes seems even plausible to me; certainly none has been experimentally supported. Exciton travel towards reaction centers located in the cytomembrane would be the ideal transducer mechanism. Whether it really is a possible mechanism depends critically on the exact spacing of the rhodopsin molecules and their interactions. These are not known at present (cf. [13]). If such exciton travel is the physiological transducer mechanism then the photo-

chemistry of rhodopsin that has been studied at high intensities *in vivo* and *in vitro* might be quite unrelated to the primary function of the bulk rhodopsin.

About the regeneration we know practically nothing. Perhaps it is here that adenyl cyclase is involved. A strong cyclase activity in the dark and a strong repressing effect of light on this activity in rods has recently been reported[14]. One may suspect that this repression of cyclase activity has something to do with the regeneration of rhodopsin. It seems most unlikely to me that it is involved in the transduction of the signal.

3. Chemotaxis in Bacteria

We will leave this story here and move on to our third case history: taxis in bacteria. That motile bacteria "chase" light, oxygen, sugars, amino acids, *etc.*, has been known for 100 years. The bacteria somehow detect chemical or light gradients and respond to them, not indeed by pursuit of the good but by avoiding the bad. In recent years the armamentaria of genetics and biochemistry have been brought to bear on these stimulus-reaction chains, with remarkable but still very incomplete results, showing that bacteria have very clever sense organs.

On the response side we know that the response does *not* consist in a changed swimming rate, faster up-gradient than down-gradient, say. Rather, it seems that the mean free path, *i.e.*, the stretch of swimming straight between tumbles or reversals, is longer uphill than downhill. More precise statements must await the application of a new technique which permits tracking of individual bacteria in three dimensions over many free path lengths[15]. It is certain that bacteria do detect rather small chemical gradients, of the order of 10^{-4} over their body length (Fig. 7). Almost certainly they detect such gradients not by measuring a concentration difference between the two ends of their body, but, since they swim very fast, about 100 body lengths between turns, by detecting the concentration difference between two positions in space, say one free path length apart.

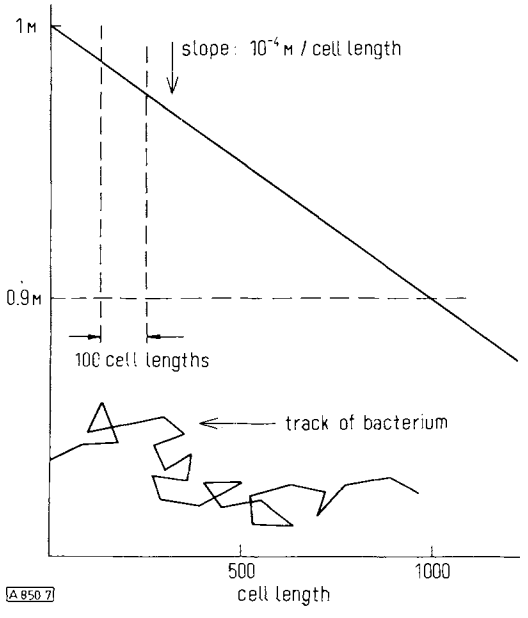


Fig. 7. Chemotaxis of bacteria. Bacteria can detect very small gradients in the concentration of some chemical compounds. The gradients may amount to a fractional change of concentration of only one part in 10000 between the two ends of the bacterial cell. Probably the cells sense the gradient not by detecting a difference in concentration between the ends of the cells but between points one hundred times further apart, since they swim fast and often nearly in a straight line for a distance of about this length. The cell would thus not sense an intracellular *space gradient* but a *time gradient* affecting the whole cell.

How do they detect? Recent work has shown that the detection is *not* done *via* a transient change in the energy metabolism, a transient increase, say, in ATP. This conclusion was reached by showing that analogs of the desirable chemicals which cannot be metabolized are nevertheless chased and that many substances that are readily metabolized are not chased[16, 17]. Detection must take place at an earlier step, prior even to the uptake of the attractant in the bacterial cell. Yet, a connection with uptake seems to exist: in the case of galactose a protein has been isolated, the gal-binder, which is necessary both for uptake and for chemotaxis[18, 19]. This protein is necessary for both these functions because when it is lost by mutation neither function persists. Yet, it is not sufficient for either: other mutations have been produced which leave the gal-binder intact but interfere *either* (some of them) with the uptake of gal *or* (others) with chemotaxis specifically for gal. The gal-binding protein is located in the periplasma of *E. coli*, *i.e.*, between the outer and inner membrane. The above findings suggest that this protein is the branch point between the route that leads to uptake and the route that leads to chemotaxis. We know a little about how the route to uptake goes on, but the one leading to the control of flagellar coordination is shrouded in a dense fog, as is, for that matter, all chemosensation, also in vertebrates and insects. Only in the case of chemosensing of acetylcholine in the neuromuscular joint, and some other chemical transmitter situations, can we point to a proximal effect, at least, the gating of ion channels in the subsynaptic membrane. How this gating is done, in molecular terms, is still quite as obscure here as it is in the case of the vertebrate rod outer segment.

4. A Chemical Self-guidance System

Let us turn, then, to the last example I propose to discuss, the avoidance response of *Phycomyces*. *Phycomyces* is a fungus, a lower fungus, lower on the scale of the taxonomists than the *Ascomycetes neurospora*, *aspergillus*, and yeast, which played such a tremendous role in the development of biochemical genetics. Almost 20 years ago I started work on this organism as a model system for sensory signal transduction since its huge unicellular fruiting structure, the sporangiophore and sporangium, reacts strikingly to light. Is it conceivable that we might learn something of general validity about signal transduction from a primitive creature? In biochemistry and genetics the study of microorganisms certainly did contribute handsomely to our understanding of molecular mechanisms and in fact revealed exceedingly broad principles of chemical organization ranging all the way from vitamins and co-enzymes to the DNA story. Our modern concepts

of the unity of the world of living organisms is based on these principles. It was therefore an obvious thought to turn to microorganisms once more for the study of general principles of signal transduction of sensory inputs.

I will not dwell here on the work concerning the responses to light of *Phycomyces*[20] since it has not yet paid off in the sense of giving us a molecular picture of the transduction chain from light input to growth rate control. In fact, the receptor pigment itself is not yet known as a chemical entity.

Instead, I would like to invite your attention to a new response, the avoidance of a solid or liquid barrier a short distance away[20–23]. This avoidance occurs by "growing away", just like the positive phototropic response is a "growing towards" the stimulating light (Fig. 8). But what

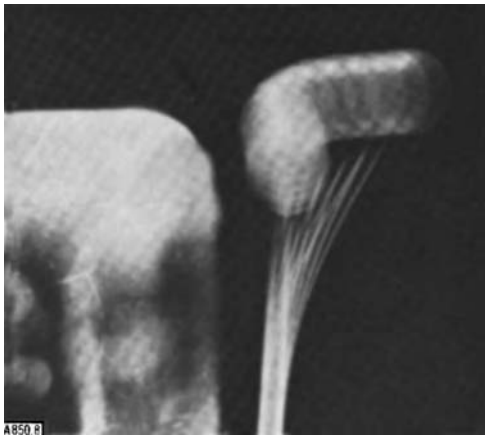


Fig. 8. Avoidance response of *Phycomyces*. The vegetative fruiting body of this fungus, the sporangiophore, possesses a chemical self-guidance system which enables it to "sense" solid objects in the vicinity and to avoid them by growing away from them. The figure is a multi-exposure, every two minutes. The pictures are taken in red light to which the fungus is totally insensitive. After the fifth exposure, a solid glass rod, diameter 5 mm, was moved up to the specimen, without touching it. Two minutes later the sporangiophore begins to grow away from the barrier. The diameter of the sporangium is 0.5 mm.

is the physical signal in this case? After considerable experimentation it turns out that we are dealing with chemical sensing of a volatile substance, the effector, emitted in minute amounts. The barrier affects the spatial distribution of the effector, such that a gradient of concentration is formed, higher on one side of the sensor (in the growing zone) than on the other. A barrier affects the distribution of the effector both by either reflecting or adsorbing the effector molecules, thus altering the boundary condition for diffusion, and by its effect on random winds, quieting them. A striking demonstration of the latter effect can be seen if a glass house of several centimeters in diameter is put over the specimen. In that case the effect is symmetric and no tropic response can be expected. But the quieting of random winds leads to a change of the average concentration of the effector near the sensor, resulting in a transient increase in growth rate within two minutes after enclosure.

We are thus dealing with a novel and clever device of nature, a kind of chemical self-guidance system remotely analogous to radar. In ordinary echo sounding, be it radar or sonar, a principal problem is to shield the sensor from exposure to the direct signal which is enormously stronger than the echo signal. Often this is done by separating emitter and sensor and by pulsing signal and sensor alternately. In our chemical radar system we may also find a separation of emitter and sensor, but the pulsing is replaced either by rapid decay or by strong adsorption of the effector.

5. Conclusions

Let us sum up, then, where we find ourselves today with respect to signal transducers. We find a vast array of phenomena, analyzed in patches, as it were, separated by large gaps which I designated in the title of this article as "*terra incognita*." This is an expression used by the map makers of the 15th century and earlier, before the age of exploration had filled in the globe's *terrae incognitae*. Columbus crossed the Atlantic four times to the new found lands which he, to the end of his life, believed to be part of the Asian continent. It took decades before the staggering truth dawned on humanity that the explorers had found a new continent and a totally unbargained for ocean.

What about our *terrae incognitae*? Will they all turn out to be part of known continents, or dare we hope for great surprises? I for one do so. And I hope that some of you will join us in these adventurous journeys of exploration.

Received: July 5, 1971 [A 850 IE]
German version: Angew. Chem. *84*, 1 (1972)

[1] *B. Müller-Hill*, Angew. Chem. *83*, 195 (1971); Angew. Chem. internat. Edit. *10*, 160 (1971); *W. Gilbert* and *B. Müller-Hill*, in *J. R. Beckwith* and *D. Zipser*: The Lactose Operon. Cold Spring Harbor Laboratory, New York 1970.

[2] *G. Adam* and *M. Delbrück* in *A. Rich* and *N. Davidson*: Structural Chemistry and Molecular Biology. Freeman, San Francisco 1968.

[3] *J. Erlichman, A. H. Hirsch*, and *O. M. Rosen*, Proc. Nat. Acad. Sci. U. S. *68*, 731 (1971).

[4] *G. N. Gill* and *L. D. Garren*, Proc. Nat. Acad. Sci. U. S. *68*, 786 (1971).

[5] *B. de Crombrugghe, B. Chen, W. Anderson, P. Nissley, M. Gottesman, I. Pastan*, and *R. Perlman*, Nature *231*, 139 (1971).

[6] *A. D. Riggs, G. Reines*, and *G. Zubay*, Proc. Nat. Acad. Sci. U. S. *68*, 1222 (1971).

[7] *U. Thurm*, Rendiconti della Senola Internationale di Fisica "E. Fermi" XLIII, 44 (1969).

[8] *G. W. Robinson*, Brookhaven Symposia in Biology *19*, 16 (1966).

[9] *J. D. McElroy, G. Feher*, and *D. C. Mauzerall*, Biochim. Biophys. Acta *172*, 180 (1969).

[10] *S. L. Bonting*: Current Topics in Bioenergetics. Academic Press, New York 1969.

[11] *J. Heller*, Biochemistry 7, 2914 (1968).

[12] *W. A. Hagins, R. D. Penn*, and *S. Yoshikami*, Biophys. J. *10*, 380 (1970).

[13] *J. Rosenkranz*, Z. Zellforsch. *111*, 228 (1970).

[14] *M. W. Bitensky, R. E. Gorman*, and *W. H. Miller*, Proc. Nat. Acad. Sci. U. S. *68*, 561 (1971).

[15] *H. C. Berg*, Rev. Sci. Instr. *42*, 868 (1971).

[16] *J. Adler*, Science *153*, 708 (1966).

[17] *J. Adler*, Science *166*, 1588 (1969).

[18] *G. L. Hazelbauer* and *J. Adler*, Nature *230*, 101 (1971).

[19] *H. Kalckar*, Science, in press.

[20] *K. Bergman, P. V. Burke, E. Cerdá-Olmedo, C. N. David, M. Delbrück, K. W. Foster, E. W. Goodell, M. Heisenberg, G. Meissner, M. Zalokar, D. S. Dennison*, and *W. Shropshire, jr.*, Bacteriol. Rev. *33*, 99 (1969).

[21] *J. K. E. Ortega* and *R. I. Gamow*, Science *168*, 1374 (1970).

[22] *D. L. Johnson* and *R. I. Gamow*, J. Gen. Physiol. *57*, 41 (1971).

[23] *R. J. Cohen, J. Matricon*, and *M. Delbrück*, in preparation.

[24] From *O. V. S. Heath*: The physiological aspects of photosynthesis. Stanford University Press, 1969; *John E. Dowling* in *John M. Allen*: Molecular organization and biological function. Harper & Row, New York 1967.

The Mode of Action of Hormones

By Roland Schauer [*]

Higher organisms having anatomically and functionally differentiated organ systems must be able to coordinate biochemical processes within and between the various organs or cells, even under rapidly changing environmental conditions. Hormones play an important part in the regulation processes: they promote numerous metabolic reactions and differentiation processes, and show considerable differences in the speed with which they act. Some hormones act almost instantaneously by stimulating adenyl cyclase and thus initiating the production of adenosine 3',5'-monophosphate (cyclic AMP), which passes on the hormone message ("second messenger") to the intracellular metabolism by modifying enzyme activities. Delayed-action hormones, mainly morphogenetic hormones, act primarily on the cell nucleus where they induce the synthesis of certain enzymes by activation of genes.

1. Introduction

For a cell to function correctly, the numerous metabolic processes occurring within it must be coordinated. Only then can the available substrates be correctly utilized and contribute most effectively to the synthesis of vital substances and to growth. There are three fundamental possibilities for cell regulation by enzymes[1].

1. "Rate-limiting enzymes" determine the rate of reaction of the substrates in the metabolic reaction chains. As long as the quantity of a rate-limiting enzyme remains constant, the quantity of substance that reacts in the metabolic pathway in question is also constant, provided that sufficient substrate (*e. g.* glucose) is present. A change in the quantity of substance metabolized is possible only if the quantity of rate-limiting enzyme in the cell is increased or decreased (Fig. 1).

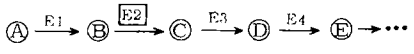


Fig. 1. Scheme of a metabolic pathway in which a substance A is converted into the product E by the successive action of several enzymes (E 1 to E 4). The enzyme that transforms its substrate most slowly (E 2 in this example) determines the rate of formation of the product E.

2. The second possibility for the regulation of the reaction rate is a stimulatory or inhibitory effect of an intermediate or final product of a reaction chain on the activity of rate-determining enzymes (Fig. 2). This mechanism is based on allosteric effects. Compounds (effectors) formed in metabolic processes interact with the enzyme protein at a site other than the active center in such a way that they change its conformation and influence the enzyme activity (end-product inhibition; feedback control; Fig. 3)[2–5].

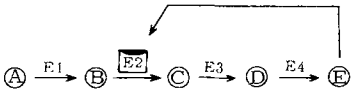


Fig. 2. Conversion of the substrate A into the product E by the action of several enzymes. The enzyme E 2 is inhibited by the end product E, which influences an allosteric action site on the enzyme (black).

An example of an allosteric effector is adenosine triphosphate (ATP) which is formed as an end product of energy metabolism, and which is needed for many energy-consuming processes. If ATP accumulates in the cell it can slow down the turnover of material *e. g.* by inhibiting the rate-limiting enzyme phosphofructokinase in the glycolytic breakdown of glucose[6]. If the ATP consumption increases, *e. g.* through muscular action, protein synthesis, or growth, the inhibitory action on the phosphofructokinase is abolished, and the glucose consumption and hence the formation of fresh ATP increase. Many examples of this type of control are known from intermediate metabolism[7, 8].

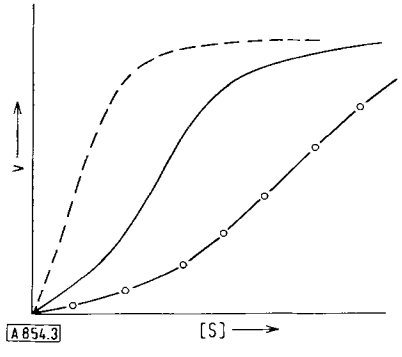


Fig. 3. Examples of the effect of allosteric modulators on the reaction rate (v) of an enzyme as a function of the substrate concentration [S]. The stimulatory effector (– – –) increases the affinity of the enzyme for the substrate, and the inhibitory effector (–o–o–) decreases it. The continuous curve shows the reaction rate without effectors.

3. The third possibility for the regulation of metabolism is a genetic control of the enzyme concentration in the cell. While some enzymes are always present in approximately constant quantities (*e. g.* many glycolysis enzymes), others are synthesized only when inducing substances act on the genetic material of the cell nucleus and make the information stored in the deoxyribonucleic acid (DNA) available for use[9, 10]. Clear examples of the initiation of enzyme synthesis by substrates were provided especially by the

[*] Doz. Dr. R. Schauer
Institut für Physiologische Chemie der Universität Bochum
4630 Bochum-Querenburg, Postfach 2148 (Germany)

investigation of the metabolism of bacteria. The best-known example is the induction of three lactose-utilizing enzymes in *Escherichia coli* simply by lactose added to the culture medium[10-12]. The opposite has also been found for bacteria; thus the enzyme synthesis can be repressed by "switching off" of a gene by the end product of a metabolic pathway. In *E. coli*, for example, histidine represses the formation of several enzymes that are necessary for the biosynthesis of this amino acid[13].

The regulation mechanisms outlined above are sufficient by themselves for a single cell, *e. g.* a bacterium. Higher organisms, on the other hand, require coordination of the metabolism not only within the cell ("intracellular regulation") but also between the cells and in particular between the various organs ("intercellular regulation"). This cooperation functions well even in the most highly organized life forms, the mammals, since the material turnover remains substantially constant, as is shown by the almost unvarying body temperature, the only slightly varying basal metabolic rate, *etc.* When the requirements of the body change, *e. g.* in illness, in cold conditions, and in times of danger, additional energy must often be made available very quickly by the intermediate metabolism. There are also periods in life, such as puberty, when pronounced changes of metabolism and new organ differentiations occur.

The possibilities available to the single cell are no longer sufficient for these changes. A central regulation in the body is therefore necessary. This is provided on the one hand by the nervous system and on the other by hormones[14]. (Of these two devices, the nervous system is a later evolutionary acquisition.) This can be illustrated by the following example. Healthy rats survive at an air temperature of 4 °C without ill effect. However, they quickly die at this low temperature if they have been artificially deprived of the ability to produce the hormone epinephrine. This hormone enables the animals to suit their metabolism to the new environmental conditions by increasing their basal metabolic rate[15-17].

2. The Nature of Hormones

The term "hormone" was first used by *Starling* and *Bayliss* in 1905 for secretin, a polypeptide formed in the upper regions of the small intestine, because it *stimulates* the secretory activity of the pancreas[18,19]. (In the classic experiment carried out by *Bayliss* and *Starling* on the dog, the production of digestive juice by the pancreas was stimulated when the mucous membrane of a section of the small intestine (jejunum) that is connected to the rest of the body only by blood vessels was wetted with dilute hydrochloric acid[18]. The same effect was achieved when a dog was injected with an extract from the mucous membrane of the acid-treated intestine.) Many substances produced in the body that exercise specifically stimulatory functions in the metabolism were subsequently classed as hormones. They belong to a very wide range of substance categories, and include *e. g.* peptides, steroids, and derivatives of aromatic amino acids and of fatty acids.

Hormones act as messengers carrying information to the organs. They are produced either in organs having this as their specific function, which are called endocrine glands (*e. g.* adrenals, thyroid, gonads, pituitary gland), or in tissues whose primary functions are entirely different; those produced in endocrine glands are called glandular hormones, while those formed in other tissues are called tissue hormones (*e. g.* secretin formed in the intestine, or histamine in the lungs, liver, and skin). Unlike the products of other glands (*e. g.* salivary, digestive, and sweat glands), hormones are released into the blood stream, a process that is known as "internal (endocrine) secretion". The hormones circulate at very low concentrations in the blood (*e. g.* about 10^{-7} to 10^{-8} mole/l for testosterone and thyroid hormones[20]), and usually act only on specific organs (target organs). (For example, the uterus and the mammary gland are the target organs of the female sex hormones.) How a hormone recognizes its target organ is still largely a mystery. It is assumed, however, (and evidence has been found to support the assumption, as will be shown later) that specific receptors in the cell membrane or in subcellular structures can selectively bind hormones circulating in small quantities in the blood to enable them to exert their effects.

This selective binding and the consequent selective action of the hormone allows the control of the metabolism of individual organs, often independently of the other organs in the body. This is an important condition for the division of work among the organs which becomes necessary, especially when unusual demands are made on the organism. To turn again to the example of secretin, this hormone is carried by the blood stream to all the organs in the body digestion, but it acts only in the pancreas[18,19].

3. The Control of Hormone Production

An essential feature of all regulatory systems is that the stimulating factors should not be free to act without any inhibition. If they were, there would be a danger of disequilibrium of the metabolic processes, particularly in the case of hormones, which generally have stimulatory functions. Metabolic dysfunction due to excessive hormone activity is prevented either by rapid breakdown of the hormone so that its duration of action is short or by control of the quantity of the hormone circulating in the blood. Epinephrine, for example, which can have a fatal effect in high concentrations by increasing the blood pressure and stimulating the heart, *etc.*[18] is rapidly broken down[21], as is acetylcholine, the transmitter substance for nervous impulses. Several other hormones, such as sex hormones, adrenocortical hormones, and thyroid hormones, inhibit their own synthesis by acting on controlling endocrine glands. The best-known organ in which this type of control occurs is the pituitary gland (appendix cerebri), which is located in man at the base of the brain approximately behind the root of the nose. This gland may be regarded as the command post for the hormonal regulation of the body[22]. It is the site of production of several peptide or glycopeptide hormones (glandotropic hormones) (Table 1), which act on the endocrine glands in the periphery of the

Table 1. Glandotropic hormones of the anterior lobe of the pituitary gland and their effects. ICSH, FSH, and LTH are also known as gonadotropic hormones because of their action on the gonads.

Hormone	Abbreviation	Effects
Adrenocorticotropic hormone (corticotropin)	ACTH	Stimulation of the synthesis of adrenocortical hormones
Thyroid-stimulating hormone (thyrotropin)	TSH	Stimulation of the synthesis of thyroid hormones
Interstitial cell-stimulating hormone (luteinizing hormone)	ICSH or LH	Stimulation of the synthesis of male and female sex hormones
Follicle-stimulating hormone	FSH	Stimulation of the maturation of the spermatozoon and of the ovum
Luteomammotropic hormone (prolactin, lactotropin)	LTH	Stimulation of the corpus luteum in the ovary and of the mammary gland

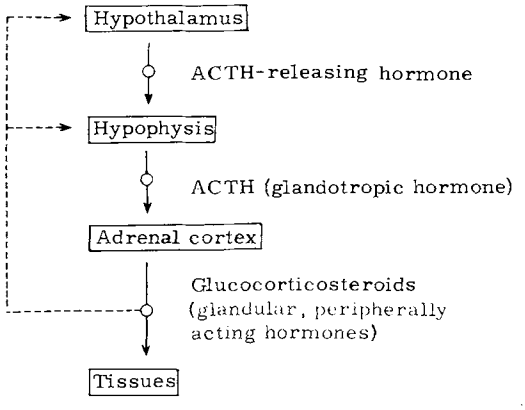


Fig. 4. Sequence of hormones that lead to the synthesis of peripheral hormones, illustrated by the case of the adrenocortical hormones; feedback inhibition of the pituitary gland and the hypothalamus by the peripheral hormones.
—○⟶ stimulatory, - - → inhibitory action.

body and cause them to synthesize specific "peripheral" hormones (Fig. 4).

The function of the pituitary gland is not autonomous, but is controlled by a higher organ, the hypothalamus (part of the diencephalon), which is situated anatomically just above the pituitary gland. Thus there exists a definite hierarchy of endocrine glands in the organisms of higher animals. Neurohormones produced in ganglion cells pass directly from the hypothalamus through short veins to the pituitary gland, where they stimulate the formation of the glandotropic hormones (Fig. 4)[23].

Because of this stimulatory action on the secretory activity of the pituitary gland, the neurohormones are called "releasing hormones" (RH). Releasing hormones have been detected, and in some cases isolated, for ACTH (corticotropin-releasing hormone, CRH), FSH (follicle-stimulating hormone releasing hormone, FSH-RH), ICSH (luteinizing hormone releasing hormone, LH-RH), and for TSH (thyrotropin-releasing hormone, TSH-RH), as well as for the growth hormone, which is also formed in the pituitary gland (growth hormone releasing hormone, GR-RH). These are also peptide hormones[22, 24–26].

The hypothalamus also is not entirely autonomous but is subject to the influence of nervous impulses from higher coordinating centers of the cerebral cortex. In this way, *e. g.* cold stimuli and particularly psychic stimuli can affect hormone production. The stimulatory or inhibitory effects of the psyche on the thyroid gland and gonads, and hence *e. g.* on the menstrual cycle, are well-known examples.

The hormones of the thyroid, the ovary, the testes, and the adrenal cortex, which are produced in the periphery of the body under the influence of the glandotropic pituitary hormones, not only act on their target organs but also can exert an inhibitory effect both on the pituitary gland and on the hypothalamus (Fig. 4)[22]. If the concentration of these hormones in the blood increases, therefore, the production of the releasing hormones in the hypothalamus and of the glandotropic pituitary hormones is reduced. In this way the body keeps the hormone effects under control.

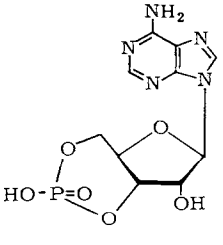
4. Modes of Action of the Hormones

Around ten years ago it was already possible to describe the many regulatory effects of various hormones on the general metabolism, the water and mineral balance, morphogenesis, growth, sexual development, the sexual functions, emotional and intellectual behavior, and defence and adaptation reactions of the organism. Apart from sexual differentiation in mammals and in man by sex hormones, the most remarkable effect is the transformation of a tadpole into a frog on administration of thyroid hormones[27]. On the molecular level, however, the mode of action of all hormones remained unknown for a long time. It was thought at first that hormones, like vitamins, could become prosthetic groups of enzymes[28]. However, no evidence supporting this assumption has ever been found. It was interesting, moreover, that the hormones usually cannot exert the same effect on isolated cell fractions, *e. g.* particle-free cell homogenates or microsomes, as they exhibit in the living organism or on the intact cell.

Some hormones, such as epinephrine, act immediately on the tissue, while others act only after hours or even days. Some, such as insulin, have both an immediate action (the permeability of the muscle cells of the diaphragm to glucose increases within a few minutes) and a delayed action (stimulation of protein synthesis after about 24 h[20]). This difference in the time taken for the hormones to act is based on different types of chemical reactions, which allow a tentative division of most hormones into two main groups.

4.1. Hormones Acting *via* Adenosine 3′,5′-Monophosphate

At least one of the effects of the hormones listed in Table 2 consists in the activation of the enzyme adenyl cyclase in the target cells of the hormones in question. This leads to the formation of adenosine 3′,5′-monophosphate ("cyclic AMP") *(1)* and pyrophosphate from ATP[29–31], a reac-



(1)

tion that was discovered by *Sutherland*'s research group during investigations on the mechanism of the liberation of glucose from the liver by epinephrine or glucagon[31].

Since the α-phosphate group of ATP rapidly undergoes ring closure to form cyclic AMP, only a short time elapses between administration or secretion of the hormone and the onset of action of those hormones that act *via* cyclic AMP. With parathyroid hormone, for example, cell cultures of bone tissue show an increase in the intracellular concentration of cyclic AMP after only 30–60 seconds[29].

Adenyl cyclase occurs in mammals, insects, and bacteria[35, 36]. In the dog, the enzyme is found in all the organs, but not in erythrocytes. The highest content is in the brain, and this is followed by the tissues that are subject to the action of the hormones that lead to the production of cyclic AMP (liver, muscle, adrenal cortex, ovary, *etc.*). The adenyl cyclase is firmly bound to cell membranes[37]. The tissues are assumed to contain hormone-specific or organ-specific adenyl cyclases, which are responsible for the selective binding of particular hormones. However, there may also exist one type of adenyl cyclase that is closely correlated sterically and functionally with specific hormone receptors in the different organs[38, 39]. This could allow the hormones that act *via* cyclic AMP to exert a selective influence on their target organs. Thus only thyrotropic hormone can

Table 2. Hormones whose effects are at least partly transmitted by cyclic AMP [31—34].

Hormone	Effects
Adrenocorticotropic hormone (ACTH)	Stimulation of the synthesis of glucocorticosteroids in the adrenal cortex
Luteinizing hormone (ICSH)	Stimulation of the synthesis of sex hormones in the ovary or testis
Thyroid-stimulating hormone (TSH)	Stimulation of the synthesis of thyroid hormones
Vasopressin (adiuretin)	Reabsorption of water in renal tubules; contraction of vascular muscle
Oxytocin	Contraction of smooth muscle, particularly of the uterus
Catecholamines (*e.g.* epinephrine)	Activation of phosphorylase in liver and muscle (increase in blood sugar level); stimulation of the tissue lipase; stimulation of cardiac and circulatory function; stimulatory action on the central nervous system
Insulin	Lowering of blood sugar level; stimulation of glucose transport through cell membranes; promotion of glucose consumption and of fat synthesis
Glucagon	Activation of phosphorylase in the liver (increase in the blood sugar level)
Melanocyte-stimulating hormone (MSH)	Regulation of the pigment distribution in the pigment cells of the skin, particularly of cold-blooded animals
Parathyroid hormone	Mobilization of calcium from the skeleton; increased phosphate excretion through the kidneys
Angiotensin	Increase in blood pressure; stimulation of the secretion of aldosterone by the adrenal cortex
Prostaglandins	Organ-specific contraction or slackening of smooth muscle; inhibition of fatty tissue lipase
Histamine	Organ-specific contraction or slackening of smooth muscle; stimulation of hydrochloric acid production in the stomach
Serotonin	Dose-dependent contraction or slackening of smooth muscle; several effects on the central nervous system

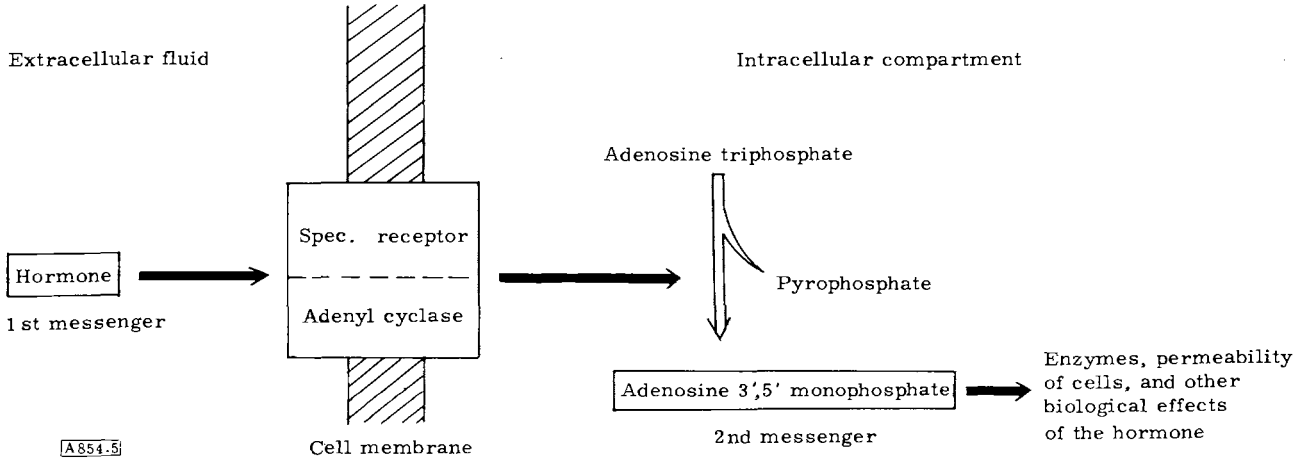
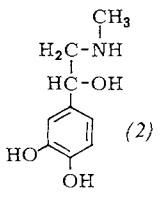


Fig. 5. Activation of the (specific?) adenyl cyclase in the cell membrane by hormones (after adsorption of the hormone on a specific receptor?). Modification of enzyme activities, cell permeability *etc.* by the second messenger. ⟶ stimulatory action, ⟹ enzyme catalysis (based on [39]).

stimulate the adenyl cyclase in the thyroid gland; this stimulation leads to the secretion of more thyroid hormone.

Cyclic AMP is also known as "second messenger", since it passes on the message of the hormone (first messenger) to the intracellular metabolism (Fig. 5)[39]. It influences the metabolic rate in the cell by acting allosterically on the rate-limiting enzymes and modifying their activity, or by activating enzymes that are present in an inactive form and so inducing a special synthesis[31,40]. Effects of cyclic AMP on many enzymes or biological systems of the animal kingdom and in bacteria are now known (for reviews see [31,34,40–43]).



(2)

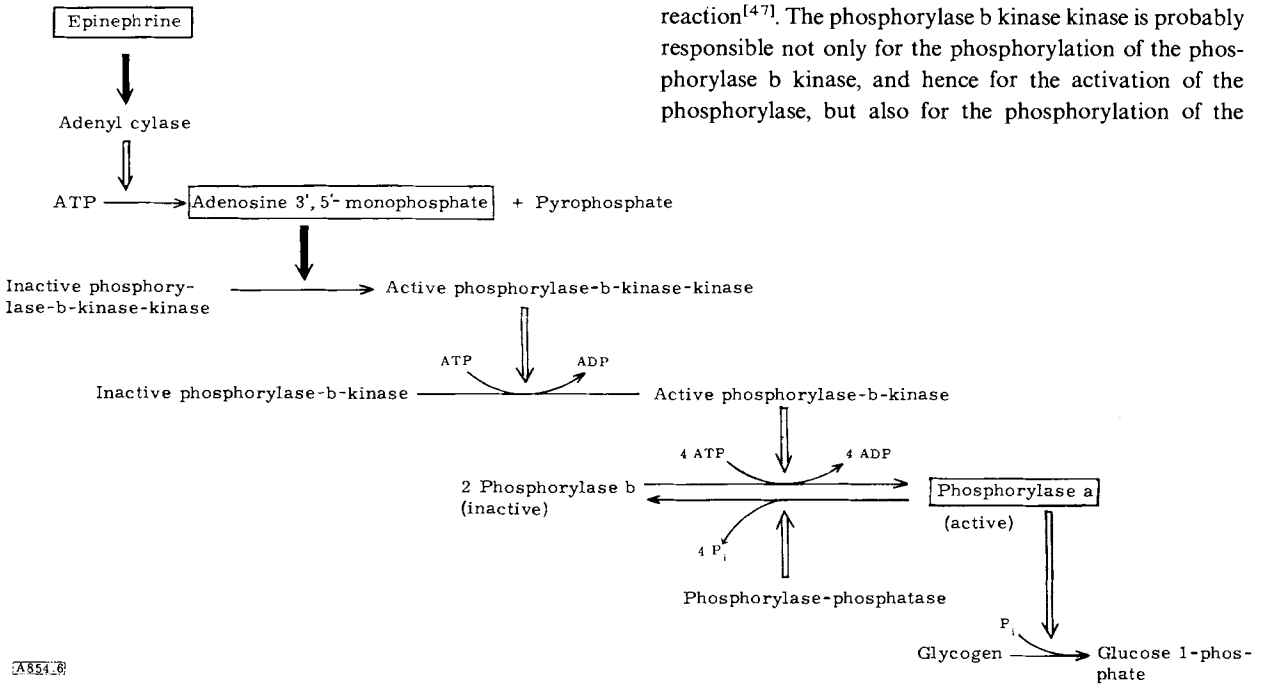


Fig. 6. Activation of glycogen phosphorylase (phosphorylase a) in muscle by epinephrine. For explanation see text. ⟶ stimulatory action, ⟹ enzyme catalysis.

By the action of cyclic AMP on isolated organs, cell cultures, cell fractions, or enzyme systems, it is possible to initiate biological effects that correspond to the known effects of hormones on the same tissue or enzymes in the intact organism. For example, both ACTH and cyclic AMP stimulate the release of corticosteroids from isolated adrenals or from cell cultures of the adrenal cortex in the same manner[33,44].

The most thoroughly investigated effects of cyclic AMP are those on enzymes concerned with the breakdown of glycogen in the liver or muscle and with the fat metabolism in fat cells of the epididymis. Under the action of epinephrine *(2)* (and also of glucagon in the liver), glycogen is degraded to glucose-1-phosphate in the liver and in muscle tissue by an enzyme called "phosphorylase". In the resting muscle phosphorylase is largely found in an inactive form (phosphorylase b) consisting of two subunits. Two phosphorylase b molecules are converted by epinephrine into the catalytically active phosphorylase a molecule, which consists of four subunits[45]. At the same time, four phosphate groups are transferred from ATP to the enzyme protein by the active phosphorylase b kinase, which must also be phosphorylated before it can act. This activation is effected by another kinase (active phosphorylase b kinase kinase), an enzyme that is itself activated by cyclic AMP, the second messenger of epinephrine[15,42,46]. As a result of an impulse of this complicated enzyme cascade, which is represented in Fig. 6, epinephrine makes more glucose available to the cell in moments when energy requirements are high. As soon as the energy demand and the epinephrine level fall, the phosphorylase phosphatase gains the upper hand, and the active phosphorylase a is dephosphorylated back to the inactive form.

According to recent investigations, these complicated regulation processes include yet another, very interesting reaction[47]. The phosphorylase b kinase kinase is probably responsible not only for the phosphorylation of the phosphorylase b kinase, and hence for the activation of the phosphorylase, but also for the phosphorylation of the glycogen synthetase. Unlike the phosphorylase, the glycogen synthetase loses most of its activity when it acquires the phosphate group. Glycogen synthesis is thus prevented at the time of the hormone-stimulated glycogen breakdown, so that large quantities of glucose-1-phosphate can be rapidly utilized for the production of energy in the glycolysis. Insulin, which opposes any increase in the blood sugar concentration, slows down the above epinephrine-stimulated process of the phosphorolytic degradation of glycogen by lowering the adenosine 3′,5′-monophosphate level in the cell (Fig. 7)[48,49].

Several hormones (ACTH, epinephrine, glucagon, TSH, LTH, and prolactin, in order of activity) activate the

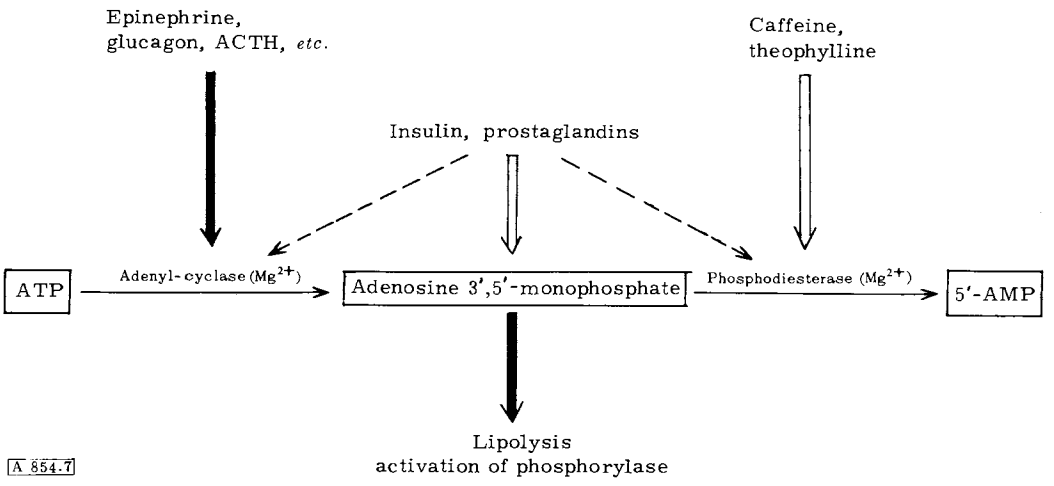


Fig. 7. Effects of hormones and of methylxanthines on the formation and degradation of cyclic AMP and hence on the lipase and phosphorylase activities in fat cells of the rat epididymis (based on [31]). ⟶ stimulation, ⟹ inhibition; - - → inhibition of adenyl cyclase or stimulation of phosphodiesterase? For further explanations see text.

triglyceride lipase in fat cells, cyclic AMP presumably again acting as an allosteric effector for all these hormones[42,50]. The result is that more fat is hydrolyzed and made available to the oxidative degradation pathway. In the fatty cells also, insulin decreases the concentration of cyclic AMP and so opposes lipolysis[51]. The same effect has also been described for prostaglandin E_1 (Fig. 7)[31].

Rapid breakdown of cyclic AMP is essential for an adaptable regulation of metabolism. This is brought about by a specific phosphodiesterase in an Mg^{2+}-dependent reaction (Fig. 7), in which adenosine 5'-phosphate (AMP) is formed[31,52]. Methylxanthines, *e.g.* theophylline and caffeine, inhibit this hydrolytic breakdown[34,53], and this explains their epinephrine-like effects (acceleration of pulse rate *etc.*). It is not yet known whether insulin and prostaglandins decrease the concentration of cyclic AMP, particularly in fat cells of the epididymis of the rat, by activation of the phosphodiesterase or by inhibition of the adenyl cyclase (Fig. 7)[34,40].

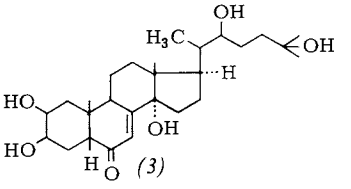
Though cyclic AMP has been recognized as the intermediary for a large number of effects of the hormones of this first group, it has not yet been established whether it is the second messenger for all the effects of these hormones. Some of the hormones listed in Table 2, such as ACTH, have been found to have an additional mode of action that is characteristic of the group of hormones to be discussed in Section 4.2.

By discovering and naming cyclic AMP as a second messenger, *Sutherland* has made a great contribution to our understanding of the mode of action of hormones on the molecular level. It is quite possible that there are other substances as well as cyclic AMP that can transmit hormone messages to the intermediate metabolism. Further cyclic nucleotides whose concentrations show a striking variation with hormonal changes have been discovered in urine (*e.g.* guanosine 3',5'-monophosphate)[54].

4.2. Hormones Inducing Enzyme Synthesis

The hormones of this group (Table 3) act on the deoxyribonucleic acid (DNA) of the cell nucleus and induce the synthesis of fresh enzymes, unlike the hormones discussed earlier which cause cyclic AMP to modify the activity of enzymes that are already present. This group also includes hormones that were listed in Table 2 (ACTH, TSH, and insulin), which influence both the genetic material and the synthesis of cyclic AMP.

The understanding of the mode of action of this group of hormones owes a great deal to *Karlson*'s investigations on the pupation hormone ecdysone *(3)*[56]. This steroid



(3)

hormone was first isolated from pupating silkworms *(Bombyx mori)*[57].

By activating certain genes in the larva, ecdysone induces the synthesis of enzymes that produce from the amino acid tyrosine the sclerotization material required for the pupation process[58,59]. This type of mode of action was first postulated from the formation of "puffs" on the chromosomes after the administration of ecdysone or shortly before the natural pupation of insect larvas[59,60]. Puffs are (reversible) thickenings of the chromosomes, in which the DNA helices are despiralized. These "opened-up" chromosome regions are assumed to contain genes that are no longer resting, but that cause the synthesis of ribonucleic acid (RNA)[61]. In fly larvas or their isolated cell nuclei, it has been possible to detect the formation of new RNA in the nucleus and an increase in the activity of the DNA-dependent RNA polymerase under the action of ecdysone (*e.g.* [62,63]). The RNA that is synthesized under the action of the hormone is messenger RNA (m-RNA), which serves as a template for protein synthesis after attachment to ribosomes. In this process[28], the genetic information stored in the DNA molecules of the nucleus is translated into the amino acid sequence of a protein that is to be synthesized. The protein that is formed under

the influence of the hormone, *i.e.* whose synthesis is induced, is in this case an enzyme, which is now used for special metabolic processes leading *e.g.* to pupation.

Table 3. Hormones whose effects are based at least partly on the induction of the synthesis of enzymes.

Hormone	Effects
Adrenocorticotropic hormone (ACTH)	Stimulation of the synthesis of steroid hormones; growth of the adrenal cortex
Glucocorticosteroids	Stimulation of gluconeogenesis (increase in the blood sugar level, protein breakdown); inhibition of inflammation; immunosuppressive action
Thyroid-stimulating hormone (TSH)	Promotion of the synthesis of thyroid hormones
Thyroid hormones (thyroxine, triiodothyronine)	Induction of respiratory enzymes, *etc.*; growth; metamorphosis.
Growth hormone (somatotropic hormone, STH)	Growth; stimulation of protein synthesis; stimulation of gluconeogenesis
Insulin	Lowering of the blood sugar level; increase in cell permeability; promotion of glycogen, protein, and lipid synthesis
Estradiol and other estrogens	Female sexual differentiation; stimulation of lipid synthesis
Testosterone	Male sexual differentiation; promotion of protein synthesis
Erythropoietin	Promotion of the formation of red blood cells [55]
Ecdysone	Initiation of the metamorphosis (pupation) of insects

Though the formation of puffs cannot be observed under the microscope in the chromosomes of mammals, it can be shown by measurements of the rate of m-RNA synthesis or by measurement of the RNA polymerase activity, as well as by inhibition of m-RNA and protein biosynthesis with antibiotics such as actinomycin or puromycin[64], that here also the hormones of Table 3 (apart from ecdysone) increase the gene activity and lead to increased protein synthesis. Moreover, the effects of these hormones appear only after several hours or a few days, the period required for the complicated and time-consuming process of m-RNA and protein synthesis. (When thyroxine is administered therapeutically, several days elapse before the respiratory functions and the processes of the oxidative phosphorylation in the tissues return to normal[65].) These processes will be illustrated further by some examples.

Thyroid hormones intensify the respiration of the mitochondria by induction of a number of respiratory enzymes, *e.g.* succinate dehydrogenase and cytochrome oxidase. On administration of a single dose of triiodothyronine or thyroxine, thyroidectomized animals exhibit an increase in the radioactivity of the RNA in the cell nucleus after only 6 hours, and a distinct increase in the activity of the Mg^{2+}-dependent RNA polymerase after 10—12 hours (Fig. 8)[66]. The rate of protein synthesis, as detected by the increased incorporation of radioactive amino acids into proteins and by an increase in the cytochrome oxidase, rises significantly only after 30 hours. These processes explain why the action of thyroid hormones is totally suppressed by actinomycin D, which inhibits the synthesis of m-RNA[67].

Particularly vigorous RNA and enzyme syntheses occur during the metamorphosis of tadpoles, which is strictly dependent on thyroid hormones[27,66]. Enzymes of many biochemical systems are induced in this process, the induction of respiratory enzymes and enzymes for urea synthesis being particularly strong.

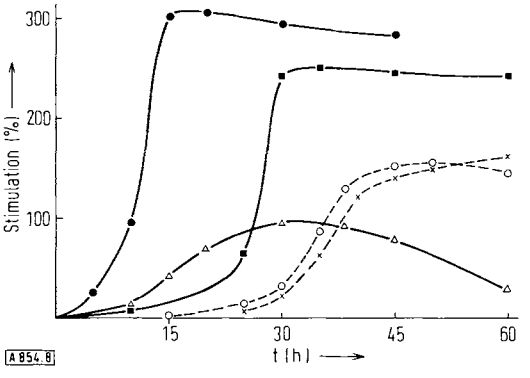


Fig. 8. Stimulation of RNA and protein synthesis in the liver of thyroidectomized rats as a function of time after a single administration of 15–22 μg of triiodothyronine.

(-●—●-) rate of synthesis of nuclear RNA *in vivo*. (-△—△-) Mg^{2+}-dependent RNA polymerase. (-■-—■-) accumulation of newly formed, radioactively labeled ribosomes and polysomes in the cytoplasm. (-○- - -○-) incorporation of ^{14}C-labeled amino acids into proteins/mg of RNA by ribosomes or microsomes *in vitro*. (-×- - -×-) cytochrome oxidase activity/mg of mitochondrial protein (after [66]). The stimulation is determined with respect to a control experiment on normal rats.

Effects on the nucleic acid and protein metabolism similar to those exerted by the thyroid hormones have also been detected for growth hormone, sex hormones, ACTH, adrenocortical hormones (listed in [65]), insulin[49], and erythropoietin[55]. The hormones insulin and glucocorticosteroids (*e.g.* cortisone), which are often used therapeutically, are particularly illuminating examples of a rational hormonal regulation of metabolic processes by induction of several enzymes (reviews in [49,68,69]).

Insulin and glucocorticosteroids have antagonistic effects on the glucose concentration in the blood. Whereas insulin decreases the blood sugar concentration by synthesis of glycogen from glucose, retardation of the breakdown of glycogen (cf. Section 4.1), and acceleration of the aerobic and anaerobic breakdown of glucose, glucocorticosteroids increase the blood sugar concentration by formation of new glucose from amino acids.

This process, which is known as gluconeogenesis, becomes very important in hunger, when too little carbohydrate is being supplied to the organism. Glucose is degraded in a complicated reaction sequence known as glycolysis, with formation of pyruvate, which can be consumed in the citric acid cycle (Fig. 9). At the beginning of the reverse process, *i.e.* gluconeogenesis, pyruvate is formed (together with other keto acids, *etc.*, which will not be considered here) from amino acids. Two molecules of pyruvate are converted into one molecule of glucose in an energy-consuming reaction chain (Fig. 9). This synthesis proceeds in part as a direct reversal of the glycolysis reactions, using the same enzymes. On thermodynamic grounds, however, some reaction steps require special enzymes, which are used only for the resynthesis of glucose from pyruvate, and which catalyze irreversible reactions[70]; these are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-diphosphatase, and glucose-6-phosphatase. The key enzymes for the rate-determining steps in glycolysis are glucokinase, phosphofructokinase, and pyruvate kinase. Whereas the key enzymes of glycolysis (including glycogen synthetase) are induced by insulin, the quantities of the key enzymes for gluconeogenesis in the liver cells are increased under the influence of glucocorticosteroids (Fig. 9). Transaminases and tryptophan pyrrolase, for example, which are involved in the start of gluconeogenesis and in the supply of pyruvate, are also induced by glucocorticosteroids[69].

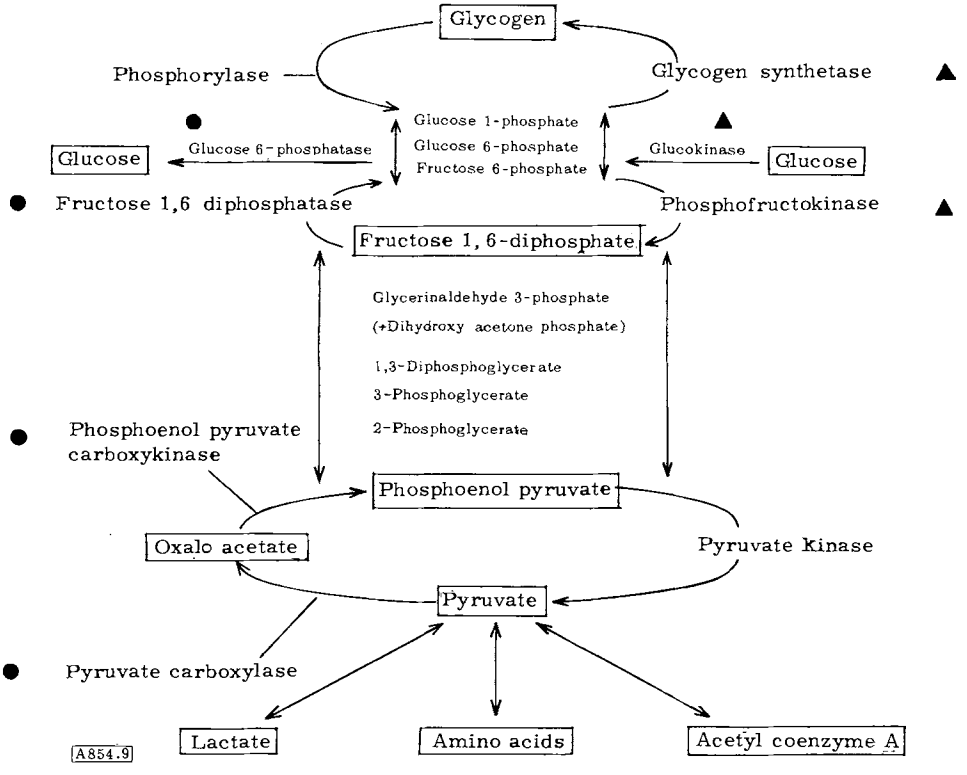


Fig. 9. Synthesis and degradation pathway of glucose (gluconeogenesis and glycolysis), schematic, with the key enzymes that catalyze the rate-determining irreversible reactions; regulation of these metabolic pathways by induction of the glycolytic key enzymes with insulin (▲) and of the gluconeogenetic key enzymes with glucocorticosteroids (●) (based on [49]).

The examples described have shown that a hormone (of group 2) can activate not just one gene but probably several. The associated induction of a group of enzymes by a single inducer (=hormone) recalls the processes, first described for bacteria by *Jacob* and *Monod*, in the induction of several enzymes by a single substrate, *e.g.* by lactose in the case of *Escherichia coli*[11,12]. The lactose here removes a specific repressor molecule from the "operator gene", and the "structure genes" can then bring about the synthesis of the m-RNA for the formation of the enzymes that transport and cleave lactose (Fig. 10).

Repressors are basic proteins, possibly histones[71], attached to the DNA; according to the current view, they shield and inactivate genes. After the repressor has been removed, the information stored in the relevant DNA section can be read by the RNA polymerase. Some repressors have already been isolated from bacteria and their binding to the genetic material detected. One example is the repressor of the lactose operon[72].

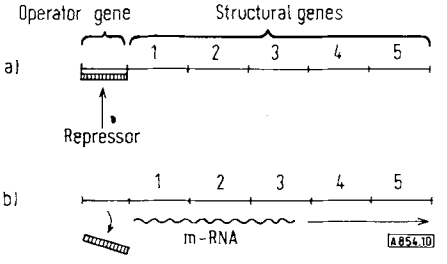


Fig. 10. a) Schematic representation of an operon [10] with repressed operator gene. b) An inductor removes the repressor (depression = induction of the operator gene). The synthesis of m-RNA on the structure genes then begins (after [65]).

It is quite conceivable that the hormonal induction of enzymes in the higher organism takes place in the same way as in bacteria. There is a steadily growing body of evidence in support of the assumption that hormones recognize specific repressors, combine with them, and remove them from the gene, possibly by changing their conformation (Fig. 11)[63].

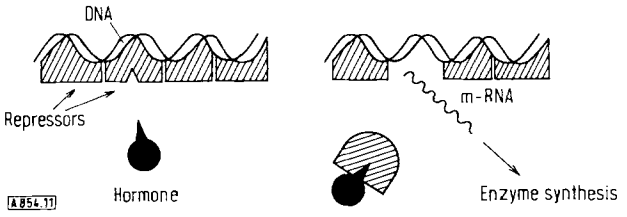


Fig. 11. Enzyme induction by hormones. Primary action of hormones on the transcription stage, presumably after removal of a specific repressor from the gene. A possible change in the conformation of the repressor molecule by the hormone is illustrated (based on [73]).

Selective binding of radioactive estradiol, hydrocortisone, testosterone, and ecdysone[74] to isolated cell nuclei of the target organs has been observed by several groups of workers (reviews in [63,75]). *Sekeris et al.*[63,76] were able to show that tritium-labeled hydrocortisone is bound to rat liver cell nuclei, and that within a few seconds it increases the RNA polymerase activity and the fraction of the nucleohistone (nuclear chromatin) that takes part in the transcription (cf. also [77]). A number of experimental findings also point to a structural change effected by hydrocortisone in the proteins bound to the nucleus (cf. Fig. 11)[63]. In cell nuclei from target organs of female sex hormones, estradiol is bound to a macromolecule fraction that can then be readily removed from the nucleus[78]. This is taken as evidence that this estrogen-binding protein could in fact be the repressor that masked the DNA and prevented it from exerting its biochemical action before the estrogen acted on it.

5. Closing Remarks

It was not the purpose of this progress report to consider all hormones and to describe their biological effects individually. The object was to present the known, presumably primary modes of action on the basis of which the hormones can be divided into two groups, *i.e.* action *via* cyclic AMP on the one hand and action *via* the induction of enzyme synthesis by specific attack on the genetic material on the other. Despite the great progress that has been made in the past ten years, our knowledge of the mode of action of these mysterious regulators of life is still far from complete. Least is known about the specific receptor in the cell membrane[79] or on the cell nucleus that enables a hormone circulating in the blood to be recognized only by cells of certain organs and to be bound by these cells in order that it may exert its specific action. Something else that has not yet been explained is the clock that one day causes the appearance of pupation or sex hormones, which mold the organism and then disappear again after a predetermined time. A great deal of experimental work is still necessary in order to find the answers to these questions.

Received: March 23, 1971 [A 854 IE]
German version: Angew. Chem. *84*, 41 (1972)
Translated by Express Translation Service, London

[1] *A. Sols* and *S. Grisolia:* Metabolic Regulation and Enzyme Action. FEBS Symposium 19. Academic Press, New York 1970.

[2] *J. Monod, J. Wyman,* and *J.-P. Changeux,* J. Mol. Biol. *12*, 88 (1965).

[3] *D. E. Koshland jr.,* Advan. Enzymol. *22*, 45 (1960).

[4] *J. C. Gerhart* and *A. B. Pardee,* Cold Spring Harbor Symp. Quant. Biol. *28*, 491 (1963).

[5] *S. Kornfeld, R. Kornfeld, E. F. Neufeld,* and *P. J. O'Brien,* Proc. Nat. Acad. Sci. U. S. *52*, 371 (1964).

[6] *O. H. Lowry* and *J. V. Passonneau,* J. Biol. Chem. *241*, 2268 (1966).

[7] *B. Chance, R. W. Estabrook,* and *J. R. Williamson:* Control of Energy Metabolism. Academic Press, New York 1965.

[8] *M. C. Scrutton* and *M. F. Utter,* Annu. Rev. Biochem. *37*, 249 (1968).

[9] *H. L. Kornberg,* Symp. Soc. Gen. Microbiol. *15*, 8 (1965).

[10] *B. N. Ames* and *R. G. Martin,* Annu. Rev. Biochem. *33*, 235 (1964).

[11] *F. Jacob* and *J. Monod,* Cold Spring Harbor Symp. Quant. Biol. *26*, 193 (1961).

[12] *F. Jacob* and *J. Monod,* J. Mol. Biol. *3*, 318 (1961).

[13] *B. N. Ames* and *B. Garry,* Proc. Nat. Acad. Sci. U. S. *45*, 1453 (1959).

[14] *D.E. Green* and *R. F. Goldberger:* Molecular Insights into the Living Process. Academic Press, New York 1967, p. 306.

[15] *L. Lundholm, E. Mohme-Lundholm,* and *N. Svedmyr* in [20], p. 101.

[16] *L. D. Carlson,* Pharmacol. Rev. *18*, 291 (1966).

[17] *E. Zeisberger* and *K. Brück,* Pflügers Arch. Ges. Physiol. *322*, 152 (1971).

[18] *P. C. Clegg* and *A. G. Clegg:* Hormones, Cells and Organisms. Heinemann Educational Books Ltd., London 1969.

[19] *J. E. Jorpes,* Gastroenterology *55*, 157 (1968).

[20] *E. E. Bittar* and *N. Bittar:* The Biological Basis of Medicine. Academic Press, New York 1968, Vol. 2.

[21] *D. Exley* and *T. D. R. Hockaday* in [20], p. 25.

[22] *H. J. Campbell* in [20], p. 47.

[23] *F. Engelhardt* in *H. Olivecrona* and *W. Tönnis:* Handbuch der Neurochirurgie I/2, Grundlagen II. Springer, Berlin 1968, p. 1.

[24] *S. M. McCann* and *A. P. S. Dhariwal* in *L. Martini* and *W. F. Ganong:* Neuroendocrinology. Academic Press, New York 1966, Vol. 1.

[25] *A. V. Schally, A. Kuroshima, J. Ishida, A. Arimura, T. Saito, C. J. Bowers,* and *S. L. Steelman,* Proc. Soc. Exp. Biol. Med. *122*, 821 (1966).

[26] *P. A. Diassi* and *Z. P. Horovitz,* Annu. Rev. Pharmacol. *10*, 219 (1970).

[27] *J. E. Eaton* and *E. Frieden:* General and Comparative Endocrinology Suppl. *2*, 398 (1969).

[28] *P. Karlson:* Umschau in Wissenschaft u. Technik *63*, 595 (1963).

[29] *T. W. Rall* and *E. W. Sutherland,* J. Biol. Chem. *232*, 1065 (1958).

[30] *D. Lipkin, R. Markham,* and *W. H. Cook,* J. Amer. Chem. Soc. *81*, 6075 (1959).

[31] Wirkungsmechanismus der Hormone. 18. Kolloquium der Gesellschaft für Physiologische Chemie. Springer, Berlin 1967.

[31a] *E. W. Sutherland, R. W. Butcher, G. A. Robison,* and *J. G. Hardman* in [31], p. 1.

[32] *L. R. Chase* and *G. D. Aurbach,* J. Biol. Chem. *245*, 1520 (1970).

[33] *J. Kowal* and *R. P. Fiedler,* Endocrinology *84*, 1113 (1969).

[34] *G. A. Robison, R. W. Butcher,* and *E. W. Sutherland,* Annu. Rev. Biochem. *37*, 149 (1968).

[35] *E. W. Sutherland, T. W. Rall,* and *T. Menon,* J. Biol. Chem. *237*, 1220 (1962).

[36] *R. S. Makman* and *E. W. Sutherland,* J. Biol. Chem. *240*, 1309 (1965).

[37] *I. Øye* and *E. W. Sutherland,* Biochim. Biophys. Acta *127*, 347 (1966).

[38] *V. T. Maddaiah,* J. Theoret. Biol. *25*, 495 (1969).

[39] *E. W. Sutherland* and *G. A. Robison,* Pharmacol. Rev. *18*, 145 (1966).

[40] *E. W. Sutherland,* J. Amer. Med. Assoc. *214*, 1281 (1970).

[41] *G. Fayet* and *S. Lissitzky,* FEBS Lett. *11*, 185 (1970).

[42] *H. Förster,* Dtsch. Med. Wschr. *96*, 251 (1971).

[43] *O. H. Lowry* in *B. Chance, R. W. Estabrook,* and *J. R. Williamson:* Control of Energy Metabolism. Academic Press, New York 1965, p. 63.

[44] *D. Schulster, S. A. S. Tait, J. F. Tait*, and *J. Mrotek*, Endocrinology *86*, 487 (1970).

[45] *E. H. Fischer, S. S. Hurd, P. Koh, V. L. Seery*, and *D. C. Teller:* Control of Glycogen Metabolism. FEBS Proc. 4th Meeting, Oslo 1967. Academic Press, New York 1968, p. 19.

[46] *R. J. De Lange, R. Kemp, W. D. Riley, R. A. Cooper*, and *E. G. Krebs*, J. Biol. Chem. *243*, 2200 (1968).

[47] *T. R. Soderling, J. P. Hickenbottom, E. M. Reimann, F. L. Hunkeler, D. A. Walsh*, and *E. G. Krebs*, J. Biol. Chem. *245*, 6317 (1970).

[48] *R. W. Butcher, J. G. T. Sneyd, C. R. Park*, and *E. W. Sutherland*, J. Biol. Chem. *241*, 1651 (1966).

[49] *G. Weber* in [20], p. 263.

[50] *L. Birnbaumer* and *M. Rodbell*, J. Biol. Chem. *244*, 3477 (1969).

[51] *R. L. Jungas*, Proc. Nat. Acad. Sci. U. S. *56*, 757 (1966).

[52] *E. W. Sutherland* and *T. W. Rall*, J. Biol. Chem. *232*, 1077 (1958).

[53] *J. A. Beavo, N. L. Rogers, O. B. Crofford, J. G. Hardman, E. W. Sutherland*, and *E. V. Newman*, Mol. Pharmacol. *6*, 597 (1970).

[54] *J. G. Hardman, J. W. Davis*, and *E. W. Sutherland*, J. Biol. Chem. *241*, 4812 (1966).

[55] *P. P. Dukes* in [31], p. 197.

[56] *P. Karlson*, Angew. Chem. *75*, 257 (1963); Angew. Chem. internat. Edit. *2*, 175 (1963).

[57] *A. Butenandt* and *P. Karlson*, Z. Naturforsch. *9b*, 389 (1954).

[58] *C. E. Sekeris* and *P. Karlson:* Mechanisms of Hormone Action. Thieme, Stuttgart 1965, p. 149.

[59] *P. Karlson*, Perspectives Biol. Med. *4*, No. 2, 203 (1963).

[60] *U. Clever* and *P. Karlson*, Exptl. Cell Res. *20*, 623 (1960).

[61] *G. Pelling*, Nature *184*, 655 (1959).

[62] *L. F. Congote, C. E. Sekeris*, and *P. Karlson*, Z. Naturforsch. *25b*, 279 (1970).

[63] *C. E. Sekeris*, Excerpta Med. Internat. Congress Ser. No. 184; Progress in Endocrinology, Proc. of the Third International Congress of Endocrinology, Mexico 1968, p. 7.

[64] *H. J. Rogers* in [20], p. 421.

[65] *K. L. Manchester* in [20], p. 221.

[66] *J. R. Tata* in [31], p. 87.

[67] *E. Reich* and *I. H. Goldberg*, Progr. Nucleic Acid Res. Mol. Biol. *3*, 183 (1964).

[68] *W. Seubert* in [31], p. 158.

[69] *H. J. Hübener* and *W. H. Staib* in *G. Weitzel* and *N. Zöllner:* Biochemie und Klinik. Thieme-Verlag, Stuttgart 1965.

[70] *H. A. Krebs*, Bull. Johns Hopkins Hosp. *95*, 19 (1954).

[71] *E. Stedman* and *E. Stedman*, Phil. Trans. *B 235*, 565 (1961).

[72] *W. Gilbert* and *B. Müller-Hill*, Proc. Nat. Acad. Sci. U. S. *58*, 245 (1967).

[73] *P. Karlson:* Kurzes Lehrbuch der Biochemie. Thieme-Verlag, Stuttgart 1970, p. 300.

[74] *H. Emmerich*, Exptl. Cell Res. *58*, 261 (1969).

[75] *W. E. Stumpf*, J. Histochem. Cytochem. *18*, 21 (1970).

[76] *M. Beato, W. Brändle, D. Biesewig*, and *C. E. Sekeris*, Biochim. Biophys. Acta *208*, 125 (1970).

[77] *M. E. Dahmus* and *J. Bonner*, Proc. Nat. Acad. Sci. U. S. *54*, 1370 (1965).

[78] *P. W. Jungblut, I. Hätzel, E. R. DeSombre*, and *E. V. Jensen* in [31], p. 58

[79] *G. A. Robison, R. W. Butcher*, and *E. W. Sutherland* in *J. F. Danielli, J. F. Moran*, and *D. J. Triggle:* Fundamental Concepts in Drug-Receptor Interactions. Academic Press, New York 1969, p. 59.

Macrocyclic Polyethers and Their Complexes[***]

By C. J. Pedersen and H. K. Frensdorff[*]

The most important, and almost unique, property of the macrocyclic polyethers ("crown compounds") is their tendency to form complexes with alkali metal salts and salts with similar cations. Such complexes are held together by electrostatic attraction between the cation and the negative end of the C—O dipoles. The stability of the polyether complexes depends primarily upon how well the cation fits into the polyether ring; other factors are the charge density of the cation and—in solution—the solvating power of the medium. Cyclic polyethers have been successfully employed, inter alia, in experiments with ionic compounds in organic solvents and in studies of ion transport in biological systems.

1. Introduction

Complexing of sodium, potassium, and related cations by neutral molecules is an uncommon phenomenon. Strong stoichiometric complexes have been observed only in the last decade[1, 2], and then only with biological materials (see Section 1.3).

Hence some of the recently synthesized macrocyclic polyethers[3, 4] have aroused considerable interest in several divisions of chemistry because they form stable complexes, both in solution and in the crystalline form, with salts of alkali and other metals.

More than sixty macrocyclic polyethers have been synthesized. They are neutral compounds containing four to twenty oxygen atoms each separated from the next by two or more carbon atoms, but the most effective complexing agents are found among those containing five to ten oxygen atoms each separated from the next by two carbon atoms. These compounds form 1:1 salt-polyether complexes in which the cation is encircled by the oxygen atoms of the polyether ring, being held there by the elec-

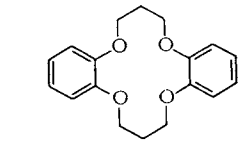
[*] C. J. Pedersen and Dr. H. K. Frensdorff[**]
Elastomer Chemicals Department
Du Pont Experimental Station
Wilmington, Delaware, 19898 (USA)

[**] To whom all correspondence should be addressed.

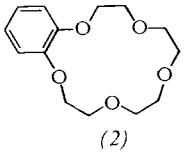
[***] Contribution No. 255 from the Elastomer Chemicals Department, E. I. du Pont de Nemours and Company, Inc.

trostatic attraction between the negatively charged oxygens of the C—O dipoles and the cation. In some cases, 2:1 and even 3:2 polyether : salt complexes are found[5]. The following cations have so far been observed to form complexes with cyclic polyethers: Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, RNH_3^+, Ag^+, Au^+, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ra^{2+}, Zn^{2+}, Cd^{2+}, Hg^+, Hg^{2+}, La^{3+}, Tl^+, Ce^{3+}, and Pb^{2+}[3]. Only a few complexes of transition metals have been reported[6].

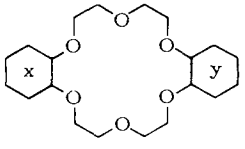
This review will deal mainly with the preparation, the chemical and physical properties, the structures, and the stabilities of these macrocyclic polyethers and their salt complexes.



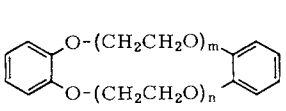
(1)



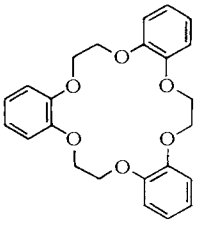
(2)



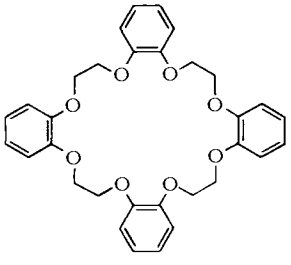
(3)



(4)



(5)



(6)

1.1. Nomenclature

The macrocyclic polyethers ("crown compounds") can be assigned unique but very cumbersome names by application of the IUPAC rules for bridged hydrocarbons (rules A-31 and A-32). Thus compound *(3f)* [*(3)*, $x=y=C_6H_{10}$] is called 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane, and compound *(5)* 2,5,12,15,22,25-hexaoxatetracyclo[24.4.0.0^{6,11}.0^{16,21}]triaconta-6(11),7,9,16(21),17,19,26(1),27,29-nonaene. The rules for fused polycyclic compounds (A-21 to A-23) likewise give unequivocal but most complicated names. A system of *ad hoc* names was therefore devised solely for the ready identification of these compounds[3]. The examples in Table 1 illustrate how these names are made up of the side-ring substituents, the total number of atoms in the polyether ring, the "crown", and the number of oxygen atoms in the main ring. The "crown names" are simple but should only be used in conjunction with formulas since they are not unambiguous. Cyclohexane rings fused to the polyether ring, as in compound *(3c)*, are termed "perhydrobenzene" in the present report; the more common, but ambiguous, term is cyclohexyl.

1.2. History

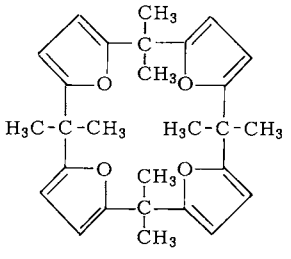
The pre-1967 literature on macrocyclic polyethers is meager and, above all, the possibility of their being complexing agents was not recognized. Among the previously reported compounds related to the crown polyethers are *(7)*[7], *(8)*[8], and *(9)*[8], as well as the cyclic tetramers of ethylene oxide[9] and propylene oxide[10].

The first crown compound, dibenzo[18]crown-6 *(3d)*, was formed as an unexpected by-product during a preparation of bis[2-(*o*-hydroxyphenoxy)ethyl] ether from bis(2-

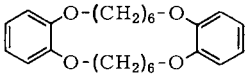
Table 1. Some representative macrocyclic polyethers with their "crown" names, methods of preparation, and melting points (see Section 2.1 for an account of synthetic methods).

Compound	Crown name	Synthesis eq.	Synthesis yield (%)	M.p. (°C)
(1)	dibenzo[14]crown-4	(3)	27	150–152
(2)	benzo[15]crown-5	(1)	62	79–79.5
(3a), x = nil, y = nil	[18]crown-6			39–40
(3b), $x=C_6H_4$, y = nil	benzo[18]crown-6	(1)	60	43–44
(3c), $x=C_6H_{10}$, y = nil	perhydrobenzo[18]crown-6			<25
(3d) ≡ *(4a)*, $x=C_6H_4$, $y=C_6H_4$	dibenzo[18]crown-6	(2)	45	164
(3e), $x=C_6H_{10}$, $y=C_6H_4$	benzoperhydrobenzo[18]crown-6			<25
(3f), $x=C_6H_{10}$, $y=C_6H_{10}$	perhydrodibenzo[18]crown-6			A: 61–62.5 B: 69–70
(4a) ≡ *(3d)*, *m* = 2, *n* = 2	dibenzo[18]crown-6	(2)	45	164
(4b), *m* = 2, *n* = 3	dibenzo[21]crown-7	(3)	36	106.5–107.5
(4c), *m* = 3, *n* = 3	dibenzo[24]crown-8	(2)	38	113–114
(4d), *m* = 4, *n* = 4	dibenzo[30]crown-10	(2)	>6	106–107.5
(4e), *m* = 5, *n* = 9	dibenzo[48]crown-16	(3)	32	<25
(4f), *m* = 9, *n* = 9	dibenzo[60]crown-20	(3)	41	<25
(5)	tribenzo[18]crown-6	(3)	28	190–192
(6)	tetrabenzo[24]crown-8	(2)	18	150–152

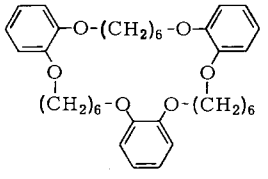
chloroethyl) ether and the sodium salt of 2-(*o*-hydroxyphenoxy)tetrahydropyran which contained a small quantity of catechol[3,4]. It was recovered from the reaction products



(7)



(8)



(9)

as a very minor component in the form of white fibrous crystals, which were quite insoluble in methanol itself but became readily soluble in it on addition of sodium salts. This observation led to the discovery of the complexing power of the crown compounds and to the synthesis of other macrocyclic polyethers.

1.3. Macrocyclic Antibiotics

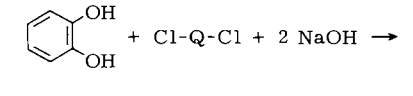
A number of antibiotics, such as valinomycin and nonactin, which contain ether, ester, and amide bonds in 32- to 36-membered rings exert interesting biological effects[11], which are related to the way in which these substances influence transport of Na^+ and K^+ across cell membranes[12]—one of the fundamental processes of living systems. Complexing of these cations by the macrocyclic antibiotics appears to be responsible for their effects on ionic transport across natural and synthetic membranes[1,2,13]. Reports on the solution properties of such complexes[1,2,14] and X-ray structural studies[15,16] have appeared recently. It will become evident in this review that the complexing properties of these biogenic macrocyclic compounds resemble those of the crown polyethers in many respects.

2. Preparation and Properties

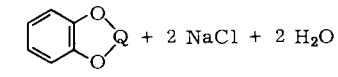
2.1. Synthetic Methods

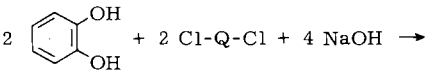
The aromatic crown polyethers are prepared by straightforward condensation methods[3,4] exemplified by the stoichiometric equations (1) to (3), in which Q and T represent divalent organic groups, generally of the type $-(CH_2CH_2O)_nCH_2CH_2-$.

The condensations are typically run in 2-butanol under reflux for 12 to 24 hours. Method (1) can be used to prepare, *e.g.*, benzo[12]crown-4 (yield 4%). Method (2) gives, for instance, dibenzo[18]crown-6 *(3d)* (see Table 1). The starting

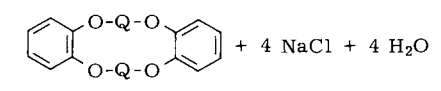


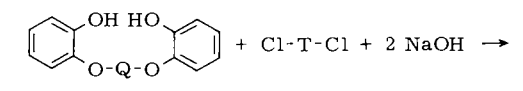
(1)



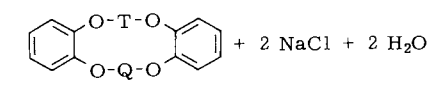


(2)





(3)



material for method (3) is made by attaching a base-stable protecting group, *e.g.* benzyl or tetrahydropyranyl, to one of the hydroxyls of catechol; two moles of this compound are then condensed with Cl—Q—Cl, and the protecting group is subsequently removed. Eq. (3) is most convenient for synthesis of uneven-numbered polyether rings, *e.g.* dibenzo[21]crown-7 *(4b)* (see Table 1).

Aromatic macrocyclic polyethers containing neutral substituents, such as alkyl or chloro, may be prepared by using suitably substituted aromatic vicinal diols. Of course, the substituents must be inert toward sodium hydroxide and the open-chain dichloropolyether.

Saturated polyethers are prepared from the corresponding aromatic ones by catalytic hydrogenation, typically in 2-butanol at 100 °C and 7—10 atm over a ruthenium catalyst[3]. Recovery of the product is best done by column chromatography on alumina, and the yields are almost quantitative.

2.2. Properties

The macrocyclic polyethers with aromatic side rings are colorless crystalline compounds. For a given polyether ring the melting point rises with the number of benzo groups (see Table 1). These compounds, particularly those containing more than one benzo group, are nearly insoluble in water and sparsely soluble in alcohols and many other common solvents at room temperature. They are readily soluble, however, in methylene chloride and chloroform[3].

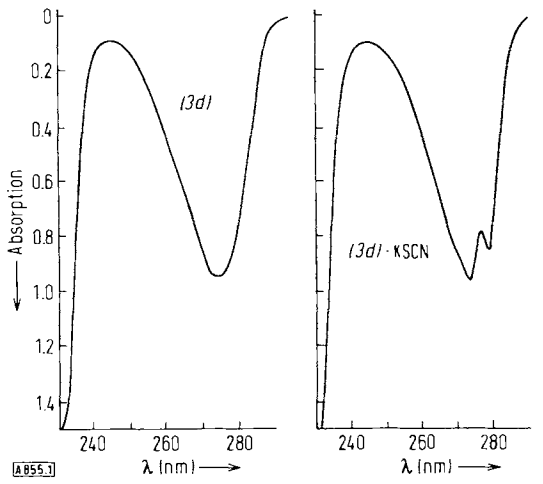


Fig. 1. Ultraviolet spectra of dibenzo[18]crown-6 *(3d)* and its KSCN complex (1.8×10^{-4} mol/l in methanol, 1 cm cell).

The saturated polyethers are colorless, viscous liquids or solids of low melting point. They are very much more soluble in all solvents than their aromatic precursors. Most of them dissolve even in petroleum ether and yet display appreciable water solubility.

While the saturated compounds do not show any absorption above 220 nm, the aromatic ones show absorption bands (in methanol) near 275 nm, which are characteristic for catechol and its ethers, with extinction coefficients of about 2200 per benzene ring (see Fig. 1). Saturated cyclic polyethers show an IR band near 1100 cm^{-1} (aliphatic ether), which is also shown by the aromatic ones in addition to another near 1230 cm^{-1} (aromatic-aliphatic ether).

Aliphatic crown compounds with two or more cyclohexane rings fused to the main ring show bridge-bond isomerism. For example, perhydrodibenzo[18]crown-6 *(3f)*, obtained by hydrogenation of dibenzo[18]crown-6 *(3d)*, can be separated into two isomers (A m.p. 61—62.5 °C; B m.p. 69—70 °C) by chromatography[17]. NMR studies[18] have shown that the bridge bonds of both isomers are *trans*, as are those of several other analogs[*].

The macrocyclic polyethers are thermally stable; for instance, dibenzo[18]crown-6 *(3d)* can be distilled at 380 °C. They must be protected from oxygen, however, at elevated temperatures. The aromatic crown compounds react like anisole or veratrole; for example, they can be halogenated, nitrated, or condensed with formaldehyde to give resins containing polyether rings.

3. Complexing of Salts and Other Compounds

Their ability to form complexes with salts and certain other compounds is the most remarkable property of the cyclic polyethers. In this section we shall discuss a number of different ways in which this complex formation manifests itself.

[*] Recent X-ray structural investigations of complexes of these isomers have led to apparently conflicting conclusions: *M. R. Truter* (personal communication) finds that isomer B in its $NaBr \cdot 2H_2O$ complex has a centrosymmetrical *trans* conformation, while *N. K. Dalley, D. E. Smith, R. M. Izatt*, and *J. J. Christensen* (Chem. Commun., in press) conclude that isomer A in its $Ba(SCN)_2$ complex is *cis-syn-cis*.

3.1. Complexing in Solution

3.1.1. Solubility Effects

The simplest, often spectacular, and potentially most useful way in which complexing by cyclic polyethers manifests itself is the solubilization of ionic compounds in organic solvents. In many cases addition of polyether causes dissolution of salts and related compounds in solvents in which they are otherwise substantially insoluble[3]. For instance, crystals of $KMnO_4$, *tert*-C_4H_9OK, or K_2PdCl_4 can be made to dissolve in aromatic hydrocarbons merely by the addition of perhydrodibenzo[18]-crown-6 *(3f)*.

In early experiments it was found that direct addition of salt and polyether to solvent was frequently not very effective, and that much more concentrated solutions could be prepared by solvent exchange: dissolving the ingredients in methanol, removing this solvent by evaporation *in vacuo*, and then redissolving in the final solvent. It later became apparent that the methanol is frequently not removed completely by this procedure, since it is often very tenaciously held by the complex and probably forms an integral part of it. The finding that addition of quite small concentrations of methanol greatly increases the quantities of salt which dissolve directly in solvents containing cyclic polyether (see Table 2) obviates the need for the solvent-exchange procedure and provides further evidence that methanol, or some analogous compound, may take part in the complex, possibly serving to complete the solvation sphere of the cation or to solvate the anion.

Table 2. Solubilization of alkali-metal halides in organic solvents by addition of 50 mmol/l of perhydrodibenzo[18]crown-6 *(3f)* [a].

Solvent	Methanol (mmol/l)	Solubility (mmol) [b] NaCl	NaBr	KCl	KBr	KI
C_6H_6	0	0.01	1.8	0.03	2.3	9.2
	250	0.48	24	8.7	30	46
CCl_4	0	0.03	2.7	0.6	4.1	0.8
	250	1.1	28	8.8	34	15
$CHCl_3$	0	1.8	37	21	41	43
	250	5.7	41	34	44	44
CH_2Cl_2	0	1.8	35	17	41	43
	250	5.8	42	33	42	44
Tetrahydro-	0	0.02	1.2	0.1	3.6	45
furan	250	0.04	5	0.4	13	50

[a] *H. K. Frensdorff*, unpublished data.
[b] Salt concentration after agitation of the polyether solution with enough salt to give 50 mmol/l solution.

While complexing of the cation is an obvious prerequisite for solubilization, the anion also plays an important role, as illustrated by the increase in solubility with anionic size (Table 2). The complexed cation is surrounded by organophilic groups and thus can be more or less easily accommodated in a nonpolar environment. However, interaction between the anion and a nonpolar solvent is much less favorable, especially for small anions of high charge density and low polarizability. Accordingly, salts of such "hard"[19] anions as fluoride or sulfate are often not solubilized appreciably by cyclic polyethers, while those of "soft" anions, *e.g.* iodide, thiocyanate, picrate, and fatty acid anions, are solubilized more easily.

Potassium and sodium hydroxide can be solubilized in benzene with perhydrodibenzo[18]crown-6 *(3f)* either by solvent exchange or by direct addition of 1% methanol to give solutions which are as much as 1 N in base. These solutions, which appear to contain methoxide as well as hydroxide anions, are capable, for instance, of readily saponifying esters of 2,4,6-trimethylbenzoic acid which are resistant to ordinary saponifying agents.

Solubilization by polyether is not a simple function of solvent polarity (cf. low solubility in tetrahydrofuran, Table 2). Specific interactions, such as solvation of the anion or competition between solvent and polyether, evidently overcome more general polarity effects in some cases.

3.1.2. Changes in Ultraviolet Spectra

All the cyclic polyethers containing benzo groups have a characteristic absorption maximum at 275 nm (in methanol). Complexing with a cation brings about distinctive changes in this band, generally by appearance of a second peak at about 280 nm (see Fig. 1), at other times by a hypsochromic shift and changed absorbance of the main band. Since the new peak is not clearly separated from the main one, it is not suitable for precise quantitative measurements. However, it has been used extensively for qualitative detection of complexing[3, 20].

3.1.3. Conductivity Changes

The existence and stoichiometry of the complexes are demonstrated simply and convincingly by conductance measurements[17]. The results in Fig. 2 clearly show the 1:1 stoichiometry of the complex formed from potassium chloride and perhydrodibenzo[18]crown-6 *(3f)*. This figure illustrates two contrasting cases: (a) in methanol the dissociation of KCl is essentially complete, and complexing, by increasing the size and thus decreasing the mobility of the cation, reduces the conductance; (b) in chloroform/methanol (90:10) KCl is largely undissociated, but complexing, by surrounding the cation with the polyether ring, shields its charge and thus greatly increases dissociation of the ion pairs, which results in an appreciable conductance increase.

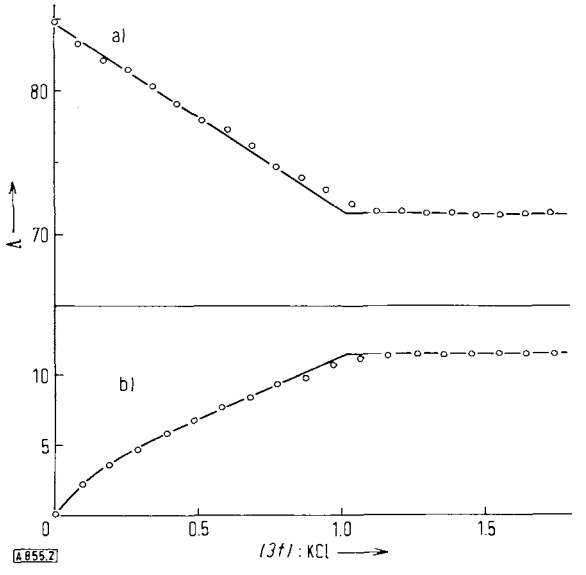


Fig. 2. Conductometric titration of KCl with perhydrodibenzo[18]-crown-6 *(3f)* a) in methanol and b) in chloroform/methanol (90:10). KCl concentration 10^{-3} mol/l [17].

3.2. Crystalline Complexes

3.2.1. Preparation

Numerous well-defined, sharp-melting, crystalline complexes of salts and cyclic polyethers have been prepared by straightforward methods, *i.e.* by bringing together the ingredients in a common solvent, in two immiscible solvents, in a medium which dissolves one of them, or in the dry state[3, 5]. Although salts with high lattice energy, such as fluorides, nitrates, and carbonates, form complexes with the cyclic polyethers in alcoholic solution, they cannot be isolated in the solid state because one or the other of the uncomplexed components precipitates when the solution is concentrated. Some typical crystalline complexes are shown in Table 3.

Table 3. Typical crystalline polyether-salt complexes [1, 5] (see Table 1 for formulas).

Polyether	m.p. (°C)	Salt	m.p. (°C)	Polyether: Salt (mol/mol)	Complex, m.p. (°C)
(1)	150–152	LiSCN	—	1:1	300
(2)	79–79.5	$AgNO_3$	210	1:1	134–135
(2)	79–79.5	NaSCN	323	1:1	162–165
(2)	79–79.5	KSCN	175	2:1	176
(2)	79–79.5	NH_4SCN	149	2:1	131–132
(3c)	<25	$Ba(SCN)_2$	—	1:1	282
(3d)	164	$NaNO_2$	271	1:1	154–157
(3d)	164	KI	685	1:1	232–234
(3d)	164	RbSCN	195	1:1	184–185
(3d)	164	RbSCN	195	2:1	175–176
(3d)	164	CsSCN	—	2:1	146–147
(3d)	164	CsSCN	—	3:2	145–146
(4d)	106–107.5	KSCN	175	1:1	176–178

As shown by several of the examples in Table 3, the complexes are not always of 1:1 stoichiometry, some polyether-cation combinations having a tendency to form 2:1, or even 3:2, complexes. As a rule, this occurs when the cation is too large to fit into the hole of the polyether ring (see Table 4), which suggests a "sandwich" structure[5].

Like most of the complexes, that formed by KSCN and dibenzo[18]crown-6 *(3d)* is stable in water containing an excess of the salt but decomposes in pure water. However, some of the complexes are stable in the presence of water, *e.g.* KI_3-perhydrodibenzo[18]crown-6.

Table 4. Polyether ring sizes and ionic diameters.

Polyether ring	Hole diameter (Å) [a]	Ion	Ionic diameter in crystal (Å)
[14]Crown-4	1.2–1.5	Li^+	1.36
[15]Crown-5	1.7–2.2	Na^+	1.94
[18]Crown-6	2.6–3.2	K^+	2.66
[21]Crown-7	3.4–4.3	Rb^+	2.94
		Cs^+	3.34
		NH_4^+	2.86
		Ag^+	2.52
		Ba^{2+}	2.68

[a] From ref. [5]; lower values estimated from Corey-Pauling-Koltun atomic models, higher values from Fisher-Hirschfelder-Taylor models.

3.2.2. Structure

The structures of four crystalline complexes have been determined by X-ray diffraction by *Truter et al.*[21,22]: NaBr-$(H_2O)_2$-dibenzo[18]crown-6; NaI-H_2O-benzo[15]-crown-5; $(RbSCN)_2$-(dibenzo[18]crown-6)$_3$; and KI-dibenzo[30]crown-10. The two sodium complexes contained water of crystallization though no water was deliberately added to the methanol in which they were prepared[22]. This observation confirms the strong propensity of Na^+ to complete its entire solvation shell (cf. Section 3.1.1).

In both of the sodium complexes the cation is located in the center of the very nearly coplanar ether oxygens. Water and bromide coordinate with the sodium in the direction perpendicular to the polyether ring, though the iodide anion does not interact directly with its sodium.

The 3:2 RbSCN complex has a very interesting structure, though not the postulated sandwich[21]. The unit cell contains four molecules of a 1:1 RbSCN-dibenzo[18]-crown-6 complex and two uncomplexed polyether molecules of crystallization. The Rb^+ is centrally located and approximately 1 Å below the plane of the ether oxygens (see Fig. 3), and the SCN group sticks out approximately perpendicular to the ether ring. In the uncomplexed molecules of polyether the O atoms are not quite coplanar.

No X-ray structure of any complex of the 2:1 polyether-cation type has been published so far. However, since these invariably involve a cation too large to fit into the hole of the polyether, they may be expected to have a structure with the cation "sandwiched" between two parallel polyether rings.

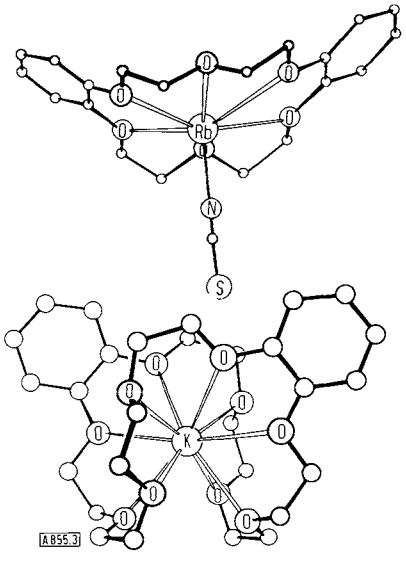


Fig. 3. Structures of typical complexes. Rubidium thiocyanate: dibenzo[18]crown-6 (above, free polyether molecule not shown), potassium iodide: dibenzo[30]crown-10 (below, anion not shown), according to *Truter et. al.* [21, 22].

Special interest resides in the complexes of much larger rings which, since they are more flexible and have enough oxygen atoms, may envelop the cations completely, as do the macrocyclic antibiotics in their complexes[14-16]. X-Ray analysis of one such complex, KI-dibenzo[30]-crown-10, has been accomplished recently[22]. It was found that this complex indeed possesses a wrap-around structure having all ten oxygen atoms coordinated with the central cation (see Fig. 3).

3.3. Complexes of Amino Compounds and Thioureas

Since ammonium ion resembles K^+ with respect to charge and size, it is not surprising that it forms similar complexes with the cyclic polyethers (see Table 3). Ammonia and unionized ammonium hydroxide, on the other hand, are not complexed because they do not carry a charge. In general, NH_3^+-substituted compounds form complexes, while those containing NH_2^+ and NH^+ groups, and quaternary ammonium ions do not[3]. Apparently the NH_3^+ group can intrude sufficiently into the polyether ring, but the others are too large to do so.

Thiourea and related compounds, such as thiosemicarbazide, as well as some of their derivatives have been found to form sharp-melting crystalline complexes with cyclic polyethers[23]. The stoichiometry of these complexes is unpredictable (from 1:1 to 6:1 thio compound: polyether), and their nature has not yet been elucidated. Inclusion complexes seem to be ruled out by the small ratios. One possibility is that at least one molecule of the sulfur compound is complexed in the zwitterion form, $^-S-C(=NH_2^+)-$, while the others merely fill up the crystal lattice.

4. Complexing Equilibria in Solution

4.1. Stability Constants

The stability constants for the polyether-cation complexes are the most straightforward measure of the strength of complexing in solution. They are defined as the equilibrium constants (in l/mol) for reactions (4) and (5) where M^+ and P represent uncomplexed cation and polyether; PM^+ and P_2M^+ 1:1 and 2:1 complex, respectively.

$$M^+ + P \underset{}{\overset{K_1}{\rightleftharpoons}} PM^+ \quad (4)$$

$$PM^+ + P \overset{K_2}{\rightleftharpoons} P_2M^+ \quad (5)$$

Such stability constants have been measured by a calorimetric titration technique[24], by potentiometric measurements with ion-selective electrodes[25], and by spectroscopic methods[26], besides being deduced indirectly from conductance and potential measurements on phospholipid bilayers[27].

4.1.1. Complexing in Aqueous Solutions

Stability constants for several cyclic polyethers with various cations are collected in Table 5. No data on benzo-substituted polyethers are available because of their generally low water solubility.

The stability constants for the [18]crown-6 polyethers with the alkali-metal cations go through a maximum at K^+ as the cationic size increases. This can be explained in terms of competition between hydration and complexing,

since at least some of the water of hydration must be stripped off the cation to accommodate it in the hole of the polyether ring. Though the smaller cations, with their high electric charge density, greatly attract both water and polyether, their tendency to undergo hydration is too strong for the polyether to compete successfully. On the other hand, the larger cations have comparatively low charge densities and, hence, low attraction for either polyether or water. Moreover, Rb^+ and Cs^+ are too large to fit into the hole of the [18]crown-6 ring, hence the complexing tendency is reduced by their inability to attain the position of maximum charge density in the plane of the ether oxygens. The comparatively high stability constants for the divalent cations Sr^{2+} and Ba^{2+} reflect their high charge densities, while those for Ag^+ are a consequence of its slight hydration tendency.

Table 5. Stability constants of polyether-cation complexes in water at 25°, based on K_1 in l/mol [a]; cf. eq. (4).

Polyether	$\log_{10} K_1$								
	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Sr^{2+}	Ba^{2+}
Perhydrobenzo[15]crown-5	<1.0	<0.3	0.6	—	—	—	—	—	—
Perhydrobenzo[18]crown-6 *(3c)*	<0.7	0.8	1.9	—	0.8	1.1	1.8	—	—
Perhydrodibenzo[18]crown-6 *(3f)* (isomer A)	0.6	1.7	2.2	1.5 [b]	1.2	1.4	2.3	3.2 [b]	3.6 [b]
Perhydrodibenzo[18]crown-6 *(3f)* (isomer B)	—	1.4	1.8	0.9 [b]	0.9	0.8	1.8	2.6 [b]	3.3 [b]
Perhydrodibenzo[21]crown-7	—	—	—	—	1.9	—	—	—	—

[a] Values from ref. [25], unless marked otherwise.
[b] Values from ref. [24].

Enthalpy changes on complexing in water, as measured calorimetrically by *Izatt et al.*[24], are small. They amount to −2 to −6 kcal/mol for reaction (4). They might be even closer to zero for some ions, *e.g.* Na^+, for which these authors found no measurable heat change[24], though potentiometry indicated measurable complexing[25].

4.1.2. Complexing in Methanol

Methanol is a particularly convenient solvent for complexing measurement and permits comprehensive study of the effect of polyether ring size and substituents on the strength of complexing[25] (see Table 6). Comparison between Tables 5 and 6 reveals that the stability constants are three to four decades higher in methanol than in water, evidently because methanol is a much weaker solvating medium and thus competes less with the polyether for the cations (cf. Section 4.1.1).

Table 6. Stability constants of polyether-cation complexes in methanol at 25°, based on K_1 in l/mol [25]; cf. eq. (4) and (5).

Polyether	$\log_{10} K_1$		
	Na^+	K^+	Cs^+
Tetramethyl[12]crown-4	1.4	—	—
Perhydrodibenzo[14]crown-4	2.2	1.3	—
Perhydrobenzo[15]crown-5	3.7	3.6 [a]	2.8 [a]
[18]Crown-6 *(3a)*	4.3	6.1	4.6
Perhydrobenzo[18]crown-6 *(3c)*	4.1	5.9	4.3
Perhydrodibenzo[18]crown-6 (isomer A) *(3f)*	4.1	6.0	4.6
Perhydrodibenzo[18]crown-6 (isomer B) *(3f)*	3.7	5.4	3.5
Dibenzo[18]crown-6 *(3d)*	4.4	5.0	3.6 [b]
Dibenzo[21]crown-7 *(4b)*	2.4	4.3	4.2
Dibenzo[24]crown-8 *(4c)*	—	3.5	3.8
Dibenzo[30]crown-10 *(4d)*	2.0	4.6	—
$CH_3(OCH_2CH_2)_5OCH_3$	1.5	2.2	—

[a] Polyether : cation = 2:1; $\log K_2 = 1.9$.
[b] Polyether : cation = 2:1; $\log K_2 = 2.9$.

The stability constant for each cation goes through a maximum with increasing polyether ring size: between-[15]crown-5 and [18]crown-6 for Na^+; at [18]crown-6 for K^+; and between[18]crown-6 and [21]crown-7 for Cs^+. These optimum ring sizes are exactly those which provide the closest fit between the cation and the "hole" (see Table 4). Table 6 also indicates the three systems in which clear evidence of 2:1 complexing in solution was found: perhydrobenzo[15]crown-5 with K^+ and Cs^+, as well as dibenzo[18]crown-6 with Cs^+. These are all cases of the cation's being too large to fit into the hole and represent combinations of cation and polyether ring of which crystalline 2:1 complexes have been found.

Comparison of the various [18]crown-6 derivatives in Table 6 shows that the effects of substitution on the polyether ring are relatively small and difficult to systematize. For instance, dibenzo[18]crown-6 complexes Na^+ more strongly than the unsubstituted parent ring or hydrogenated analogs, but the reverse is true for K^+ and Cs^+.

As illustrated by the last entry in Table 6, the stability constants of an open-chain polyether are three to four decades lower than those of its cyclic analog([18]crown-6). Evidently entropic forces work against complete envelopment of the cation by the non-cyclic polyether.

4.1.3. Complexing in Other Solvents

Very few data are available for solvents less polar than methanol. Since competition by solvation would become less significant, one expects stability constants to be higher, especially for the smallest cations. However, the results will be complicated by more or less extensive ion-pair formation, so that anion effects will become appreciable.

Wong, Konizer, and *Smid*[26] have reported some stability constants for alkali metal fluorenyl compounds in tetrahydrofuran as determined by spectroscopic methods. These authors found the stability constants for the fluorenylsodium ion pair to be above 10^6 l/mol with perhydrodibenzo[18]crown-6 *(3f)* and di(methylbenzo)[18]-crown-6 compared to 150 l/mol for dibenzo[14]crown-4 *(1)* and 450 l/mol for $CH_3(OCH_2CH_2)_5OCH_3$. They

found fluorenylsodium to be more strongly complexed in tetrahydrofuran than its potassium analog, while the reverse was true in oxetane.

4.2. Distribution between Phases

Since the polyether complexes display appreciable solubility in certain organic solvents, salts can often be extracted from aqueous solutions into organic solvents containing polyethers. Extraction is efficient only if the anion is large and highly polarizable, as for instance picrate, which has the additional advantage of an absorption near 360 nm for easy analysis. Accordingly, picrate extraction has been used extensively for quantitative determination of relative complexing power[4, 20]. The typical results in Table 7 show how extraction of any given cation is most efficient with polyethers of the ring size for which the stability constant indicates optimum strength of complexing.

Table 7. Extraction of picrates into methylene chloride containing polyether [20]. Initial concentrations: alkali hydroxide 0.1 mol/l; alkali picrate 7×10^{-5} mol/l; polyether 7×10^{-5} mol/l. Equal volumes of water and CH_2Cl_2. No measurable extraction of cation takes place in the absence of either picrate or polyether.

Polyether	Picrate extracted (%)			
	Li^+	Na^+	K^+	Cs^+
Di(*tert*-butylperhydrobenzo)[14]crown-4	1.1	0	0	0
tert-Butylperhydrobenzo[15]crown-5	1.6	19.7	8.7	4.0
Dibenzo[18]crown-6	0	1.6	25.2	5.8
Perhydrodibenzo[18]crown-6	3.3	25.6	77.8	44.2
Perhydrodibenzo[21]crown-7	3.1	22.6	51.3	49.7
Perhydrodibenzo[24]crown-8	2.9	8.9	20.1	18.1

When extraction results are available over wide concentration ranges, they can be analyzed in terms of the following equilibria[17]:

$$M^+_{aq} + A^-_{aq} + P_{org} \overset{K_E}{\rightleftharpoons} PMA_{org} \quad (6)$$

$$PMA_{org} \overset{K_D}{\rightleftharpoons} PM^+_{org} + A^-_{org} \quad (7)$$

where M^+ is the cation, A^- the extractable anion, P the polyether, PM^+ the complex cation, and PMA the complex ion pair, while the subscripts refer to the phases. Equilibrium constants for several systems are shown in Table 8. Under the conditions of Table 7 extraction of the cation is not very efficient, since the low concentrations of picrate and polyether are limiting. The equilibrium constants can be used to predict how much greater the extraction efficiency will be at higher concentrations. It is interesting to note that these extraction measurements permit evaluation of dissociation constants, K_D, and that the results indicate appreciable dissociation of the complex ion pairs in methylene chloride at submillimolar concentrations, in agreement with the conductance results (see Section 3.1.3) in similar solvents.

That extraction efficiency depends not only on strength of complexing but also on the solubilities of all the species in both phases is indicated by the lower extraction of sodium picrate by dibenzo[18]crown-6 *(3d)* compared to perhydrodibenzo[18]crown-6 *(3f)* (Table 7), even though the stability constant of the aromatic polyether is higher, at least in methanol (Table 6). In order to make these solubility effects more explicit, the extraction equilibrium constant K_E was analyzed in terms of the aqueous stability constant and the partition coefficients for polyether and for complex[17]. This analysis showed that the latter partition coefficient is a most important factor and varies through many orders of magnitude.

Table 8. Equilibrium constants for picrate extraction with polyether-containing organic solvents [17]; see eq. (6) and (7).

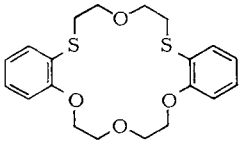
Polyether	Cation	Solvent	K_E (l/mol)^2	K_D (mol/l)
Perhydrodibenzo[18]crown-6 *(3f)*	K^+	CH_2Cl_2	2×10^6	4×10^{-5}
Perhydrodibenzo[18]crown-6 *(3f)*	K^+	n-C_6H_{14}	4×10^3	$< 1 \times 10^{-6}$
Dibenzo[18]crown-6 *(3d)*	K^+	CH_2Cl_2	7×10^5	4×10^{-6}
Perhydrodibenzo[18]crown-6 *(3f)*	Na^+	CH_2Cl_2	1.5×10^4	1×10^{-4}

5. Polyethers Containing Other Heteroatoms

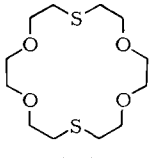
5.1. Monocyclic Polyethers Containing Nitrogen and Sulfur

5.1.1. Preparation

More than a dozen cyclic polyethers have been reported in which one or more sulfur atoms have been substituted for oxygen[28–30]. They are prepared by condensation methods similar to those used for the ordinary polyethers. The synthesis is, in many cases, facilitated by the greater reactivity of thiol groups compared to phenol.

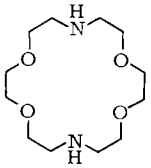


(10)

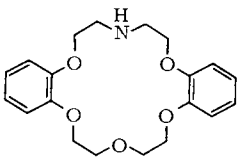


(11)

Mention has also been made of several cyclic polyethers in which one or two NH or NR groups replace oxygen[25, 31]. Synthesis of these compounds is accomplished typically by reaction of a diamine (*e.g.* $(CH_2OCH_2CH_2NH_2)_2$) with a diacid chloride (*e.g.* $(CH_2OCH_2COCl)_2$) and subsequent reduction of the resulting cyclic diamide[32].



(12)

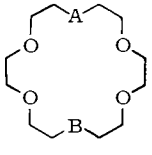


(13)

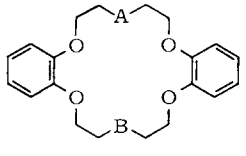
5.1.2. Complexing Properties

As judged by the effect of salts on the UV spectra and by the picrate extraction method, complexing of alkali and alkaline earth cations is greatly decreased by substitution of S for O in the polyether ring, while complexing of Ag^+ is either increased or unaffected[30]. These conclusions were confirmed by the formation of crystalline silver nitrate complexes and the failure of attempts to prepare such complexes of KSCN with sulfur-containing polyethers.

Similar effects are observed when one or two nitrogens are substituted for oxygen, as shown quantitatively by the K^+ stability constants (see Table 9), which decrease in the



I



II

Table 9. Effect of nitrogen and sulfur substitution in the polyether ring on the complexing properties, based on K_1 in l/mol [25].

Polyether				log K_1	
Type	A	B	Formula	K^+ in methanol	Ag^+ in water
I	0	0	*(3a)*	6.1	1.6
II	0	0	*(3d)*	5.0	—
II	NR [a]	0		4.1	—
I	NH	0		3.9	3.3
II	NH	0	*(13)*	3.2	—
I	NH	NH	*(12)*	2.0	7.8
II	NH	NH		1.6	—
I	S	S	*(11)*	1.2	4.3

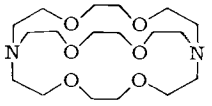
[a] R = n-C_8H_{17}.

same order as the electronegativities, O > NR > NH > S[25]. In other words, the electrostatic attraction between the cation and the heteroatoms diminishes with the negative charge on the latter.

Nitrogen substitution greatly enhances Ag^+ complexing (see Table 9), just as sulfur was noted to do. Evidently the principal forces involved here are not simple electrostatic ones, but rather covalent bonding analogous to that present in the numerous well-known complexes of Ag^+ with amines and other nitrogen-containing compounds. Indeed some open-chain amine compounds have Ag^+ stability constants of the same order of magnitude as the corresponding cyclic amino polyethers[33].

5.2. Bicyclic Amine Polyethers

Preliminary reports have started to appear of bicyclic polyethers *(14)* containing amine bridge atoms[31]. They are made by an extension of the method used for the preparation of monocyclic amine polyethers[31] (see Section 5.1.1) in analogy to the preparation of bicyclic amines by *Simmons* and *Park*[34].



(14)

These bicyclic compounds have remarkable complexing properties, as demonstrated by their aqueous stability constants. Preliminary results[31, 35] obtained by a "pH-metric" method for compound *(14)* are Ba^{2+} (log K_1 9.5), Sr^{2+} (8.0), K^+ (5.4), Ca^{2+} (4.4), Rb^+ (4.4), Na^+ (3.9), *i.e.* two or more decades above the [18]crown-6 derivatives, in spite of the nitrogen atoms in the rings. Evidence of complexing was also obtained by NMR, solubilization in chloroform, and formation of crystalline complexes[31, 35, 36].

Bicyclic amine polyethers form complexes with the same cations as the cyclic polyethers. The complexes, which are termed "cryptates"[31], are formed by "encapsulation" of the cation within the cavity of the compound, as demonstrated by X-ray analysis of the crystalline KSCN complex[36]. Evidently the cation is held in the cavity under the influence of the negative charges of the six oxygen and two nitrogen atoms. Complexation in solution is pH sensitive, since protonation of the amino nitrogens prevents complex formation, apparently because of repulsion between the two positively charged nitrogen atoms and the cation. It is interesting to note that encapsulation of cations by the bicyclic polyether amines has a parallel in the encapsulation of anions by bicyclic amines which contain no oxygen atoms[37].

6. Applications

6.1. Organic Chemistry

Many salts or salt-like compounds of alkali and alkaline earth metals are used in organic synthesis, frequently under inefficient conditions, *i.e.* low concentrations or two-phase operation, because of their limited solubility in organic solvents. It is evident that the crown polyethers can help to overcome such difficulties in many cases, not only by solubilizing the salts but also by increasing the dissociation of ion pairs (cf. Section 3.1.3) to provide highly reactive, unsolvated anions. A related effect, more subtle than complete dissociation of ion pairs, is the conversion of contact ion pairs into solvent-separated ones. It has been demonstrated convincingly that this can be brought about by crown polyethers[26, 38].

Examples of such organic applications of crown polyethers based on solubilization and enhanced reactivity are sa-

ponifications by KOH in benzene (cf. Section 3.1.1) and oxidations by $KMnO_4$ in benzene[3, 39]. The cyclic polyethers have also been found to exert profound effects on the course of a number of different reactions involving alkali-metal cation-carbanion ion pairs[40–43].

A related development of great significance is the dissolution of potassium and cesium metal in tetrahydrofuran and diethyl ether by perhydrodibenzo[18]crown-6[44], which promises to extend greatly the range of solvents in which solvated electrons and related species can be obtained.

These examples, all published very recently, are just a hint of the impact which the crown polyethers will assuredly have on organic chemistry in studies of reaction mechanism and in syntheses involving such reagents as alkyllithium compounds, Grignard reagents, alkali salts of carbanions, and alkali metals.

6.2. Biophysics

The discovery of the complexing properties of the crown polyethers aroused much interest among the investigators of ionic transport phenomena because of the similar properties of the macrocyclic antibiotics (see Section 1.3). For the first time synthetic materials were available for systematic study of structural effects. Crown polyethers have indeed been found to affect cationic transport across bilayer membranes[13], though these effects are somewhat different from those of the antibiotics. Moreover, methods developed for studying the cyclic polyethers in solution, *i.e.* picrate extraction (see Section 4.2), have been profitably applied to the antibiotics[45].

The authors are indebted to Dr. R. N. Greene of this laboratory for many helpful suggestions and to several of the authors quoted for supplying pre-publication manuscripts.

Received: February 22, 1971 [A 855 IE]
German version: Angew. Chem. *84*, 16 (1972)

[1] *Z. Stefanac* and *W. Simon*, Microchem. J. *12*, 125 (1967).

[2] *L. A. R. Pioda, H. A. Wachter, R. E. Dohner,* and *W. Simon*, Helv. Chim. Acta *50*, 1373 (1967).

[3] *C. J. Pedersen*, J. Amer. Chem. Soc. *89*, 7017 (1967).

[4] *C. J. Pedersen*, J. Amer. Chem. Soc. *89*, 2495 (1967); *92*, 391 (1970).

[5] *C. J. Pedersen*, J. Amer. Chem. Soc. *92*, 386 (1970).

[6] *A. C. L. Su* and *J. F. Weiher*, Inorg. Chem. *7*, 176 (1968).

[7] *R. G. Ackman, W. H. Brown*, and *G. F. Wright*, J. Org. Chem. *20*, 1147 (1955).

[8] *A. Lüttringhaus* and *I. Sichert-Modrow*, Makromol. Chem. *18–19*, 511 (1956).

[9] *D. G. Stewart, D. Y. Waddan*, and *E. T. Borrows*, Brit. Pat. 785 229 (Oct. 23, 1957).

[10] *J. L. Down, J. Lewis, B. Moore*, and *G. W. Wilkinson*, Proc. Chem. Soc. *1957*, 209; J. Chem. Soc. *1959*, 3767.

[11] *W. McMurray* and *R. W. Begg*, Arch. Biochem. Biophys. *84*, 546 (1959).

[12] *C. Moore* and *B. C. Pressman*, Biochem. Biophys. Res. Commun. *15*, 562 (1964).

[13] See *e.g.* "Symposium on Biological and Artificial Membranes", Fed. Proc. *27*, 1269 (1968).

[14] *J. H. Prestegard* and *S. I. Chan*, Biochem. *8*, 3921 (1969); J. Amer. Chem. Soc. *92*, 4440 (1970).

[15] *B. T. Kilbourn, J. Dunitz, L. A. R. Pioda*, and *W. Simon*, J. Mol. Biol. *30*, 559 (1967).

[16] *M. Pinkerton, L. K. Steinrauf*, and *P. Dawkins*. Biochem. Biophys. Res. Commun. *35*, 512 (1969).

[17] *H. K. Frensdorff*, J. Amer. Chem. Soc. *93*, 4684 (1971).

[18] *E. G. Brame*, to be published.

[19] *R. G. Pearson*, Science *151*, 172 (1966).

[20] *C. J. Pedersen*, Fed. Proc. *27*, 1305 (1968).

[21] *D. Bright* and *M. R. Truter*, Nature *225*, 176 (1970); J. Chem. Soc. *B 1970*, 1544.

[22] *M. A. Bush* and *M. R. Truter*, Chem. Commun. *1970*, 1439; J. Chem. Soc. *B 1971*, 1440.

[23] *C. J. Pedersen*, J. Org. Chem. *36*, 1690 (1971).

[24] *R. M. Izatt, J. H. Rytting, D. P. Nelson, B. L. Haymore*, and *J. J. Christensen*, Science *164*, 443 (1969); J. Amer. Chem. Soc. *93*, 1619 (1971).

[25] *H. K. Frensdorff*, J. Amer. Chem. Soc. *93*, 600 (1971).

[26] *K. H. Wong, K. Konizer*, and *J. Smid*, J. Amer. Chem. Soc. *92*, 666 (1970).

[27] *S. G. A. McLaughlin, G. Szabo, G. Eisenman*, and *S. Ciani*, Biophysical Soc. Abstr. *10*, 96a (1970); *D. Vasquez*: "Symposium on Molecular Mechanisms of Antibiotic Action on Protein Biosynthesis and Membranes". Springer Verlag, in press.

[28] *J. R. Dann, P. P. Chiesa*, and *J. W. Gates, Jr.*, J. Org. Chem. *26*, 1991 (1961).

[29] *L. Montillaro, M. Russo, L. Credali*, and *C. DeChecci*, J. Chem. Soc. *C 1966*, 428.

[30] *C. J. Pedersen*, J. Org. Chem. *36*, 254 (1971).

[31] *B. Dietrich, J. M. Lehn*, and *J. P. Sauvage*, Tetrahedron Lett. *1969*, 2885, 2889.

[32] *H. Stetter* and *J. Marx*, Liebigs Ann. Chem. *607*, 59 (1957).

[33] *J. R. Lotz, B. P. Block*, and *W. C. Fernelius*, J. Phys. Chem. *63*, 541 (1959).

[34] *H. E. Simmons* and *C. H. Park*, J. Amer. Chem. Soc. *90*, 2428 (1968).

[35] *J. M. Lehn, J. P. Sauvage*, and *B. Dietrich*, J. Amer. Chem. Soc. *92*, 2916 (1970); Chem. Commun. *1971*, 440.

[36] *B. Metz, D. Moras*, and *R. Weiss*, Chem. Commun. *1970*, 217.

[37] *C. H. Park* and *H. E. Simmons*, J. Amer. Chem. Soc. *90*, 2431 (1968).

[38] *T. E. Hogen Esch* and *J. Smid*, J. Amer. Chem. Soc. *91*, 4580 (1969).

[39] Chem. and Eng. News *48*, No. 9, p. 26 (1970).

[40] *G. Fraenkel* and *E. Pechhold*, Tetrahedron Lett. *1970*, 153.

[41] *D. J. Cram*, Abstracts of the 21st Nat. Organic Chem. Symposium, Salt Lake City, June 1969, p. 7.

[42] *J. Almy, D. C. Garwood*, and *D. J. Cram*, J. Amer. Chem. Soc. *92*, 4321 (1970).

[43] *S. W. Staley* and *J. P. Erdman*, J. Amer. Chem. Soc. *92*, 3832 (1970).

[44] *J. L. Dye, M. G. DeBacker, V. A. Nicely*, J. Amer. Chem. Soc. *92*, 5226 (1970).

[45] *G. Eisenman, S. Ciani*, and *G. Szabo*, J. Membrane Biol. *1*, 294 (1969).

Vibration-Spectroscopic Studies on Solid Compounds[**]

By Hermann J. Becher[*]

Considerably improved possibilities are now available for the investigation of the optical vibrations in lattice compounds by Raman and IR spectroscopy. These spectra can be interpreted on the basis of the models and findings of molecular vibration spectroscopy. For simple lattice types simple frequency equations are found for the optical lattice vibrations with in-phase vibration motions in all unit cells (wave vector $k=0$). As an approximation, the force constants that occur in these equations may be interpreted as stretching force constants. For typical ionic lattices, the influence of Coulomb forces due to the lattice polarization that occurs during the vibrational motion must be taken into account. As is shown by the example of some spinels, the assignment of lattice vibrations can be facilitated by model calculations.

1. Introduction

Corresponding to the line being followed by the author in his work, this article on vibrations in lattice compounds is based on the methods of molecular vibration spectroscopy. Raman and IR spectroscopic studies provide the experimental foundations. As far as possible, the bands observed should be assigned to vibrational motions of particular atoms in the structure as a whole, consideration being given to symmetry conditions and coupling of internal coordinates to normal coordinates. Such assignments may be based on model calculations with suitably estimated force constants, without which the coupling relationships in the normal coordinates usually cannot be clearly seen. In more complete calculations, efforts are made to obtain force constants for simple basic types of lattice compounds from the assigned vibrations with the aid of suitable potential functions, with the object of using these force constants for further model calculations and discussing them in connection with bonding questions.

Theoretical physics, on the other hand, has developed models that enable the lattice dynamics of solids and hence their complete optical, dielectric, and thermal behavior to be represented in a closed theory[1]. Only a few references can be made to these developments in the following discussions.

Whereas only $3n-6$ fundamental vibrations are possible in a molecule containing n atoms, a lattice has a practically infinite number of vibrational degrees of freedom. In order to be able to apply the approaches of molecular vibration spectroscopy to lattice vibrations, a limited number of degrees of freedom must be chosen from this infinite array for representation purposes. The theory of lattice vibrations shows that a single unit cell may be chosen as the basis of such a representation of the vibrational behavior[1-3]. For a unit cell containing n atoms, the possibilities of motion can be described by $3n$ coordinates. Three degrees of freedom of this motion lead to translations of the entire unit cell, while $3n-3$ belong to the optical vibrations of the lattice. The infinite multiplicity of the lattice vibrations arises from the fact that the vibrational motion of one unit cell may be out of phase with that of adjacent unit cells in the lattice. In the description of the optical vibrations that appear in the Raman and IR spectra, we can largely confine ourselves to the limiting case in which the vibrational motions of all the unit cells in the lattice are in phase. The number, symmetry behavior, and optical visibility of the vibrations in the Raman and IR spectra can be determined, according to group theory, from factor-group analysis, which replaces the point-group analysis of an isolated assembly of atoms[2-4].

2. Improvement of the Experimental Principles for the Investigation of Optical Lattice Vibrations

In earlier vibration-spectroscopic studies on solid compounds, the experimental principles were often insufficient to allow the correlation of the results with the predictions of a factor-group analysis. Fresh possibilities have been offered by recent improvements in the technique of Raman and IR spectroscopic studies. Raman spectroscopy has profited greatly from excitation with laser beams, since this allowed a huge increase in the excitation intensity in a very small volume, as well as a substantial decrease in the problems presented by stray light and the color of many compounds. In IR spectroscopy, the extension of the investigation range to ever lower wave numbers is of great importance, since the vibrations in many lattice compounds occur at very low wave numbers because of the small force constants.

Figures 1—3 should give some idea of these widened possibilities. Figure 1 shows the IR spectrum of solid barium trithiocarbonate embedded in Nujol between polyethylene windows in the frequency range 350—30 cm^{-1}. The vibrations that are essentially due to movements in the CS_3^{2-} ions in this compound have already been described in the literature[5]. The double band at 325 cm^{-1} also belongs to this group. In addition, there is a group of bands at 130 cm^{-1}, which must be assigned to translational and rotational movements of the ions in the lattice. An uncompensated band due to the window material is observed at 73 cm^{-1}.

[*] Prof. Dr. H. J. Becher
Anorganisch-chemisches Institut der Universität
44 Münster, Gievenbecker Weg 9—11 (Germany)

[**] Based on a lecture to the GDCh "Festkörperchemie" group in Bonn, October 1, 1970.

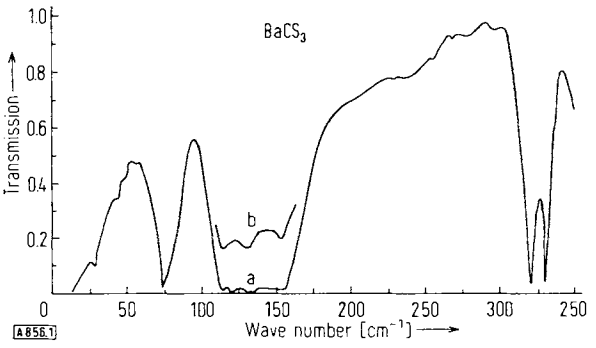


Fig. 1. IR spectrum of $BaCS_3$; ground in Nujol; measurement range 25—350 cm^{-1}. Layer thickness at b less than at a.

Figure 2 shows the Raman spectrum of polycrystalline, deep red chromium trioxide[6]. Together with the IR spectrum of this compound, the bands observed can be assigned to chain vibrations and CrO_2 group vibrations of the CrO_3 chains forming the lattice. This assignment is facilitated by consideration of the spectral changes observed on the transition from the dichromate ion *via* trichromate and tetrachromate to chromium trioxide[6].

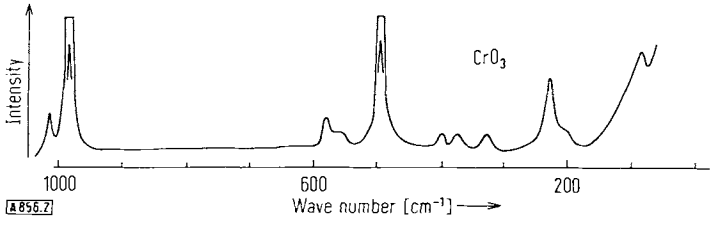


Fig. 2. Raman spectrum of CrO_3; 50—1000 cm^{-1}. Excitation with He—Ne gas laser [6].

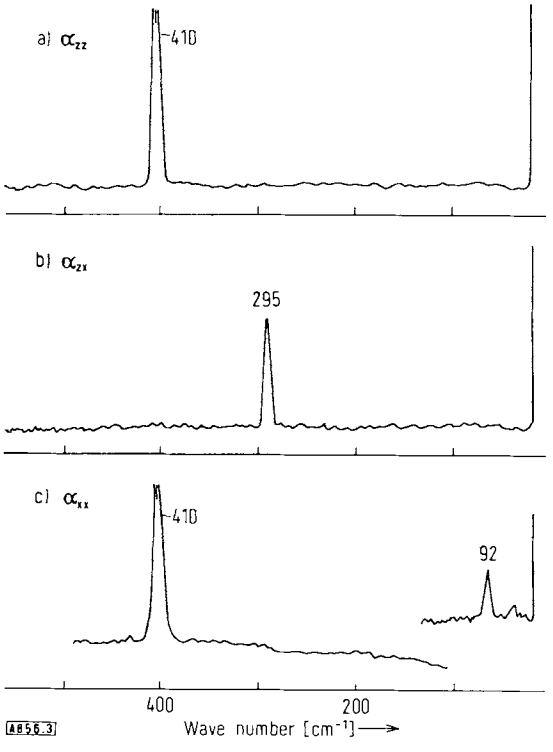


Fig. 3. Raman spectrum of an MgF_2 single crystal with various orientations of the crystal with respect to the laser beam [7]. Excitation with Ar ion laser. α_{zz}, α_{zx}, α_{xx} = components of the polarizability tensor. Assignment of the lattice vibrations: 410 = A_{1g}, 295 = E_g, 92 = B_{1g}.

Figure 3 shows the Raman spectrum of a single crystal of magnesium fluoride[7]. MgF_2 crystallizes in the rutile lattice. The three-dimensional lattice in this case is built up from bonds of a single type; there are no longer any isolated groups present. The assignment of the bands observed to the optical vibrations deduced from the factor-group analysis is conclusively established by their behavior with respect to the axes of symmetry of the crystal, which can be characterized by the investigation of the single crystal with polarized laser radiation.

3. Number and Symmetry Properties of the Vibrations of Lattice Compounds

3.1. Lattice Compounds with Characteristic Lattice Complexes

If the lattice compounds contain complex cations or anions, the observed vibration spectra can be approximately deduced from the expectations for the individual structural units. The expected normal vibrations for an isolated structural group are first enumerated from the point-group analysis. The second step is to determine the positional symmetry of the structural group in the lattice as a whole, which will generally be different from that of the isolated group[8]. The enumeration of the expected spectrum of the single structural unit according to its positional symmetry is known as site-group analysis. For structural groups of higher symmetry, site-group analysis generally leads to splitting of degenerate vibrations and to violation of the selection rules that apply to the group in isolation. In a third approximation step, the correlation between the various complex groups in the unit cell is considered. Factor-group analysis is used here, the possibilities of motion in a unit cell being classified according to its transformation by the operations of the factor group[2-4]. The factor group is given by the space group of the lattice when all operations that contain the translation group of the space group are regarded as unit operations. (The factor group is isomorphous with the point group that can be assigned to the space group.) Whereas the point-group analysis and the site-group analysis give only the internal vibrations of the complex structural unit in question, the factor-group analysis gives all the vibrational degrees of freedom of the unit cell. Those that are mainly due to movements of atoms within the individual complex structural units can be enumerated separately.

As an example, Table 1 shows the enumeration of the internal vibrations of the WO_4^{2-} ions in a scheelite lattice[9, 10]. Since the "spectroscopic" unit cell of scheelite contains two WO_4^{2-} units, the factor-group analysis leads to twice as many WO_4^{2-} vibrations as the site-group analysis.

The concept of "internal vibrations" has been found useful for numerous ionic compounds with oxo anions[10-12]. One frequently (but not always, owing to the band widths) observes the splitting predicted by the site-group analysis

Table 1. Internal vibrations of the WO_4^{2-} ions in scheelites: a) isolated anion, point group T_d; b) anion in the static lattice potential, site group S_4; c) two anions in the unit cell, factor group C_{4h}.

T_d	S_4	C_{4h}	Assignment
A_1(ia,p)	A(ia,p)	A_g(ia,p), B_u(ia,v)	$\nu_s WO_4$
E(ia,dp)	A(ia,p)	A_g(ia,p), B_u(ia,v)	$\delta_s WO_4$
	B(a,p)	B_g(ia,p), A_u(a,v)	
F_2(a,dp)	B(a,p)	B_g(ia,p), A_u(a,v)	$\nu_{as} WO_4$
	E(a,dp)	E_g(ia,dp), E_u(a,v)	
F_2(a,dp)	B(a,p)	B_g(ia,p), A_u(a,v)	$\delta_{as} WO_4$
	E(a,dp)	E_g(ia,dp), E_u(a,v)	

(i)a = (in)active; (d)p = (de)polarized; v = forbidden.

and the expected violations of selection rules for isolated anions. The translational and rotational vibrations of the complex anions within the lattice are generally situated far below the stretching vibrations, and usually even below the deformation vibrations of the anion itself. It follows that the force constants for the equilibrium changes in the anion are much greater than the force constants that describe the movements of the cations and anions in relation to one another.

3.2. Simple Lattices Having One Type of Bonding[13]

The total number of vibrational degrees of freedom can be characterized by the mode of motion of the atoms within a unit cell and by the phase difference between motions in this mode in successive cells. The phase difference is assumed to be propagated periodically through the lattice. Optical vibrations are possible only if at least two atoms are present in a unit cell. The spectroscopic unit cell is the smallest lattice unit that cannot be produced by a simple translation. A face-centered unit cell thus has no optical vibration. If a unit cell contains two atoms belonging to two different primitive sublattices, these must oscillate with respect to each other in an optical vibration.

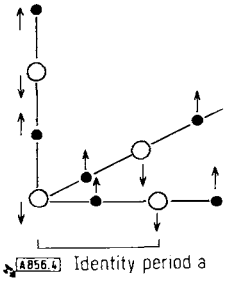


Fig. 4. Schematic representation of the optical lattice vibration of NaCl for $k=0$.

This mode of action is triply degenerate for all cubic lattices, corresponding to displacements parallel to the three equal axes. Figure 4 illustrates this for the case of the NaCl lattice.

The periodic phase difference of the vibrational motion of adjacent unit cells leads to a wave, which runs through the lattice and is characterized by a wave vector k. The value of the wave vector is zero when all the unit cells vibrate in phase, *i.e.* the corresponding wavelength is infinite. It has the value π/a when the phases of the vibrational motion in adjacent unit cells are opposed; a is the unit translation period. The wave vector is generally expressed in units of π/a for the characteristic lattice directions such as [001], [011], and [111]. The frequency of a lattice vibration depends on the mode of motion in a unit cell and on the wave vector k. From $k=0$ to $k=1$, a continuum is to be expected; this continuum is known as a branch. Each branch may be assigned to a particular vibrational motion of the atoms in a unit cell.

The factor-group analysis gives the number and the symmetry behavior of the vibrations for which $k=0$. A complication results from the fact that the vibrational motion in a cell and its propagation in the lattice as a wave may be parallel or perpendicular to each other. In the former case we speak of longitudinal branches, and in the latter case of transverse branches, of the lattice vibrations. Longitudinal and transverse branches differ in their frequency ranges when the vibrational motion leads to lattice polarization. They are also different when $k=0$. The longitudinal vibration can be observed in the IR spectrum of thin crystal films if the incident radiation has a field component normal to the surface of the crystal film[14]. The splitting into longitudinal and transverse branches can be represented in a continuum theory taking the refractive index and the dielectric constant of the lattice compound into account[13].

Figure 5 shows the dependence of the lattice vibrations of sodium iodide on the wave vector for three characteristic lattice directions. Two optical and two acoustic branches are recognized in each case; on the one hand the Na and I atoms in each unit cell oscillate in opposite directions, while on the other they oscillate in the same direction. The factor-group analysis for the NaCl lattice gives a triply degenerate vibration of the class F_{1u}. The frequency of the transverse optical branch in Figure 5 for $k=0$ corresponds to this expectation.

The assignment of the observed IR and Raman spectra of lattice compounds on the basis of the factor-group analysis is thus complicated on the one hand by the possible splitting into transverse and longitudinal optical branches. Further complications may arise through the occurrence of multiphonon transitions[13]. Combined transitions of this type are possible not only between different optical branches but also between optical and acoustic branches when $k \neq 0$, provided that the wave vector of the combined phonon is close to zero. Thus at low layer thicknesses, the IR spectrum of NaCl contains only a single band, corresponding to the expected transverse optical fundamental vibration; at greater layer thicknesses, this is joined by other bands in the form of shoulders at higher wave numbers[15]. This shows that for a reasonable assignment,

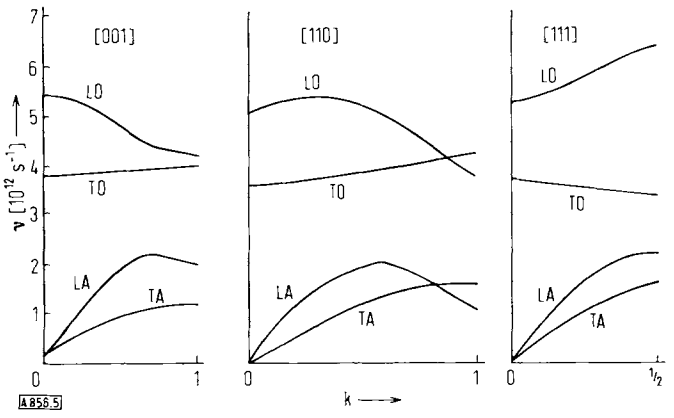


Fig. 5. Lattice dispersion curves for NaI after *Martin* [13]. Representation of the dependence of the frequency on the wave vector along three lattice lines. k in units of π/a. LO and TO = longitudinal and transverse optical; LA and TA = longitudinal and transverse acoustic.

it is necessary not only to establish the number of transverse optical vibrations expected and their symmetry properties but also to estimate their approximate frequencies.

4. Calculation of Force Constants from the Vibrations of Simple Lattices ($k \approx 0$)

4.1. Diamond and Sphalerite Lattices

The transverse optical vibration of a simple AB lattice leads to periodic motion of the two sublattices in relation to each other. The frequency of this lattice vibration, as in the case of a diatomic molecule, can be correlated with the reciprocal mass of the vibrating atoms and the force constant describing the displacement of the atoms from their equilibrium position[16]. This force constant is generally a combination of the force constants belonging to internal coordinates (distances and angles defining the relative positions of neighboring atoms), since the coordinate of the lattice vibration can be represented by a linear combination of the internal coordinates describing the equilibrium distances and equilibrium angles in the lattice. For atomic lattices such as diamond, silicon, or silicon carbide, it seems reasonable to make use of what has been found with the valence force fields of molecular compounds. The potential functions of many molecules can be satisfactorily described by stretching and deformation force constants of the bond lengths and angles if additional interaction constants belonging to neighboring bond lengths and angles are taken into account[17]. The application of the FG[*] method to the transverse optical lattice vibration with $k=0$ for the diamond lattice gives eq. (1) for the corresponding eigenvalue of the secular equation $F.G-\lambda=0$[16].

$$\lambda = \tfrac{4}{3} \cdot 2\mu_c \cdot F_v \qquad (1)$$

λ is found from the observed frequency by the formula $\lambda = \nu^2 \times 10^{-6} \times 0.5891$. The conversion factor is such that ν is to be given in cm^{-1}, F_v in mdyn/Å, and the masses of the vibrating atoms in atomic weight units. The following force constant should be taken into account in the potential function as force constants of internal coordinates and corresponding interaction constants:

f_r = stretching force constant of a bond;
f_{rr} = interaction constants of the neighboring bonds;
f_α = deformation force constant of a bond angle;
$f_{\alpha\alpha'}$ = interaction constant of two opposite bond angles on the same atom;
$f_{\alpha\alpha^*}$ = interaction constant of two bond angles adjacent to a bond;
$f_{r\alpha}$ = interaction constant of a bond with its adjacent bond angle;
$f_{r\alpha'}$ = interaction constant of a bond with a bond angle lying opposite.

The resultant force constant of the lattice vibration is thus found to be[18]:

$$F_v = f_r - f_{rr} + 4(f_\alpha - f_{\alpha\alpha'} + f_{\alpha\alpha^*}) - 4\sqrt{2}(f_{r\alpha} - f_{r\alpha'})$$

The value found for F_v from the lattice vibration of the diamond lattice is 4.7 mdyn/Å[18]. Roughly the same value is obtained when the above combination is formed from the results of valence force calculations for the CC bonds in saturated hydrocarbons[19]. It is remarkable that the F_v value almost coincides with that calculated for the stretching force constant of a CC single bond. In combinations between bond coordinates and the angle coordinates enclosed by these bonds, the contribution of the deformation force constants is evidently largely compensated by the contribution of the interaction constants between valence coordinates and angle coordinates. This relationship, which has been formulated elsewhere[20], makes it possible to obtain an approximate value for the stretching force constant in such combinations of stretching and deformation force constants even when the partial quantities are unknown. The force constants F_v were therefore calculated from the lattice vibrations of a series of tetrahedrally coordinated AB lattices. The results are summarized in Table 2. This table also contains some stretching force constants of molecular compounds that contain the same type of bond as one of the lattice compounds mentioned.

It can be seen that the force constant of the lattice vibration has approximately the value that may be expected for the stretching force constant of the bond between two neighboring atoms in the lattice. Comparison is made difficult by some uncertainty regarding the exact position of the lattice vibration. This is particularly true in the case of BeO, whose spectrum contains a broad band with three maxima. It is possible that the band at 950 cm^{-1} is due to a longitudinal vibration and the doublet at 720/850 cm^{-1} to the hexagonal symmetry of the wurtzite lattice. In this case it is convenient to take an average of the values 1.3 and 1.8 mdyn/Å calculated from the bands at 720 and 850 cm^{-1} as the force constant of the BeO lattice.

It is interesting to compare the force constants and the bond lengths in the isoelectronic lattices diamond, cubic

[*] FG method: Calculation of normal vibrations with the aid of F- and G-matrices for potential and kinetic energy; cf. [17].

Table 2. Transverse optical lattice vibration ($k=0$) and force constant of tetrahedrally coordinated AB lattices.

Lattice	ν (cm^{-1})	F_v [a] (mdyn/Å)	d_{AB} [b] (Å)	f_{AB} [c] (mdyn/Å)
Diamond	1332 [21]	4.7	1.54	4.4 [19]
Boron nitride (cubic)	1090 [22, 23]	3.2	1.57	2.9 [27]
Beryllium oxide (hexagonal)	720, 850, 950 [24] [25]	1.3–2.3	1.64	
Silicon carbide	833 [15]	2.6	1.89	3.0 [28]
Boron phosphide	820 [23]	2.4	1.97	2.0 [29]
Silicon	507 [26]	1.6	2.35	1.7 [28]
Zinc sulfide (cubic)	312 [13]	0.9	2.34	
Gallium phosphide	366 [13]	1.3	2.36	
Cadmium sulfide	241 [13]	0.6	2.52	
Indium phosphide	307 [13]	1.3	2.54	

[a] According to eq. (1) with $\mu_A+\mu_B$ for $2\mu_c$; [b] shortest distance in lattice; [c] stretching force constant of the AB bond in comparable molecular compound (C_2H_6 and homologs, $BH_3 \cdot NH_3$, $BH_3 \cdot PH_3$, Si_2H_6 and CH_3SiH_3).

boron nitride, and beryllium oxide. The force constant decreases very markedly in this order, while the bond length increases, though to a much smaller extent. A similar variation is found for the isoelectronic lattices GaP and ZnS and for InP and CdS. The marked decrease in the force constant in these isoelectronic series is evidently connected with the increasing polarity of the lattice bond. This situation is very evident in the typical ionic lattices described in the next section.

4.2. Ionic Lattices of the NaCl Type

For a lattice of the NaCl type, we find that the transverse optical lattice vibration ($k=0$), after conversion into λ, is given by the equation[16]:

$$\lambda = 2(\mu_A+\mu_B)F_v \qquad (2)$$

F_v is again a linear combination of force constants of internal coordinates. In the case of typical ionic lattices, it is reasonable to consider only the change in the force of repulsion between neighboring particles and the change in the Coulomb forces in the lattice instead of stretching and deformation force constants and the corresponding interaction constants. This model for the description of the lattice dynamics is known as the rigid ion sphere model[13]. Since the sublattices of the cations and of the anions vibrate as rigid units in relation to each other in the transverse optical lattice vibration ($k=0$), only the changes in the Coulomb forces between oppositely charged particles need be considered. F_v then contains, in addition to the force constant for a pair of immediately neighboring ions, the derivatives of the Coulomb forces between a particle and the more distant ions having the opposite charge. Instead of by stepwise summation of the derivatives of these Coulomb forces, their sum can be obtained by application of the continuum theory to the lattice vibration by introduction of the polarization of the lattice into the equations of motion[13]. In the case under discussion this leads to the equation

$$F_v \doteq f - \frac{4\pi}{3} \cdot \frac{q^2}{2d_0^3} \qquad (3)$$

f is the force constant for a pair of ions, q is the ionic charge, and d_0 is the distance between a pair of ions.

However, it is easy to show that this expression is not enough for a satisfactory reproduction of the complete lattice dynamics. In a first improvement, polarizable ions are introduced, and these are characterized by effective charges as well as by their polarizability. From the lattice frequency at $k=0$ and from the dielectric constants of the crystal at high and at low frequencies, one can determine the force constant f for two neighboring ions, the polarizability, and the effective charge of the ions. The measurements and their evaluation show that for alkali metal halides, the effective charge of the ions is approximately 80% of an elementary charge. However, the effect of this smaller effective charge on the lattice vibration is partly offset by the polarizability[13].

A shell model is used in more recent attempts to represent the lattice dynamics[30, 31]. In this model one considers forces between ion cores and rigid, spherically symmetrical shells of negative charge. The course of the individual branches in the lattice dynamics of alkali metal halides can be satisfactorily represented with the aid of such a model, as is shown in Figure 5. If one confines oneself to the transverse optical vibration with $k=0$, the resultant force constant F_v can be calculated first from the observed values with the aid of eq. (2), and can then be used to determine the force constant of a pair of ions from eq. (3). The results are shown in Table 3. When the Coulomb forces are taken into account, on application of eq. 3, a full unit charge is taken as the charge on the ion.

In the case of the alkali metal halide lattices, the influence of lattice polarization on the resultant force constant of the lattice vibration can also be taken into account by calculating the force constant from the frequency of the longitudinal lattice vibration at $k=0$[32]. This leads directly to a force constant in which the influence of the long-range forces is already eliminated by the lattice polarization. The values for the alkali metal halides are about 5—10% lower than the values calculated from eq. (3) for the force constant f (Table 3). The difference is due to the fact that the full ionic charge was used in the evaluation of eq. (3), whereas the effective charge is somewhat smaller.

As well as the force constants, Table 3 also contains the equilibrium distances and (for further comparison) the force constants and equilibrium distances in the gaseous molecules NaCl, NaBr, KCl, and KBr[33]. It can be seen that the force constants F_v obtained directly from the lattice vibrations are very small. They also show no variation for the various alkali metal halides, such as one might expect from the equilibrium distances and from the force constants in the molecular compounds NaCl and KCl. This variation is evidently masked by the influence of the Coulomb forces to the more distant oppositely charged ions, whose derivatives according to eq. (3) are opposite

in sign to the force constant of a pair of neighboring ions. The force constant f of a pair of neighboring ions in the lattice is also small when *e.g.* the result for NaCl in the lattice is compared with that for NaCl molecules. This is not unexpected, since the polarization of the sodium and

Table 3. Transverse optical lattice vibration ($k=0$) and force constant in alkali metal halide lattices of the NaCl type.

	F				Cl				Br			
	ν	F_ν [a]	f [b]	d_0	ν	F_ν	f	d_0	ν	F_ν	f	d_0
Li	304	0.14	0.73	2.01	204	0.07	0.35	2.57	173	0.06	0.29	2.75
Na	246	0.19	0.57	2.31	164	0.11	0.32	2.81	135	0.10	0.28	2.98
K	192	0.14	0.40	2.66	144	0.11	0.27	3.14	116	0.11	0.24	3.29
Rb	160	0.12	0.33	2.81	119	0.11	0.24	3.27	90	0.10	0.22	3.42

ν in cm^{-1}; [a] force constant according to eq. (2) in mdyn/Å; [b] f according to eq. (3) in mdyn/Å; d_0 in Å.

	f	d_0
NaCl (Molecule)	1.19	2.51
NaBr (Molecule)	1.05	2.64
KCl (Molecule)	0.87	2.79
KBr (Molecule)	0.84	2.99

chloride ions will influence the electron density distribution differently in the lattice, where they are octahedrally surrounded by oppositely charged particles, and in an NaCl molecule.

The determination of the force constant of an ion pair in the lattice from the force constant of the lattice vibration according to eq. (3) depends on the assumption that the effective charge on the ion in the lattice can be estimated. As was mentioned earlier, the more complete lattice dynamics show that the effective charge must be taken as only about 80% of the full ionic charge even for alkali metal halides. With more highly charged ions in the lattice, even smaller fractions of the full ionic charge must be expected. Corresponding data can be evaluated for MgO and CaO, both of which have lattices of the NaCl type. Table 4 shows the observed transverse and longitudinal lattice vibrations at $k=0$[32] and the force constants calculated from them with the aid of eq. (2). For the ion sphere model with polarizable ions having an effective charge q, the value of q can be determined from eq. (3) if the force constant from the transverse lattice vibration is used for F_ν and the force constant from the longitudinal lattice vibration for f. The latter is justified, since the Coulomb forces of the lattice polarization do not affect the force constant for the longitudinal lattice vibration.

Table 4. Lattice vibrations ($k=0$) and force constants of MgO and CaO.

		ν (cm^{-1})	F_ν [a] (mdyn/Å)	q [b] (charge units)
MgO	TO	403	0.47	1.39
	LO	717	1.46	
CaO	TO	286	0.28	1.56
	LO	577	1.12	

TO = transverse optical; LO = longitudinal optical.
[a] According to eq. (2); [b] according to eq. (3) for the condition $f=F_\nu$ (LO).

4.3. Calcium Fluoride

The force constants F_ν for CaF_2 can be calculated from the transverse and longitudinal components of the lattice vibration F_{1u}, and the effective charge can be determined in the same way as for CaO (Table 5). q in this case is the effective charge of the calcium ion and the sum of the charges of two fluoride ions, since the two fluoride sublattices vibrate in phase in the class F_{1u}. The effective charges found for the calcium ions are approximately equal to those in CaO. From the Raman-active lattice vibration of CaF_2 in F_{2g}, a force constant can also be calculated that is independent of the long-range forces of the lattice polarization, since no polarization of the lattice occurs in the corresponding vibration model. The transverse and longitudinal components of the lattice vibration therefore have the same frequency in F_{2g}. The calculated force constant is somewhat smaller than that from the longitudinal lattice vibration in F_{1u}. This shows that interaction forces of neighboring valence coordinates must also be taken into account in the assessment of the calculated force constants. Without these interaction forces, only approximate values can be found for the stretching force constants in the lattice, as is to be expected from findings with the simple valence force model in molecular compounds.

Table 5. Lattice vibrations ($k=0$) and force constants of CaF_2.

		ν (cm^{-1})	F_ν (mdyn/Å)	
in F_{1u}	TO	266	0.34	from $\lambda=\frac{8}{3}(\mu_{Ca}+\frac{1}{2}\mu_F)F_\nu$
	LO	482	1.11	
in F_{2g}	(TO=LO)	322	0.87	from $\lambda=\frac{4}{3}\mu_F F_\nu$

q according to eq. (3) for the condition $f=F$ (LO) in $F_{1u}=1.46$ charge units.

5. Spinel Lattice. Assignment of the IR-Active Vibration and Calculation of Force Constants

For the spinel lattice, the factor-group analysis gives four IR-active lattice vibrations in the class F_{1u}[34]. IR-spectroscopic studies have been carried out on a large number of spinels. We shall be concerned for the present only with Na_2MoO_4 and Na_2WO_4, which may be regarded as lattices with complex structural groups. The spectroscopic findings are summarized in Table 6. Of the four

expected IR-active vibrations, only two are observed. These can be approximately described as the stretching and deformation vibrations of the tetrahedral oxo anions. The "external vibrations", *i.e.* movements of the anions with respect to the cations, should occur at much lower wave numbers, since the stretching force constants to be expected for sodium-oxygen pairs are very small in comparison with those of the MoO and WO bonds.

Table 6. Observed IR bands (cm^{-1}) of the spinels Na_2MoO_4 and Na_2WO_4. Comparison with the solution spectra.

Na_2MoO_4	MoO_4^{2-} solution	Na_2WO_4	WO_4^{2-} solution
838	840 (νMoO_4)	835	833 (νWO_4)
≈325	318 (δMoO_4)	320	322 (δWO_4)

Force constants (mdyn/Å) from the vibrations of the "isolated" anions of class F_2:

	MoO_4^{2-}	WO_4^{2-}
$F(\nu)$	5.5	5.9
$F(\delta)$	0.35	0.4

A different situation is found for $MgAl_2O_4$. Figure 6 shows the vibration modes for the tetrahedral and the crosslinked octahedral structural units of the lattice that are possible in the class F_{1u} by symmetry combination of Cartesian coordinates[35]. The coordinates chosen for the tetrahedral structural units can be transformed in such a way that one of them becomes a valence coordinate and the other an angle coordinate. Such a transformation into pure stretching and deformation coordinates is not possible in the case of the octahedral units. The vibration modes represented in Figure 6 are coupled in the normal coordinates, since the oxygen ions belong to both coordination polyhedra. A simplification results if the angle-retaining forces are disregarded in the vibration modes of the octahedral unit. The frequency equations for the four IR-active lattice vibrations of the spinel lattice can then be divided into two blocks of two vibrations each, in which one vibration of the octahedron is coupled with the stretching vibration of the tetrahedron, and the other vibration of the octahedron with the deformation vibration of the tetrahedron. According to this model, for the spinel lattice in the case of $MgAlO_4$ we expect three vibrations in the stretching vibration region for the octahedron and the tetrahedron and one in the deformation vibration region.

The IR spectra of various compounds of the spinel type with bonding similar to that in $MgAl_2O_4$ have been found to contain two strong bands in the expected stretching vibration region, accompanied in some cases by a weaker band in the form of a shoulder at higher wave numbers[34]. The two strong bands can be plausibly assigned to the vibration modes that arise from the coupling of a stretching coordinate of the tetrahedral unit with a stretching coordinate of the octahedral unit. A weaker band in the form of a shoulder could be the expected third stretching vibration. Calculations for the assignment of the two strong bands have been carried out for various spinels (Table 7). It is found that plausible values for the stretching force constants are obtained for the first four compounds only if the stretching coordinate of the tetrahedral unit

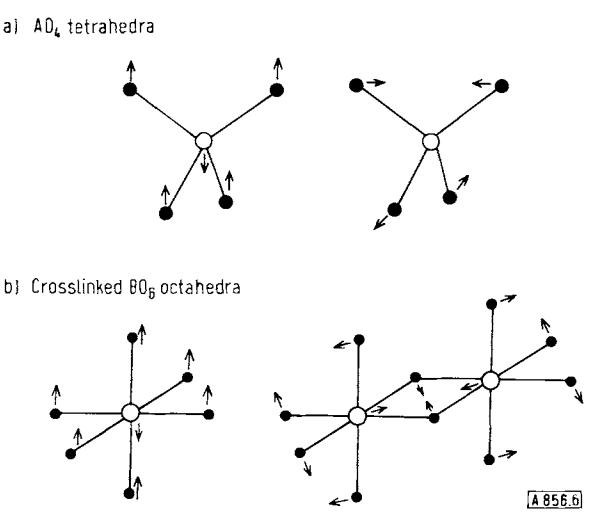


Fig. 6. Vibration modes for the F_{1u} vibrations of the spinel lattice; A in tetrahedral and B in octahedral sites of the oxygen packing.

predominates in the lower vibration in each case. The situation is reversed for the last two spinels, which have Cr in the B sites. However, the coupling between the two stretching vibrations is considerable. Real solutions for the force constants are obtainable from the observed frequencies only if the interaction force constant of the bonds from an oxygen atom to a metal atom in the tetrahedral group and to one in the octahedral group is positive. The calculated force constants depend on the value of this interaction constant. Within these solution ranges, only those values for the force constants in which the interaction term is as small as possible, so that one is at the limit of the real solution region, are plausible and bear comparison within the whole series. These values are given in the following table. They show that the force constants for the MgO and AlO bonds are both around 1.9 mdyn/Å. Because of the higher effective nuclear charge of aluminum, one would expect a greater force constant for the AlO bond than for the MgO bond. However, the influence of the higher nuclear charge of aluminum is evidently offset by the smaller coordination number of the magnesium. In agreement with the result of the calculation, the MgO and AlO distances in $MgAl_2O_4$ are almost identical. The force constant of the MgO bond is considerably greater in $MgAl_2O_4$ and $MgCr_2O_4$ than in MgO, and thus also shows the influence of the coordination number.

Table 7. Evaluation of two IR-active vibrations in spinels of the type AB_2O_4.

B	A	ν_B	ν_A	F_{AB}	F_B	F_A
Al	Mg	690	538	0.2	1.86	1.82
Al	Mn	649	529	0.5	1.87	2.29
Al	Fe	671	562	0.5	1.81	2.85
Al	Co	680	562	0.5	1.88	2.85
Al	Zn	667	562	0.5	1.93	2.51
Cr	Mg	508	645	0.35	2.03	1.87
Cr	Co	526	627	0.75	2.17	2.80

ν_A and ν_B: coupled stretching vibrations of the AO_4 tetrahedron and of the BO_6 octahedron respectively; ν in cm^{-1}.
F_A = stretching force constant in the AO_4 tetrahedron in mdyn/Å.
F_B = stretching force constant in the BO_6 otahedron in mdyn/Å.
F_{AB} = interaction constant.

A similar influence of the coordination number of the force constant and hence the position of the lattice vibration can be seen in the spectra of FeO (NaCl lattice) and Fe_3O_4 (inverse spinel type). For the first of these compounds the lattice vibration is situated at $400\,cm^{-1}$, while the second, like the spinels discussed above, gives two strong bands at 375 and $570\,cm^{-1}$[36]. Of these bands, the first is more strongly determined by the stretching coordinates of the octahedrally coordinated iron, and the second by those of the tetrahedrally coordinated iron. It has been shown[36] that in the spectrum of FeO, in addition to the strong band at $400\,cm^{-1}$, a weak band at $590\,cm^{-1}$ appears at the composition $Fe_{0.95}O$, the intensity of this band increasing with increasing iron deficiency. It is concluded from its position that the Fe^{3+} ions present in the defect structure occupy tetrahedrally coordinated lattice sites. This conclusion is in agreement with the foregoing characterization of the stretching vibrations in spinel lattices by stretching coordinates of the tetrahedrally and octahedrally coordinated groups.

Received: November 4, 1970 [A 856 IE]
German version: Angew. Chem. *84*, 8 (1972)
Translated by Express Translation Service, London

[1] *M. Born* and *K. Huang*, Dynamical Theory of Crystal Lattices. Oxford University Press, London 1954.

[2] *S. Bhagavantam* and *T. Venkatarayudu*, Proc. Indian Acad. Sci. *9A*, 224 (1939); Theory of Groups and its Application to Physical Problems. Bangalore Press, Bangalore 1951.

[3] *D. F. Hornig*, J. Chem. Phys. *16*, 1063 (1948); *W. Vedder* and *D. F. Hornig*, Advan. Spectrosc. *2*, 189 (1961).

[4] *H. Winston* and *R. S. Halford*, J. Chem. Phys. *17*, 607 (1949).

[5] *B. Krebs*, *A. Müller*, and *G. Gattow*, Z. Naturforsch. *20b*, 1017 (1965).

[6] *R. Mattes*, Habilitationsschrift, Universität Münster 1970.

[7] *S. P. S. Porto*, *P. A. Fleury*, and *T. C. Damen*, Phys. Rev. *154*, 522 (1967).

[8] *R. S. Halford*, J. Chem. Phys. *14*, 8 (1946).

[9] *R. K. Khanna* and *E. R. Lippincott*, Spectrochim. Acta *24A*, 905 (1968).

[10] *K. Ulbricht* and *H. Kriegsmann*, Z. Anorg. Allg. Chem. *358*, 193 (1968).

[11] *R. G. Brown* and *S. D. Ross*, Spectrochim. Acta *26A*, 945 (1970).

[12] *H. Hezel* and *S. D. Ross*, Spectrochim. Acta *22A*, 1949 (1966).

[13] *D. H. Martin*, Advan. Phys. *14*, 39 (1965).

[14] *D. W. Berreman*, Phys. Rev. *130*, 2193 (1963).

[15] *Landolt-Börnstein*, Zahlenwerte und Funktionen, Vol. I/4, 6th Edit. Springer-Verlag, Berlin 1955.

[16] *T. Shimanouchi*, *M. Tsuboi*, and *T. Miyazawa*, J. Chem. Phys. *35*, 1597 (1961).

[17] *H. J. Becher*, Fortschr. Chem. Forsch. *10*, 156 (1968).

[18] *H. J. Becher*, unpublished.

[19] *J. H. Schachtschneider* and *R. G. Snyder*, Spectrochim. Acta *19*, 117 (1963); *21*, 169 (1965).

[20] *H. J. Becher* and *K. Ballein*, Z. Physik. Chem. (Frankfurt) *54*, 302 (1967).

[21] *J. J. Fox* and *A. E. Martin*, Phil. Trans. Roy Soc. London *A232*, 463 (1934).

[22] *H. J. Becher* and *H. Baechle*, unpublished.

[23] *S. S. Mitra*, Phys. Rev. *155*, 1039 (1967).

[24] *S. Tolksdorf*, Z. Physik. Chem. *132*, 161 (1928).

[25] The Sadtler Standard Spectra, Inorganics and related compounds Sadtler Res. Lab., Philadelphia PA 1967.

[26] *H. Palevsky*, *D. J. Hughes*, *W. Kley*, and *E. Tunkelo*, Phys. Rev. Lett. *2*, 258 (1959).

[27] *W. Sawodny* and *J. Goubeau*, Z. Physik. Chem. (Frankfurt) *44*, 227 (1965).

[28] *J. L. Duncan*, Spectrochim. Acta *20*, 1807 (1964).

[29] *W. Sawodny* and *J. Goubeau*, Z. Anorg. Allg. Chem. *356*, 288 (1968).

[30] Shell model: *B. G. Dick* and *A. W. Overhauser*, Phys. Rev. *112*, 90 (1958).

[31] *W. Cochran*, Rep. Progr. Phys. *26*, 1 (1963).

[32] After measurements by *G. R. Wilkinson*, Phys. Dep. Kings College, London; Lecture: Conf. Mol. Spectrosc. Brighton, 17.—19. April 1968.

[33] *J. G. Herzberg*: Spectra of Diatomic Molecules. D. Van Nostrand, Princeton 1950.

[34] *W. B. White* and *B. A. DeAngelis*, Spectrochim. Acta *23A*, 985 (1967).

[35] *H. D. Lutz*, Z. Naturforsch. *24a*, 1417 (1969).

[36] *P. Tarte*, *J. Preudhomme*, *F. Jeannot*, and *O. Errard*, C. R. Acad. Sci. Paris *C (269)*, 1529 (1969).

X-Ray Spectroscopic Investigation of Chemical Bonding in Solids[**]

By Alfred Faessler[*]

When an atom is incorporated into a molecule or a crystal, its X-ray spectrum undergoes characteristic changes, the study of which leads to important information on the nature of the chemical bonding and on the electronic structure in a substance. A number of examples are given to illustrate the possibilities of the X-ray spectroscopy of bonded atoms. Special attention is given to the displacement of the Kα lines, from which conclusions can be drawn regarding the charge on a bonded atom, as well as to the investigation of the emission bands resulting from valence electron transitions, which yields information on the energy band structure of the solid. X-ray spectroscopic studies on free molecules and theoretical work on the calculation of the molecular orbitals of simple molecules are finally reported.

1. Introduction

The influence of chemical bonding on the characteristic X-ray spectrum has attracted growing attention in recent years, since it has been shown that the spectrum of the bonded atom yields valuable information concerning the electronic structure and the nature of the chemical bonding in molecules and crystals.

How does the X-ray spectrum of an atom change when it is incorporated into a molecule or crystal? To answer this question, let us consider an element of the 3rd period, *e.g.* silicon, in a compound that exists in the solid state. In such a case, the valence electrons, *i.e.* the M electrons in the case of silicon, occupy an energy band as shown in the simplified level diagram (Fig. 1). The possible X-ray transitions are shown in the diagram.

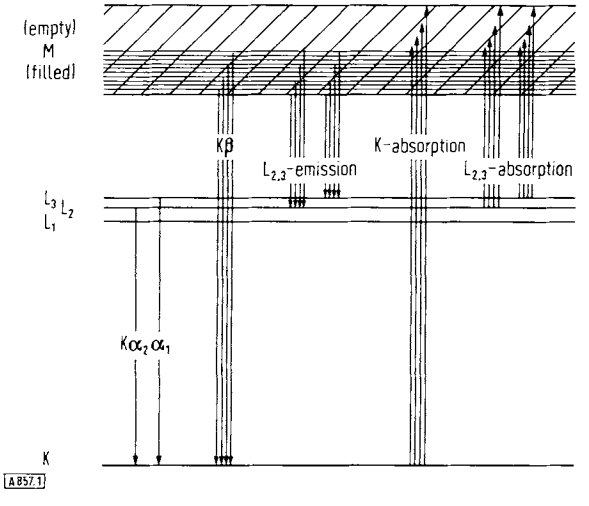


Fig. 1. Simplified level diagram with the possible X-ray transitions for elements of the 3rd period. The horizontal shading denotes the occupied part of the valence band.

[*] Prof. Dr. A. Faessler
Sektion Physik der Universität
8 München 22, Geschwister-Scholl-Platz (Germany)

[**] From a lecture delivered to the GDCh "Festkörperchemie" group on October 2, 1970 in Bonn (Germany).

The transitions of the valence electrons into the K or $L_{2,3}$ level give rise to emission bands whose position, width, and structure are characteristic of the solid in question and yield information on the occupied part of the energy band system. The absorption spectra, which correspond to electron transitions from the K and $L_{2,3}$ levels into the free valence electron levels, provide information about the unoccupied part of the energy band system.

The effect of bonding can be seen not only in transitions involving valence electron levels but also in the internal transition $L_{2,3} \rightarrow K$, which leads to the emission of the $K\alpha_{1,2}$ doublet. The main effect of chemical bonding on the doublet lines is a change in wavelength; this is accompanied by a small change in their width and symmetry. The wavelength changes in particular are subject to simple rules, which allow the deduction of the charge of the atom in the compound in question.

Finally, the influence of chemical bonding can also be seen, very clearly in some cases, in the non-diagram or satellite lines, which are due to multiply ionized atoms.

2. Displacements of Absorption Edges and Emission Lines

2.1. K Absorption Edge of Sulfur

The dependence of an X-ray spectrum on bonding was first observed in the K series of phosphorus, sulfur, and other elements of the 3rd period, since the effects in these cases can be detected even with simple spectroscopic aids and the radiation lies in an easily accessible wavelength range. It was found that the position of the K absorption edge of an element differs from compound to compound, and even among the various modifications of an element. Systematic studies on this phenomenon were carried out in particular by *Stelling*[1] between 1920 and 1930. They showed that the wavelength at which the edge occurs is generally greatest for the element, while for the compounds it is found that the higher the oxidation state in which the element is present, the shorter is the wavelength or the

higher the energy of the edge. The position of the edge is also influenced by neighbors bonded in the first sphere.

These simple empirical rules have been successfully used by *Stelling* for the investigation of chemical constitutions, and it is not surprising that the simple procedure aroused great interest among chemists. However, the method did not live up to expectations; it failed even in relatively simple problems. Thus *Stelling* found three absorption edges in the case of sodium thiosulfate, $Na_2S_2O_3$, instead of two as expected from the structural formula. This result, which was incomprehensible at that time, is now known to be due to a phenomenon known as the fine structure of the absorption edge, which also hinders the location of the principal absorption jump, and hence the determination of the oxidation state of the absorbing element, in other cases. Moreover, the relation between the position of the edge and the bonding state is not as simple as was originally thought. It was recognized only later that in addition to the position of the edge, its fine structure must generally also be taken into account in drawing conclusions regarding the bonding of the atom in question.

2.2. Kα Doublet of Sulfur

Effects of chemical bonding were also discovered at an early date in the *emission spectra* of light elements. Here an experimental difficulty was encountered in the systematic investigation of this phenomenon. It was found that on excitation with electrons on the anticathode of an X-ray tube, many substances undergo uncontrollable changes even at low intensities, so that it is frequently impossible to obtain the spectrum of an element in a given compound.

However, even the earliest measurements showed the nature and the magnitude of the influence of chemical bonding on the emission spectra. A surprisingly large effect was found for the Kα lines of the elements of the 3rd period. Close examination of the experimental findings revealed indications that the wavelength changes observed for the Kα lines depend in a clearer manner on the bonding state of the emitting atom than the changes in the wavelengths and structures of the Kβ lines and absorption edges. Particularly simple relationships were therefore to be expected for the dependence of the Kα doublet on bonding if the interfering effects during excitation could be avoided.

This type of reasoning led the author to the idea of investigating the influence of chemical bonding on the Kα doublet of sulfur with fluoresence excitation. The experimental means were available for the production of intense fluorescent radiation even from elements having low atomic numbers. They had been developed for chemical analysis with secondary X-ray beams (nowadays known as X-ray fluorescence analysis), and could also be used for the investigation of the relation between the X-ray spectrum and the bonding state.

The expectation that simple, clear rules would be found for the Kα lines by the fluorescence method was fully confirmed on investigation of a series of inorganic sulfur compounds[3]. Like the absorption edge, the Kα doublet moves to higher energies with increasing oxidation state of the element in the compound in question. In this case, however, the findings were fully consistent, unlike those for the absorption edges. All compounds with positively charged sulfur exhibit a shift to higher energies in relation to elementary sulfur, while compounds with negatively charged sulfur exhibit a shift to lower energies. Thus all sulfides, without exception, show a shift of the Kα doublet to lower energies, whereas the displacement of the K absorption edge is to lower energies for some sulfides and to higher energies for others, an indication that the situation is more complicated in the case of the absorption edges. The investigation of sodium thiosulfate, in agreement with the structural formula, gave two doublets, one corresponding to sulfur in the oxidation state +6 and the other to sulfur in a lower oxidation state. The relative positions of the two doublets are such that the $K\alpha_2$ line of the first sulfur atom overlaps with the $K\alpha_1$ line of the second. Figure 2 shows the Kα spectrum of the sulfur in thiosulfate, which consists of three lines, and the Kα doublet of sulfur in a sulfate and in a sulfide. Sulfide and sulfate give the extreme positions for the doublet; the energy difference in this case is not less than 1.33 eV, a surprisingly high value when one considers that the chemical bond energies are only a few electron volts. Accurate measurement of the wavelength showed that the $K\alpha_1$ line of the central sulfur atom does not coincide exactly with that of the sulfur in sulfate, just as the wavelength of $K\alpha_2$ of the second sulfur atom is not equal to that of $K\alpha_2$ of sulfide or elementary sulfur. Even within the "same oxidation state", therefore, we find small displacements that depend on the nature of the bonding partner.

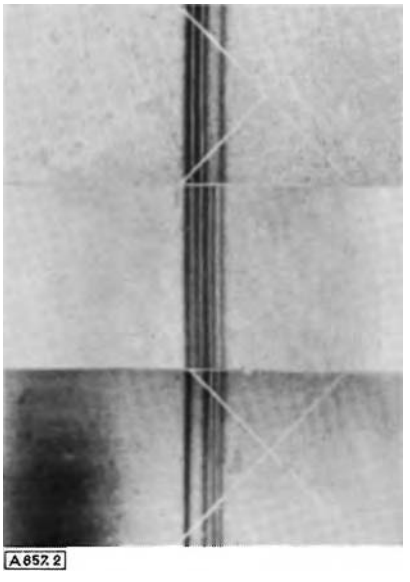


Fig. 2. Kα lines of sulfur in Na_2SO_4 (top), $Na_2S_2O_3$ (center), and ZnS (bottom). The two outer lines are reference lines (Co $K\alpha_1$ and $K\alpha_2$, 3rd order). The three lines of $Na_2S_2O_3$ result from the overlap of two doublets, whose positions are approximately as in Na_2SO_4 and ZnS.

Together with *M. Becke-Goehring*, the author later investigated a large number of chemically and crystallographically well-defined sulfur compounds[4]. The result of the earlier measurements were substantially confirmed by this

work, particularly the relation between the position of the doublet and the oxidation state of the sulfur. To supplement the earlier findings, a compound containing sulfur in the oxidation state +2 was also investigated; in this case we found a doublet whose position lay between those of S^0 and S^{IV}.

It was also found that within one and the same oxidation state, the doublet is increasingly displaced to higher energies with increasing electronegativity of the bonding partner. This relation has been confirmed for several series of compounds. In general, therefore, the doublet is displaced to higher energies as the positive charge on the atom is increased.

In addition to thiosulfate, a number of other compounds containing sulfur in different oxidation states were investigated. Polythionates gave results similar to those found for thiosulfate. There were again two overlapping doublets, indicating sulfur atoms in two different oxidation states. Dithionate, on the other hand, gives a single Kα doublet, corresponding to the fact that the two sulfur atoms in dithionate have the same formal oxidation number +5.

An interesting example in this connection is tetrasulfur tetranitride S_4N_4, whose molecule forms an eight-membered "ring". According to the formal view, the sulfur atoms should be in two different oxidation states, *i.e.* +2 and +4. The X-ray spectroscopic study gave a single, well-defined Kα doublet, whose position corresponds to the oxidation state +3. In this case, therefore, the sulfur atoms are not in different oxidation states, as one would expect from the classical valence theory, but the electron distribution in the system is evened out by delocalization. It also follows that sulfur may be regarded as the positive component of the compound, and S_4N_4 may be treated as a nitride. The derivative $S_4(NH)_4$ gave an S Kα doublet whose position corresponds to the oxidation state +2.

The measurement of the wavelengths of the S Kα doublet frequently allows a decision between two possible structural formulas. For example, it was found that "formaldehyde sodium sulfoxylate" (rongalite) contains sulfur in the oxidation state +4, and should therefore be regarded as a salt of hydroxymethanesulfinic acid.

2.3. Kα Doublet of Aluminum, Silicon, and Phosphorus

The rules found for the influence of the oxidation state and the electronegativity of the bonding partner in the case of sulfur were confirmed on extension of such studies to the Kα doublet of the elements phosphorus, silicon, and aluminum. As far as the influence of the electronegativity is concerned, it can now be said with greater precision, on the basis of measurements by *Fichter*[5] on the Kα doublet of phosphorus, that the displacement is approximately proportional to the difference between the electronegativities of the two bonding partners (Fig. 3).

Läuger established in the case of aluminum that not only the nearest but also the next-nearest neighbors can influence the Kα spectrum of an atom[6]. A distinct influence

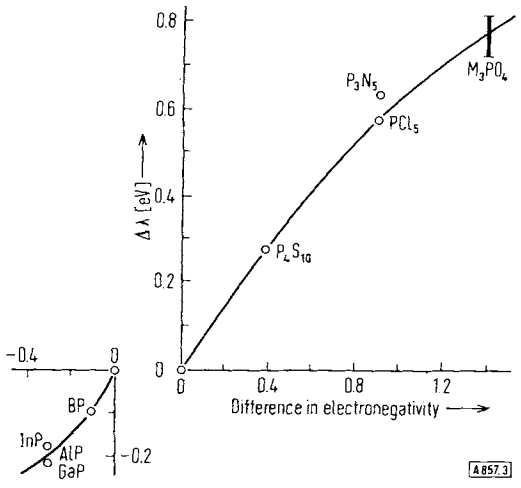


Fig. 3. Displacement of the P Kα doublet as a function of the difference in electronegativity of the bonding partners.

of coordination is also observed in the case of aluminum. On transition from tetrahedral to octahedral coordination, the doublet is considerably displaced to shorter wavelengths, so that it seems possible to obtain information on the coordination in aluminum compounds by accurate measurement of the wavelengths of the Kα lines.

A displacement of the P Kα doublet to higher wavelengths is found for the semiconducting III, V compounds BP, AlP, and InP; it follows from this, in agreement with other results, that the bonding in these semiconductors has a certain ionic component, and that phosphorus is the negative partner.

It is sometimes possible to investigate the spectra of both partners in a compound, as in the case of phosphorus sulfides. In agreement with the chemical properties, a shift to lower wavelengths is found for P Kα and a shift to higher wavelengths for S Kα, *i.e.* phosphorus is the positive partner and sulfur the negative. The displacement of P Kα increases with increasing number of sulfur atoms[5].

Many problems of chemical bonding in solids are encountered with silicon, whose K spectrum has been thoroughly investigated by *Krämer*[7]. In a series of compounds of silicon with the metals lithium, magnesium, and calcium, a displacement of the Si Kα doublet to longer waves, indicating a negative charge on the Si atom, was found only for Mg_2Si and Ca_2Si, which may also be regarded stoichiometrically as silicides. No shift or only a very small shift to lower wavelengths is found for the other metal compounds of silicon; this means that these are alloy-like compounds, as can also be deduced from their other physical and chemical properties.

The position of Si Kα for silicon carbide SiC indicates that this compound has an essentially homopolar structure; though a slight shift of the doublet to shorter waves points to a positive charge on the Si atom, the shift is much smaller than in the case of SiO_2, so that it is not permissible to regard SiC as an ionic crystal, as has occasionally been done on the basis of other physical measurements.

The two lower oxides of silicon, Si_2O and SiO_3, were also identified with the aid of the Kα doublet (Table 1).

Table 1. Wavelengths λ (in X units) of the Si-Kα doublet of elementary Si, "Si_2O", SiO_3, and SiO_2. δλ (in X units) and δE (in eV) denote the shifts of the doublet of silicon in the oxides [*] in relation to the doublet of elementary silicon.

Substance	λ		δλ	δE
	$K\alpha_1$	$K\alpha_2$	(mean)	
Si	7111.16	7113.77	—	—
"Si_2O"	09.32	12.00	1.81	0.44
Si_2O_3	08.89	11.55	2.25	0.55
SiO_2	08.69	11.36	2.44	0.60

[*] The oxide of the oxidation state +1 was in the form of a derivative $SiOR = Si_2O \cdot R_2O$, hence the designation "Si_2O".

If the electronegativities of oxygen and of silicon are taken into account, the positions of the Si Kα lines for the two compounds are in agreement with the assumption that each Si atom is surrounded by three Si atoms and one O atom in Si_2O, and by one Si atom and three O atoms in Si_2O_3.

The Si Kα spectrum of technical SiO shows an overlapping of several doublets, which cannot be resolved, but it can be said with certainty that this product is not a mixture of Si and SiO_2 alone; it is presumably a mixture of Si, SiO_2, and the lower oxides. It has not been possible to answer the question whether a definite silicon monoxide exists. (We once received a product for investigation that gave an Si Kα doublet at the wavelength expected for the oxidation state +2 of silicon, but the chemical analysis of this product did not correspond to the composition SiO; the investigations could not be continued at that time for reasons beyond our control.)

Among the oxygen compounds of silicon, a number of silicates have also been investigated. The position of the Si Kα doublet of various silicates varies over a wide range of wavelengths; this variation can be correlated with the various silicate structures. It may be assumed that investigations of this nature could contribute to the elucidation of silicate structures. It is interesting to note that the wavelength of P Kα is also different for different phosphates (cf. Fig. 3), though the scatter in this case is smaller; in the case of S Kα in sulfates, the scatter just exceeds the error limits.

To conclude the discussion of the dependence of the Kα lines on bonding, it should be mentioned that a systematic variation with bonding is found not only for the position of the lines but also for their width and shape; though these effects are not very pronounced, they have been used for the clarification of questions of chemical bonding[8].

The Kα satellites, *i.e.* lines due to doubly ionized atoms, show the influence of chemical bonding much more strongly than the principal lines $K\alpha_{1,2}$[9]. The displacements are roughly twice as large as for the latter, and are accompanied by pronounced changes in the widths and relative intensities of the lines. It is therefore perfectly reasonable to study the dependence of the satellite lines on bonding in greater detail, though their low intensity results in some difficulty in the measurements.

It should be added that the dependence of the wavelength of the Kα doublet on bonding has been detected even for elements with higher atomic numbers with the aid of special apparatus and measuring methods[10].

3. Valence Electron Transitions in Solids

3.1. Emission Bands

3.1.1. Elements and Compounds

In the discussion of the emission bands, which are due to valence electron transitions and are investigated in order to elucidate the electronic structure of a solid, we shall again confine ourselves to elements of the 3rd period. To obtain as much information as possible, it is essential to measure both the Kβ bands and the L bands, since only the part of the valence band with p symmetry is covered by the K bands and only those with s and d symmetry by the L bands.

The Kβ bands of these elements lie in a wavelength range for which crystal spectrographs are suitable; the K spectrum *e.g.* of silicon extends from 6.7 to 7.1 Å. The L bands lie in the region of ultrasoft X rays; the L band of silicon appears at 125—145 Å. Work in this wavelength range is nowadays carried out almost exclusively with concave grating spectrographs. The strong absorbability of the radiation imposes stringent requirements regarding the vacuum and the cleanness of the surfaces of the substances under investigation.

What results have been obtained so far in studies on valence electron transitions? One important result is the essentially direct confirmation of the fundamental concepts of the energy band model. In monographs on solid-state physics and in any detailed textbook, one can find diagrams showing that the emission bands due to the transitions of the valence electrons have a more or less symmetrical intensity distribution for nonconductors, corresponding to the fact that the valence band is fully occupied, whereas the emission band in the case of metals is unsymmetrical and shows a steep descent on the high-energy side, corresponding to the Fermi edge.

However, it is by no means easy to obtain X-ray spectroscopic data that provide information on the energy band structure of a given solid and can be compared with the results of theoretical work. The difficulties that arise are partly experimental, but they are also partly due to problems of a fundamental nature.

To obtain the true intensity distribution from the measured intensity distribution for a given emission band in the ultrasoft region, the reflecting power of the grating and the quantum yield of the photocathode of the multiplier, both of which depend on the wavelength, must first be taken into account; allowance must generally also be made for the window curve of the spectrograph.

Since the ultrasoft X rays come only from a very thin surface layer of the anode, contamination of the anode surface by oxidation, by carbon from the pump oil, *etc.* can lead to considerable falsification of the spectra. Finally, the absorption in the preparation itself must be considered, since this can lead to appreciable changes in the true intensity distribution if the high-energy part of the emission band and the low-energy side of the absorption band are situated close together or even overlap.

All these apparatus effects and interfering effects were taken into account in the measurement of the $L_{2,3}$ emission band of metallic aluminum (Fig. 4) by *Neddermeyer* and *Wiech*[11]. The band shows the steep descent on the high-energy side corresponding to the Fermi energy, which is characteristic of a metal, a fine structure in addition to the maximum between 67 and 72 eV, and finally the less steep descent on the low-energy side. At about 60 eV, this descent gives way to a shallow tail, which ends at about 42 eV after a small maximum at 45 eV. The small maximum is due to the transition $L_{2,3} \rightarrow L_1$. The long tail is a secondary effect, and is due to Auger transitions in the valence band. From the fourfold magnification of the low-energy part of the band, it can be seen that a satellite about 15 eV wide, known as the plasmon satellite, is also superimposed on the tail. After subtraction of the component that is not due to direct valence electron transitions, and on the assumption that the low-energy part of the spectrum follows an $E^{1/2}$ law, the actual width of the Al $L_{2,3}$ emission band is found to be 11.05 ± 0.2 eV, which agrees satisfactorily with the theoretical value of 11.64 eV.

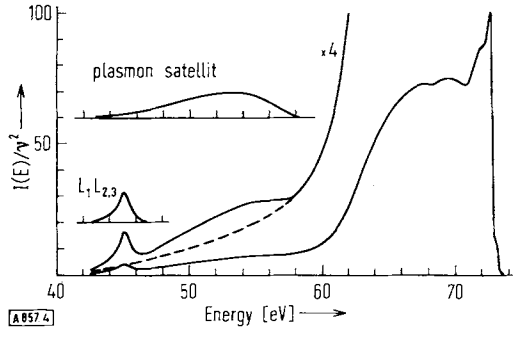


Fig. 4. $L_{2,3}$ emission band of aluminum metal. Low-energy part of the band (above) in fourfold magnification, with plasmon satellite and $L_1L_{2,3}$ line.

A comparison of the intensity distribution of an emission band with the results of theoretical calculations has only recently become possible. It has occasionally been asked whether it is in fact possible to obtain X-ray spectroscopic data that allow such a comparison. It has now been shown that the answer is yes, though possibly with certain reservations. One example, in which very satisfactory agreement was achieved between the emission bands measured in the experiment and the results of calculations, is that of elementary silicon. Figure 5a shows a plot of the state density N(E) for silicon, as determined by *Klima*[12] from energy band calculations. Because of the selection rules, the energy bands differ considerably from the N(E) curves. To allow substantially direct comparison with the bands found in the experiment, *Klima*[12] calculated the intensity distribution of the K and L emission bands using the matrix elements of the transition probability. The widths of the K and L levels and the influence of the Auger effect were also taken into account semi-empirically. Figure 5b shows the intensity distribution calculated in this way for the $L_{2,3}$ band of silicon, and Figure 5c shows the band measured by *Wiech* and *Zöpf*[13]. Figure 5d similarly shows the calculated Kβ band of silicon and the band measured by *Läuger*[6]. The measured and calculated intensity distributions agree well in both cases. The emission bands contain characteristics corresponding to the main characteristic points of the N(E) curve.

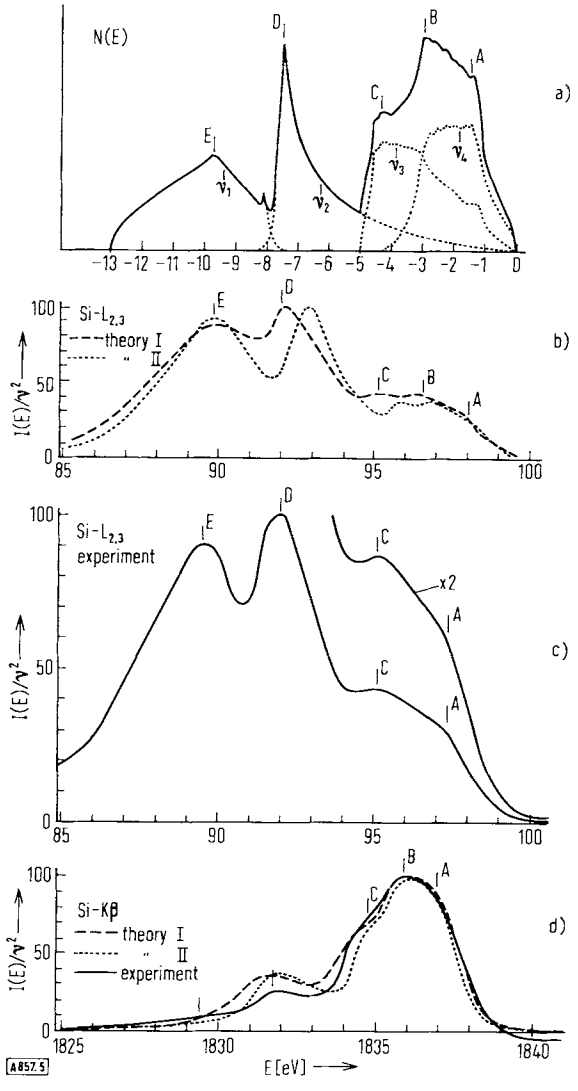


Fig. 5. a) N(E) curve for elementary silicon; b) L emission band calculated according to two different theories; c) measured L emission band; d) calculated and measured Kβ band.

The above example is probably the only one in which such good agreement is found between experiment and theory, even when the other experimental methods for the determination of band structures are included. Nevertheless, the consistency of a comprehensive body of experimental data within itself also suggests that the X-ray spectra contain the essentials of the electronic structure of a solid, at least in favorable cases.

Figure 6 shows the Kβ band of elementary silicon and the K band of carbon (diamond) together[13]. The two bands largely agree in their overall course, corresponding to the fact that silicon and diamond are crystals with homopolar bonding and with similar lattices. A different form is found for the Si Kβ band of quartz (Fig. 7), which is a crystal having a different structure, with 50% homopolar and 50% heteropolar bonding. As can be seen in Figure 7, the Si $L_{2,3}$

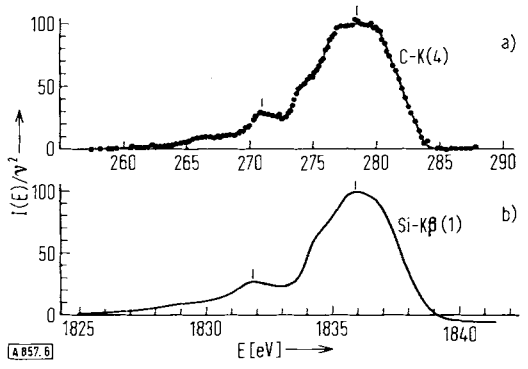


Fig. 6. a) K band of carbon (diamond) and b) Kβ band of elementary silicon.

band of SiO_2 is again similar to the P $L_{2,3}$ bands of $AlPO_4$ and Na_3PO_4[14]. The similarity is understandable, since the Si atom in SiO_2 and the P atom in $AlPO_4$ and Na_3PO_4 are tetrahedrally surrounded by four O atoms.

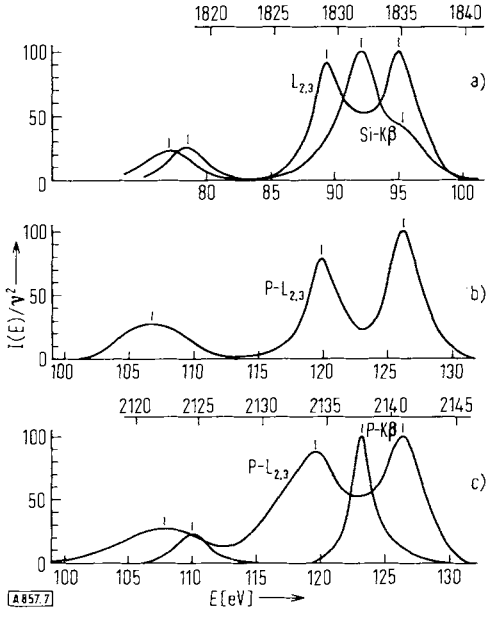


Fig. 7. a) Si Kβ and Si $L_{2,3}$ bands of quartz, b) P $L_{2,3}$ band of $AlPO_4$, and c) P Kβ and P $L_{2,3}$ bands of Na_3PO_4.

3.1.2. Alloys

X-ray studies have also been carried out on alloys. The results obtained so far are not yet entirely understandable, but they are sufficiently interesting to induce further studies. A typical example is a series of investigations by *Neddermeyer* on Mg/Al alloys[15]. Since the Mg $L_{2,3}$ and Al $L_{2,3}$ bands lie in the same wavelength region, they can be measured with the same apparatus. Both bands have characteristic structures.

According to the rigid band model, one would expect a similar valence band for both atoms, and hence the same width and shape of the emission bands of both components. However, the measurements do not yield the expected result. The widths are different, the value for the Mg band being 6—10 eV, while that for the Al band is more than 10 eV. The bands also differ in shape; the band of each component shows a characteristic change in the intensity distribution with increasing concentration of the other component in the alloy. With increasing aluminum concentration, the intensity of the low-energy part of the Mg $L_{2,3}$ band decreases (Fig. 8), while with increasing magnesium concentration, the intensity of the high-energy part of the Al $L_{2,3}$ band increases (Fig. 9). Moreover, the Fermi level, which should exhibit a large shift according to the rigid band model, is displaced measurably but only by a small amount.

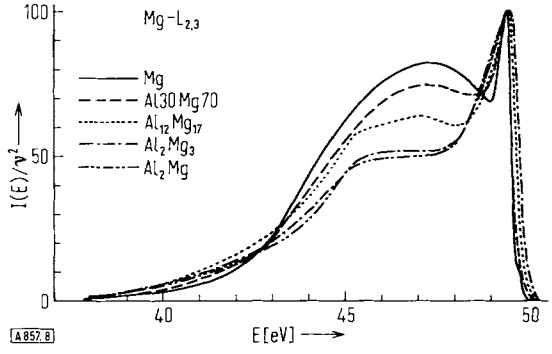


Fig. 8. Mg $L_{2,3}$ band of magnesium in various Mg/Al alloys.

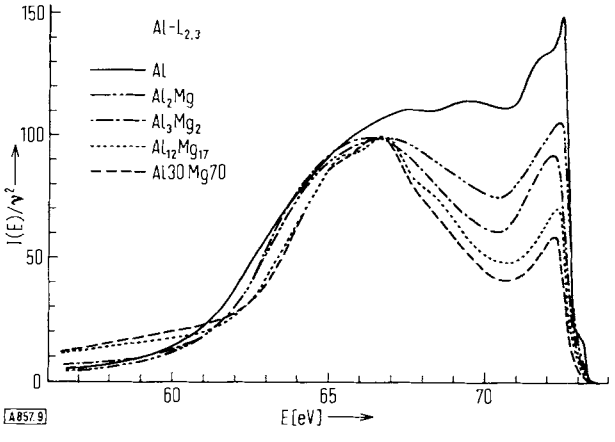


Fig. 9. Al $L_{2,3}$ band of aluminum in various Mg/Al alloys.

These findings, which will not be discussed in detail, can be qualitatively understood if the electron density is assumed to be higher in the vicinity of the trivalent aluminum atoms than in the neighborhood of the bivalent magnesium atoms, *i.e.* if one assumes that the electrons are not uniformly distributed in the crystal. However, we must await the results of further investigations; above all, it is again necessary in this case to measure the Kβ bands of the two elements as well as the L bands.

3.2. Absorption Spectra

On absorption of X rays, an electron is promoted from an inner shell into an unoccupied level; as was mentioned in Section 1, therefore the absorption spectra yield information on the unoccupied states of the energy band system. The absorption spectra are not easy to obtain in the region

of ultrasoft X rays, since very thin absorbing layers (a few hundred to a few thousand Å) are required and continuous radiation of sufficient intensity cannot be produced in this wavelength range by conventional means. Synchrotron radiation has therefore recently been used to record absorption spectra. In such spectra, one observes characteristic structures, which correspond to transitions into exciton states of the condensed phases[16]. However, investigations of this nature have so far contributed very little to the elucidation of chemical bonding in solids.

The same is true of the extended or Kronig fine structure of the absorption spectra; this is the name given to the fluctuations of the absorption coefficient that appear on the high-energy side of many K and L edges and extend over a range of a few hundred electron volts.

On the other hand, the fine structure close to the edge, which is also known as Kossel fine structure, is of interest to the chemist. The following example shows the type of question that can be answered by investigation of this edge fine structure. The K absorption edge of transition elements exhibits a step, which corresponds to the transition of the photoelectron produced by the absorbed X ray into the unfilled 3d states (Fig. 10). Nickel charged with hydrogen does not exhibit this step, and it follows that the 3d vacancies are filled by the electrons given up by the dissolved hydrogen[17]. This explanation is supported by the fact that nickel charged with hydrogen is no longer ferromagnetic, though the disappearance of the ferromagnetism could also be due to expansion of the lattice, since the exchange integral is very strongly dependent on the lattice constant. After desorption, the step reappears in the absorption edge in the same form, and the metal has also regained its ferromagnetism.

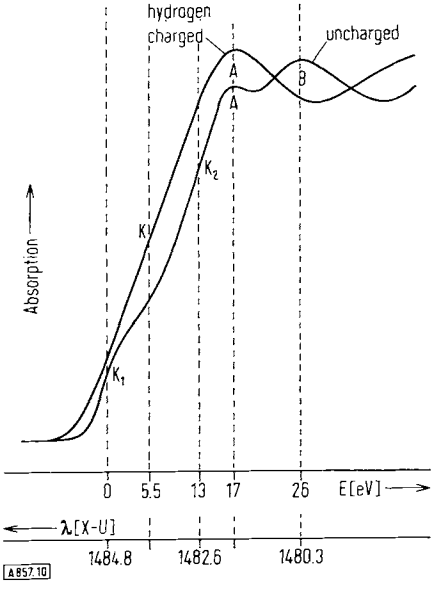


Fig. 10. Ni K absorption edge for pure and hydrogen-charged nickel.

However, the fine structure close to the edge is in general probably less important for problems of the solid state than for the study of chemical bonding in molecules and complexes. The investigation of edge fine structure for the transition elements is particularly promising for coordination chemistry, as has been shown by a series of investigations[18].

In this discussion of absorption spectra and their use, reference must also be made to an important method for the investigation of the structure of the unoccupied states of a solid, which does not fall strictly within the scope of X-ray spectroscopy, but is closely related to it. This is the isochromat method[19], in which an isochromat of the bremsstrahlung produced in the metal in question is recorded. The isochromat intensity is proportional to the state density in the unoccupied part of the conduction band. The method has the advantage that the resolution is not limited by the width of an inner level, and it can therefore also be applied to metals with high atomic numbers.

4. Investigations on Free Molecules

There have been few reports on investigations on the relation between the X-ray emission spectrum and chemical bonding in gaseous compounds, though such investigations may be expected to make valuable contributions to molecular physics. A brief account of X-ray spectroscopic studies on the electronic structure of free molecules may be justified at this point, since the results may also help with the interpretation of the spectra of solids.

4.1. K Spectrum of Chlorine in Gaseous Compounds

With a specially constructed tube, *Gilberg*[20] was able to obtain the Kα and Kβ spectra of chlorine in a number of organic chlorine compounds, molecular chlorine, hydrogen chloride, and phosgene.

It was found that the displacements of the Kα lines do not follow the rules found for the other elements of the 3rd period, and also for solid compounds of chlorine. The reason for this surprising behavior probably lies in the fact that the displacements caused by chemical bonding, which should not be very large, are masked by the influence of molecular vibrations. The differences in the line widths also indicate that the Kα lines are influenced by molecular vibrations.

The Kβ spectrum of chlorine consists of several strongly overlapping lines. The widths of the lines are given by the natural width of the K level. On the basis of optical and

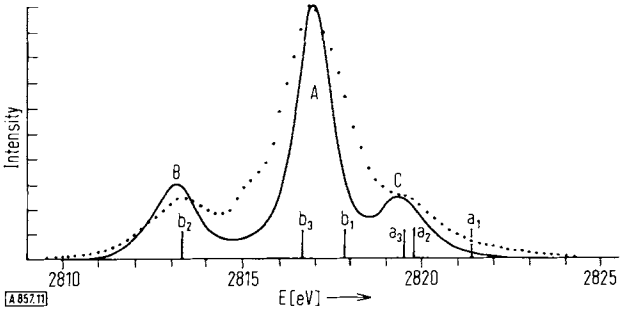


Fig. 11. Cl Kβ spectrum of HCl; the vertical lines a_1 to b_3 denote the positions of calculated satellites.

β-spectroscopic data, as well as of *ab initio* calculations by *Schrenk*[21], *Gilberg* was able to assign the lines to certain molecular orbitals. Figure 11 shows the Cl Kβ spectrum of HCl. The line A is assigned to the highest π orbital of the HCl molecule, which accepts the two lone pairs of electrons of the chlorine that are not involved in the bond. The line B corresponds to the highest σ orbital, which is very strongly involved in the bond. The line C is a satellite due to doubly ionized Cl atoms[21].

For methyl chloride, the spectrum consists of two lines (Fig. 12), of which the line A corresponds to the highest e orbital, which, as in HCl, again accepts the non-bonding electron pairs of chlorine, while the line B corresponds to the highest a_1 orbital, which is strongly involved in the C—Cl bond. The interpretation of this spectrum was possible through *ab initio* calculations by *Schmittinger*[22].

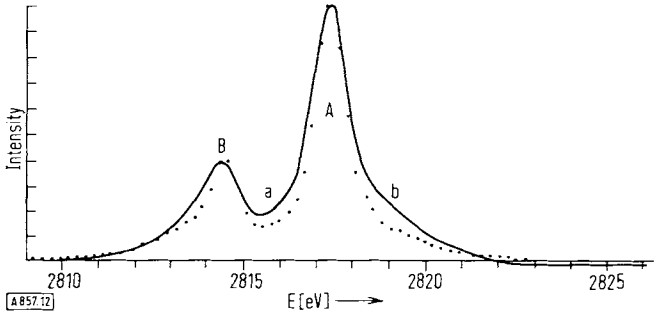


Fig. 12. Cl Kβ spectrum of CH_3Cl.

Figure 13 shows the spectra of the first four *n*-alkane derivatives. By analogy with the spectra of HCl and CH_3Cl, it is to be expected that the line A, which appears in the same position in all the spectra, is attributable to the orbitals of the lone pairs of electrons on the Cl atom, and the line B to the bonding orbitals.

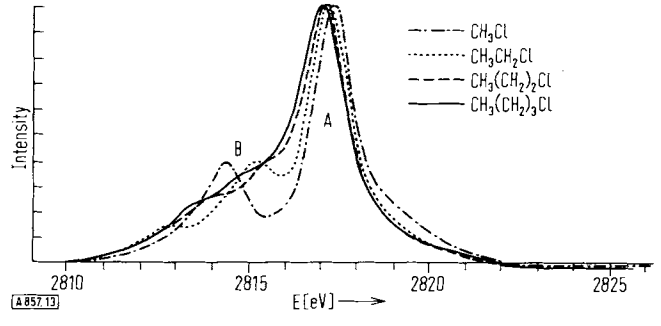


Fig. 13. Cl Kβ spectra of alkyl chlorides.

If the chlorine atoms are bonded to carbon atoms that participate in double bonds, the Cl Kβ spectrum contains five characteristic lines (Fig. 14). The interpretation of these lines is not yet complete, but it is probable that the line A again corresponds to the orbitals of the line pairs of electrons on the chlorine, and the line A′ to the orbital that effects the π bonding of the C=C double bond.

The Kβ spectrum of chlorine in chlorobenzene (Fig. 15) is very similar to the spectra of the ethylene derivatives. It again contains five lines, of which A is attributable to the

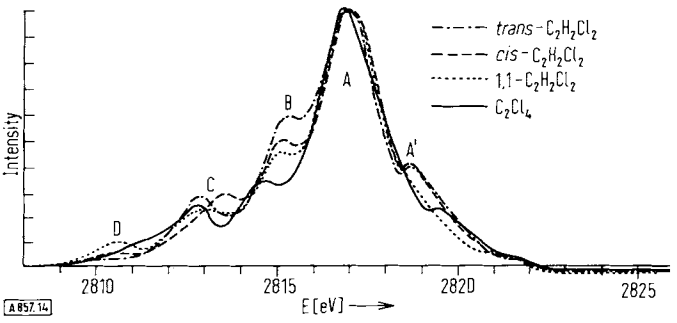


Fig. 14. Cl Kβ spectra of chlorine derivatives of ethylene.

lone pairs of electrons on the chlorine and A′ to the π electrons of the benzene ring. This similarity of the spectra suggests a similarity of the states of the valence electrons of the carbon atoms in the ethylene derivatives and in chlorobenzene.

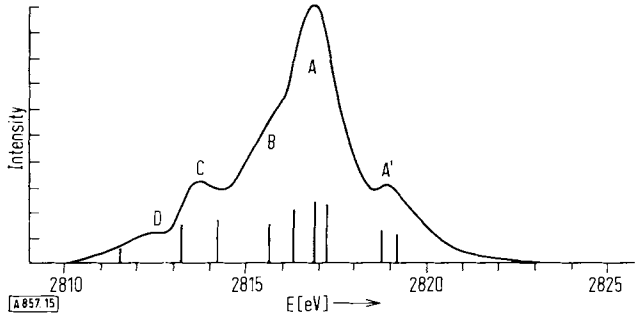


Fig. 15. Cl Kβ spectrum of C_6H_5Cl.

4.2. Ab Initio Calculations for Simple Molecules

The investigations on gaseous substances are particularly interesting, since free molecules are the simplest systems in which chemical bonding can be studied. Moreover, through the use of large computers, it is now possible to calculate the X-ray levels of small molecules and the corresponding wave functions in the SCF approximation.

Schrenk, whose calculations were mentioned in Section 4.1, has written an SCF program on the basis of the Roothaan-Hall method for molecules with closed shells or with one vacancy in a shell. The program is therefore suitable for the calculation of X-ray states in molecules in the adiabatic approximation; the same states can also be calculated by the Koopmans theorem.

The calculation of the ionization stages S, S^{2+}, S^{4+}, and S^{6+} for the sulfur atom, gave values that agree well with those of *Gianturco* and *Coulson*[23]. The X-ray levels of the molecules H_2, SO_2, HCl, and Cl_2 were also calculated for the first time by the adiabatic method, which gives better values for the bond energies than the Koopmans theorem. The calculated bond energies agree well with the values found in electronic spectroscopy.

The special value of the work is probably that it deepens our understanding of the change in the X-ray levels on chemical involvement of an atom. In agreement with the

experiment, it is found that the X-ray levels move to higher energies with increasing ionization of the atom. The inner orbitals are practically unchanged on ionization in the outermost shell. The displacement of the X-ray levels is mainly due to the changed interaction of the corresponding orbitals with the outermost shell.

The displacement of the X-ray levels on incorporation of an atom into a molecule is due to two effects. On the one hand, the ionization energy is increased by interaction of the orbital with the newly added atomic nuclei, while on the other it is decreased by interaction of the orbital with the modified valence electron shell and the newly added electrons. Depending on which of these effects predominates, the ionization energy will increase as in SO_2, or decrease, as in H_2S.

Since the satellites due to double ionization appear with considerable intensity in the X-ray spectra of molecules, it should be emphasized again that satellites can also be approximately calculated, as was indicated in Section 4.1.

Received: March 29, 1971 [A 857 IE]
German version: Angew. Chem. *84*, 51 (1972)
Translated by Express Translation Service, London

[1] *O. Stelling*, Dissertation, University of Lund 1923, and numerous publications, especially in Z. Physik. Chem. 1925—1934.

[2] *G. v. Hevesy, J. Böhm*, and *A. Faessler*, Z. Physik *63*, 74 (1930); *E. Alexander* and *A. Faessler*, ibid. *68*, 260 (1931).

[3] *A. Faessler*, Z. Physik *72*, 734 (1931).

[4] *A. Faessler* and *M. Goehring*, Naturwissenschaften *39*, 169 (1952).

[5] *M. Fichter*, Dissertation, Universität München 1966.

[6] *K. Läuger*, Dissertation, Universität München 1968; J. Phys. Chem. Solids *32*, 609 (1971)

[7] *H. Krämer*, Dissertation, Universität München 1960.

[8] *A. Meisel* and *A. Szargan*, Z. Physik. Chem. (Leipzig) *233*, 136 (1968).

[9] *W. Heinle*, Diplomarbeit, Universität München 1965.

[10] *O. J. Sumbaev*, Soviet. Phys. JETP *30*, 927 (1970).

[11] *H. Neddermeyer* and *G. Wiech*, Phys. Lett. *A 31*, 17 (1970).

[12] *J. Klima*, J. Phys. C—Solid State Phys. *3*, 70 (1970).

[13] *G. Wiech* and *E. Zöpf*, Proc. 3rd IMR Symp. Electronic Density of States, Nat. Bur. Std. (U.S.) Spec. Publ. 323 (1970), in press.

[14] *G. Wiech*, Z. Physik *216*, 472 (1968).

[15] *H. Neddermeyer*, Proc. 3rd IMR Symp. Electronic Density of States, Nat. Bur. Std. (U.S.) Spec. Publ. 323 (1970), in press.

[16] *H. Haensel, G. Keitel, B. Sonntag, C. Kunz*, and *P. Schreiber*, Phys. Stat. Sol. (a) *2*, 85 (1970).

[17] *A. Faessler* and *R. Schmid*, Z. Physik *190*, 10 (1966).

[18] *D. Heintz*, Dissertation, Universität München 1969.

[19] *K. Ulmer*, lecture, Summer school "Superconductivity" in Steibis 1967.

[20] *E. Gilberg*, Z. Physik *236*, 21 (1970).

[21] *H. Schrenk*, Dissertation, Universität München 1969.

[22] *P. Schmittinger*, Dissertation, Technische Hochschule München 1968.

[23] *F. A. Gianturco* and *C. A. Coulson*, Mol. Phys. *14*, 223 (1968).

COMMUNICATIONS

Structure of $(CH_3OBC_5H_5)_2Co$, a Derivative of the Aromatic Hydridoborinate Anion[**]

By *Gottfried Huttner* and *Bernhard Krieg*[*]

Derivatives of the hydridoborinate ion $[HBC_5H_5]^-$, which is isoelectronic with benzene, were first stabilized as π-ligands in cobalt complexes by *Herberich et al.*[1]. Recently the synthesis of the free 1-phenyl-1-borabenzene anion has also been reported[2]. We have studied the structure of bis(methoxoborinato)cobalt in order to determine whether the ligand is bonded to the metal *via* all six ring atoms or whether the boron atom, like the methylene group in π-cyclohexadienyl-metal complexes, does not participate in the metal-ligand bond.

Bis(methoxoborinato)cobalt[3], $[(CH_3OBC_5H_5)_2Co]$ *(1)*, crystallizes in the monoclinic space group $P2_1/c$ with $a=6.76$, $b=8.14$, $c=11.61$ Å; $\beta=99.73°$; $Z=2$; $d_{exp}=1.444$[4], $d_{calc}=1.440$ g cm^{-3}. 3715 non-zero X-ray diffraction intensities were collected with a two-circle diffractometer for two different crystals. After Lorentz, polarization, and absorption corrections the data were reduced to a common scale ($R_1=3.0\%$). There remained 932 independent, non-zero structure factors. The structure was solved by Fourier methods and refined by the method of least squares to $R_1=0.044$. All hydrogen atoms were located and their parameters were refined. The result of the analysis is shown in the Figure and the most important inner-molecular distances and angles are given in the Table.

The crystallographic symmetry of the molecule is C_i ($\bar{1}$) since the Co atom occupies a center of inversion in space group $P2_1/c$. The six-membered ring has mirror symmetry (mirror plane through C3, B, and Co) within the limits of error; it is not strictly planar, the ring atoms lying alternately above and below the best plane defined by them. The individual deviations are significant but only small in magnitude (0.02 Å on average). The resulting chair conformation is characterized by a mean torsion angle of 5.3° (see Table). The C—C distances in the ring are all approximately equal and lie in a range (1.400 Å on average) that is typical of the delocalized system of complex-bonded cyclohexadienyl ligands (1.401 Å in tricarbonyl-π-cyclohexadienylmanganese[5]). In contrast to cyclohexadienyl complexes, in which the $BOCH_3$ group is replaced by a methylene group, the boron atom in *(1)* does not project out of the best plane of the ring by any more than the other ring atoms. The angle between the best plane defined by the atoms C1, C2,...C5 and the plane C1—B—C5 is only

[*] Dr. G. Huttner and Dipl.-Chem. B. Krieg
Anorganisch-chemisches Laboratorium
der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[**] Transition metal complexes of cyclic π-ligands, Part 2. We wish to thank the Bayerische Akademie der Wissenschaften for computer time and the Deutsche Forschungsgemeinschaft for their support of this work.—Part 1: *G. Huttner* and *B. Krieg*, Angew. Chem. *83*, 541 (1971); Angew. Chem. internat. Edit. *10*, 512 (1971).

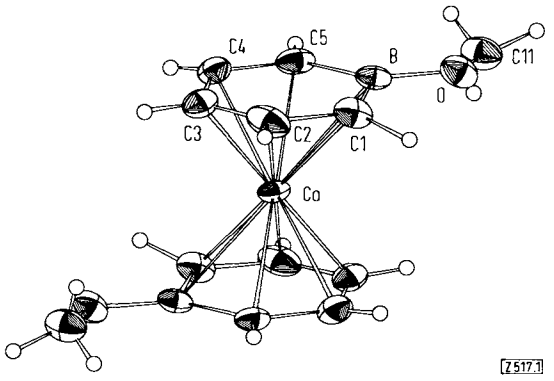


Fig. Molecular structure of bis(methoxoborinato)cobalt.

Table. Interatomic distances and angles in bis(methoxoborinato)cobalt.

Distances (Å)			
B –C(1)	1.525±0.007	B –(C(5)	1.520±0.008
C(1)–C(2)	1.394±0.009	C(5)–C(4)	1.386±0.010
C(2)–C(3)	1.418±0.009	C(4)–C(3)	1.402±0.010
B –O	1.395±0.007	O –C(11)	1.410±0.009
Co –C(1)	2.248±0.005	Co –C(5)	2.232±0.005
Co –C(2)	2.164±0.006	Co –C(4)	2.141±0.006
Co –C(3)	2.057±0.006	Co –B	2.348±0.007
Angles (°)			
C(1)–B–C(5)	114.8±0.5	C(1)–B–O	118.8±0.5
C(5)–B–O	126.2±0.5	B –O–C(11)	121.2±0.5
Torsion angles (°)			
B –C(5)–C(4)–C(3)	–5.6	C(5)–C(4)–C(3)–C(2)	6.1
C(4)–C(3)–C(2)–C(1)	–5.9	C(3)–C(2)–C(1)–B	5.2
C(2)–C(1)–B –C(5)	–4.4	C(1)–B –C(5)–C(4)	4.5

2.3°; in cyclohexadienyl-metal complexes the corresponding angle is about 40°[6]. It therefore appears that the boron atom, in contrast to the methylene group in cyclohexadienyl complexes, participates in metal-ligand bonding.

The cobalt-ligand bond lengths vary systematically: The distance from the metal to the "central" carbon atom Co—C3 (2.057±0.006 Å) is the shortest, the bonds to the atoms C2 and C4 (mean value 2.153±0.011 Å) are considerably longer but still shorter than the distance to the "terminal" carbon atoms C1 and C5 (mean value 2.240 ±0.008 Å). This pattern of distances arises because the metal atom is displaced away from the boron atom toward the carbon atom C3. Added to this effect is the slight puckering of the ring. The cobalt-boron distance (2.348 ±0.008 Å) is the longest metal-ring distance in the complex. Although considerably longer than the Co—B distances in carborane complexes[7] it is certainly still within the range of a strong cobalt-boron interaction and thus indicates participation of the boron in complex bonding.

The distance between the boron and the ring carbon atoms C1 and C5 has a mean value of 1.523±0.008 Å and is therefore only slightly shorter than a B_{sp^2}—C_{sp^2} single bond[8]. The B—O distance of 1.395±0.007 Å corresponds to the bond length of 1.37±0.02 Å that is typical for trigonal borates[9], thus indicating considerable double bond character.

The bonding in complex *(1)* is not necessarily typical for the complexing behavior of a borinato ligand: The methoxo substituent on the boron atom could exert a significant influence on the structure; the electronic configuration of the central atom exceeds the inert gas configuration by one electron in the paramagnetic complex studied. This electron could have a weakening effect on the bonding. Further structural studies are in progress to clarify these questions.

Received: August 25, 1971 [Z 517 IE]
German version: Angew. Chem. *84*, 29 (1972)

[1] *G. E. Herberich, G. Greiss,* and *H. F. Heil,* Angew. Chem. *82*, 838 (1970); Angew. Chem. internat. Edit. *9*, 805 (1970).

[2] *A. J. Ashe* and *P. Shu,* J. Amer. Chem. Soc. *93*, 1804 (1971).

[3] *G. E. Herberich, G. Greiss, H. F. Heil,* and *J. Müller,* Chem. Commun. 1328, *1971*; single crystals were kindly provided by Dipl.-Chem. *H. F. Heil*, München.

[4] Measurements by Dipl.-Chem. *H. F. Heil.*

[5] *M. R. Churchill* and *F. R. Scholer,* Inorg. Chem. *8*, 1950 (1969).

[6] A review is to be found in ref. [5].

[7] *D. St. Clair, A. Zalkin,* and *D. H. Templeton,* Inorg. Chem. *8*, 2080 (1969).

[8] *H. Hess,* Acta Crystallogr. *B 25*, 2334 (1969), found a value of 1.583 Å for the B_{sp^2}—C_{sp^3} single bond length in 1,3,5-tris(dimethylamino)-1,3,5-triboracyclohexane. The difference of 0.03 Å between the covalent radii of C_{sp^3} and C_{sp^2} leads to an estimate of 1.55 Å for a B_{sp^2}—C_{sp^2} single bond length which is in good agreement with the B—C distance in *p*-bromophenylboronic acid of 1.54 Å: *Z. V. Zvonkova* and *P. Gluskova,* Kristallografia, USSR, *3*, 559 (1958) (Engl. Edit.: Crystallography *3*, 564 (1958)).

[9] *V. F. Ross* and *J. O. Edwards* in *E. L. Mutterties:* The Chemistry of Boron and its Compounds. Wiley, New York 1967, p. 196.

$Ge_{38}P_8I_8$ and $Ge_{38}As_8I_8$, a New Class of Compounds with Clathrate Structure

By *Hans-Georg von Schnering* and *Heinz Menke*[*]

Preparations of germanium phosphides under the conditions of chemical transport reactions with I_2 as transport vehicle[1] yielded small amounts of cubic crystals whose X-ray structure analysis showed them to be $Ge_{38}P_8I_8$.

In order to prepare pure samples of the isotypic compounds $Ge_{38}P_8I_8$ *(1)* and $Ge_{38}As_8I_8$ *(2)*, stoichiometric amounts of the elements are heated in a quartz ampoule, the starting materials being kept at 900°C. After a few days the products *(1)* and *(2)* respectively deposit as well formed crystals in the colder part of the ampoule (800°C). The hard and brittle crystals, which have a silvery metallic sheen, are stable to attack by water and dilute acids and alkalis; they rapidly dissolve, however, in oxidizing alkaline melts. The synthesis is favored by a small excess of iodine because slight amounts of GeI_4 are invariably formed (readily removed with H_2O). Otherwise crystals are obtained which have a yellow, red, green, or blue tint.

In a vacuum, compound *(1)* is degraded to germanium between 550 and 650°C. No information could be obtained about possible intermediates such as germanium phosphides[2]. In the mass spectrum the fragments I^+, P_2^+, and P_4^+ are not recorded at temperatures below 440°C[3].

Compounds *(1)* and *(2)* form cubic crystals of space group $P\bar{4}3n - T_d^4$ with $a = 10.507$ and 10.611 Å, respectively. The atoms of $Ge_{38}P_8I_8$ occupy the following positions: 24 Ge(1) in 24(i) with $x = -0.0027$, $y = 0.1190$, $z = 0.3069$; 6 Ge(2) in 6(c); 8 Ge(3) in 8(e) with $x = 0.1841$; 8 P in 8(e) with $x = 0.8148$; 6 I(1) in 6(d) and 2 I(2) in 2(a) [225

[*] Prof. Dr. H.-G. v. Schnering and H. Menke
Anorganisch-chemisches Institut der Universität
44 Münster, Gievenbecker Weg 9 (Germany)

reflections *hkl*, diffractometer data, $Mo_{K\alpha}$ radiation, $R = 0.068$]. The 38 Ge atoms and the 8 P atoms together form a tetrahedral skeleton having (6+2) large cavities that are occupied by I atoms. The structure is thus completely analogous to those of the gas hydrates of type $Xe \cdot 5.75\,H_2O\,[Xe_8(H_2O)_{46}]$ or the correspondingly built phases K_8Ge_{46}, *etc.*[4] in which the cavities are occupied by Xe and K respectively. The Ge and P atoms are arranged regularly in the E_{46} skeleton: Every P and every Ge(2) is bound to four Ge neighbors, every Ge(1) and Ge(3) to three Ge and one P neighbors (Ge—Ge = 2.45 – 2.50 Å; Ge—P = 2.38 – 2.40 Å). The distances to the I atoms are 3.57 – 3.90 Å for I(1) and 3.35 – 3.46 Å for I(2). On the basis of their tetrahedral coordination and electron balance the P atoms can be regarded as phosphonium ions P^+ and the two compounds *(1)* and *(2)* characterized by the formulas $Ge_{38}P_8^+I_8^-$ and $Ge_{38}As_8^+I_8^-$ (compare also the large distances between the iodine atoms). If these views are correct then the compounds should be semiconductors. Conductivity measurements[5] and attempts to extend this novel class of compounds by variation of the main group elements are currently in progress.

Received: August 30, 1971 [Z 518 IE]
German version: Angew. Chem. *84*, 30 (1972)

[1] *H. Schäfer:* Chemische Transportreaktionen. Verlag Chemie, Weinheim 1962; Academic Press, New York 1964.

[2] Experiments by *C. Brendel*, Münster.

[3] Experiments by *K. Rinke, M. Binnewies*, and *H. Rabeneck*, Münster.

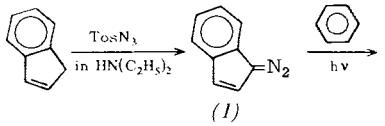
[4] *J. Gallmeier, H. Schäfer*, and *A. Weiss*, Z. Naturforsch. *24b*, 665 (1969).

[5] Jointly with *A. Rabenau*, Stuttgart.

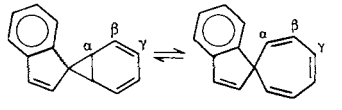
1-Diazoindene and Spiro[indene-1,7′-norcaradiene]

By *Dieter Rewicki* and *Christian Tuchscherer*[*]

Unlike 5-diazocyclopentadiene[1] and 9-diazofluorene[2], 1-diazoindene *(1)* has not hitherto been isolated. We have now prepared *(1)* by reaction of tosyl azide with indene in diethylamine[3]. Diazoindene is stable indefinitely below 0 °C and can be chromatographed and distilled without decomposition.



(1)



(2a) *(2b)*

Photolysis of diazoindene *(1)* in benzene gives a 45% yield [based on reacted *(1)*] of spiro[indene-1,7′-norcaradiene] *(2a)* which is in rapid equilibrium with spiro[2,4,6-cycloheptatriene-1,1′-indene] *(2b)*. The valence tautomers *(2a)* ⇌ *(2b)* have comparable thermal stabilities with the analogous fluorene derivatives[4]: They are transformed into isomeric hydrocarbons only after several hours' heating at 100 °C.

The NMR spectrum in CS_2 at 38 °C exhibits peaks at $\tau = 2.90$ (4 H/m); 3.49 (1 H/d), $J = 5.4$ Hz; 3.72 (4 H/m); 3.90 (1 H/d), $J = 5.4$ Hz; 5.88 (2 H/m). The peaks at $\tau = 2.90$, 3.49, and 3.90 are due to the aromatic protons and the protons on C-3 and C-2 in the indene part of the molecule. The signals at $\tau = 3.72$ and 5.88 are the time-averaged signals of the β,γ-protons and the α-protons, respectively.

The position of the α-proton signal itself evidences a fluctuating norcaradiene-cycloheptatriene system[5]. The multiplet at $\tau = 5.88$ is shifted downfield by a rise in temperature and upfield by drop in temperature, as expected for a low-energy norcaradiene component. Marked broadening is observed, above all for the signals at $\tau = 5.88$ and 3.72, below −80 °C; at −105 °C the signal at highest field is only just recognizable. The individual isomer spectra, which could provide information about the stereochemistry of *(2a)*, could not be observed.

The position of the averaged α-proton peak ($\tau = 5.88$) at room temperature and the expected position of the α-proton signals in *(2a)* and *(2b)* ($\tau = 4.8$ and 7.0)[4] afford a ratio of *ca.* 1:1 for the valence tautomers. In contrast, the equilibrium lies predominantly on the norcaradiene side[6] in the corresponding cyclopentadiene system at room temperature, and preponderatingly on the cycloheptatriene side in the fluorene system[4]. The preference for the cycloheptatriene form with increasing degree of ring fusion can be explained in terms of likewise increasing steric hindrance in the norcaradiene form.

1-Diazoindene (1):

A mixture of indene (58 g) and diethylamine (100 ml) are treated at 0 °C with tosyl azide (98.5 g) and allowed to stand for *ca.* 70 h at 0 °C. To the deep red mixture is added water (250 ml) and the mixture is extracted with light petroleum (40—80 °C) until the extract is only yellow. The combined extracts are washed with water (5 ×), dried over Na_2SO_4, and concentrated in vacuum. The resulting deep red liquid is fractionally distilled under N_2 in 50-ml portions over a short Vigreux column: At a bath temperature of 50—70 °C unreacted indene distills over under oil-pump vacuum, and on evacuation with a Hg-diffusion pump diazoindene *(1)* (b.p. 80—95 °C) is collected in the receiver. (Caution! At a bath temperature in excess of 120 °C the contents of the distillation flask, predominately tosyl azide, decompose explosively.) Distillation over a 10-cm Vigreux column furnished 10.3 g of *(1)* as a dark-red oil of b.p. 67 °C/10^{-3} torr; yellow-red crystals of m.p. 23—25 °C (from petroleum ether), yield 15%. NMR (CCl_4): $\tau = 2.1$—3.1 (4 H/m); 3.23 (1 H/d), $J = 5.5$ Hz; 3.78 (1 H/d); $J = 5.5$ Hz. IR (in CCl_4 and CS_2): 3660, 3075 (w), 2068 (vs), 1469 (w), 1420 (s), 1380, 1307, 1212, 1207, 1088 (w), 761, 750, 702 cm^{-1} (m). UV/visible (in *n*-heptane): 490 (1.27), 328 (4.066), 265 (4.261) nm (log ε). MW: 142 (determined by mass spectrometry).

Spiro[indene-1,7′-norcaradiene] ⇌ spiro[2,4,6-cycloheptatriene-1,1′-indene] (2a) ⇌ (2b):

Diazoindene *(1)* (6.6 g) in anhydrous benzene (300 ml) is irradiated in a quartz recycling apparatus for 20 h with a 150-W high-pressure mercury arc lamp. During this period 60% of the calculated amount of N_2 is evolved. The benzene is evaporated off under vacuum and the residue chromato-

[*] Prof. Dr. D. Rewicki and Ch. Tuchscherer
Institut für Organische Chemie der Freien Universität
1 Berlin 33, Thielallee 63/67 (Germany)

graphed in light petroleum (40—60 °C) on Al_2O_3 (Woelm, basic, activity grade III). *(1)* and *(2a)*⇌*(2b)* are eluted almost simultaneously [total amount 5.0 g, composition as determined by NMR: 2.6 g *(1)* and 2.4 g *(2a)*⇌*(2b)* [45% yield based on reacted *(1)*]. Fractions containing more than 40% *(2a)*⇌*(2b)* are combined, the solvent evaporated off, and the residue recrystallized from *n*-pentane: 1.2 g of colorless crystals, m.p. 76—78 °C (after repeated recrystallization from *n*-pentane). 0.7 g of *(1)* could be recovered. IR (in CCl_4 and CS_2): 3080, 3055, 3030 (m), 1615 (w), 1471, 1460 (m), 1090, 1028, 1008 (w), 940 (m), 765, 742, 725 (s) cm^{-1}. UV/visible (in *n*-heptane): 303 (3.568), 290 (3.668), 257 (4.118) nm ($\log \varepsilon$). MW: 192 (determined by mass spectrometry).

Received: August 30, 1971 [Z 520 IE]
German version: Angew. Chem. *84*, 31 (1972)

[1] *W. von E. Doering* and *C. H. DePuy*, J. Amer. Chem. Soc. *75*, 5955 (1963).

[2] *H. Staudinger* and *O. Kupfer*, Ber. Dtsch. Chem. Ges. *44*, 2197 (1911).

[3] *T. Weil* and *M. Cais*, J. Org. Chem. *28*, 2472 (1963).

[4] *H. Dürr* and *H. Kober*, Angew. Chem. *83*, 362 (1971); Angew. Chem. internat. Edit. *10*, 342 (1971).

[5] *H. Günther* and *H. Görlitz*, Tetrahedron *25*, 4467 (1969).

[6] *D. Schönleber*, Chem. Ber. *102*, 1789 (1969).

Reaction of Phenyl Radicals with Methanol

By *Eckehard König*, *Hans Musso*, and *Uwe-I. Záhorszky*[*]

It has hitherto been assumed that phenyl radicals abstract H atoms only from the α-C—H bonds of alcohols since the O—H bonds are more stable by at least 10 kcal[1,2], although *Bartlett* and *Nozaki*[3] have deduced a slight amount of alkoxyl radical formation from analysis of the decomposition products of dibenzoyl peroxide in ethanol, and the studies by *Melander*[1] are surrounded by a 10% error in this respect. In order to elucidate the mechanism of reduction of diazonium salts with complex hydrides[4–6] it was necessary for us to know the ratio in which phenyl radicals abstract hydrogen from the C—H and O—H bonds of methanol. We therefore decomposed nitrosoacetanilide, phenylazotriphenylmethane, and dibenzoyl peroxide in variously deuterated samples of methanol with almost complete exclusion of oxygen. The yields of benzene were determined by gas chromatography (±2%) and the degree of deuteration by mass spectrometry (±0.3%).

Table. (Yields) and degrees of deuteration of benzene (both given as percentages).

Source of radicals	Conc. (mol/l)	CH_3OH	CH_3OD	CD_3OH	CD_3OD
C_6H_5—N—$COCH_3$		(53)	(45)	(15)	(7)
NO	0.9	0.0	0.6	52	79
C_6H_6—N=N—$C(C_6H_5)_3$		(68)	(60)	(32)	(24)
	0.12	0.0	0.4	45	74
$(C_6H_5CO_2)_2$		(32)	(30)	(25)	(22)
	0.45	0.0	0.7	48	86

The data in the Table show that the degree of deuteration of the benzene formed in CH_3OD was about 1% while comparable figures for CD_3OH and CD_3OD were about 50% and about 80%, respectively, for phenyl radicals of different origin; the degree of deuteration was found to increase with increasing dilution[7].

Paying due attention to the yields and to isotope effects ($k_{C-H}/k_{C-D}=6-8$, $k_{O-H}/k_{O-D}=5-8$)[8] we have calculated the ratio in which phenyl radicals abstract H atoms from the CH_3 and OH groups as 9:1; thus a C—H bond reacts only three times as fast as the O—H bond. Consideration of the bond energies alone would suggest a much lower tendency for loss of hydrogen from the O—H group (C—H 95.5, O—H 103 kcal/mol[9]; 92 and 102 kcal/mol, resp.[10]). It therefore appears that only a small part of the difference in bond energies is effective in the transition states of the two competing reactions. Phenyl radicals therefore react more specifically with methanol in solution than do methyl radicals in the gas phase ($k_{C-H}/k_{O-H}=1.2$)[10].

Received: September 1, 1971 [Z 521a IE]
German version: Angew. Chem. *84*, 33 (1972)

[1] *L. Melander*: Isotope Effects on Reaction Rates. Ronald Press, New York 1960, p. 105; Ark. Kemi *3*, 525 (1951); *C. Walling*: Free Radicals in Solution. Wiley, New York 1957, p. 480.

[2] *D. F. DeTar* and *M. N. Turetzky*, J. Amer. Chem. Soc. *77*, 1745 (1955).

[3] *P. D. Bartlett* and *K. Nozaki*, J. Amer. Chem. Soc. *69*, 2299 (1947).

[4] *M. Bloch*, *H. Musso*, and *U.-I. Záhorszky*, Angew. Chem. *81*, 392 (1969); Angew. Chem. internat. Edit. *8*, 370 (1969).

[5] *E. König*, *H. Musso*, and *U.-I. Záhorszky*, Angew. Chem. *84*, 33 (1972); Angew. Chem. internat. Edit. *11*, 45 (1972).

[6] See also *J. B. Hendrickson*, J. Amer. Chem. Soc. *83*, 1251 (1961); *A. Rieker*, *P. Niederer*, and *D. Leibfritz*, Tetrahedron Lett. *1969*, 4287; *C. E. McKenna* and *T. G. Traylor*, J. Amer. Chem. Soc. *93*, 2313 (1971).

[7] The somewhat differing degrees of deuteration are due, on the one hand, to differing concentrations in some cases, and to varying H and H_2O contents of the samples used (deuteration: CH_3OD 99%, CD_3OH 98%, CD_3OD 99%) on the other. And in addition the differences in the complicated decomposition mechanisms also account for the differences in yields.

[8] Determined from the decomposition of nitrosoacetanilide and phenyldiazonium tetrafluoroborate [5]. These values will have to be determined more accurately by another method.

[9] From the gas phase reaction with iodine; *F. R. Cruickshank* and *S. W. Benson*, J. Phys. Chem. *73*, 733 (1969).

[10] *P. Gray*, *A. A. Herold*, and *A. Jones*, Chem. Rev. *71*, 247 (1971).

Phenyldiimine in the Reduction of Diazonium Salts by Sodium Tetrahydridoborate

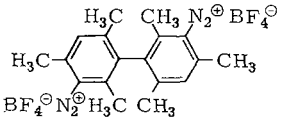
By *Eckehard König*, *Hans Musso*, and *Uwe-I. Záhorszky*[*]

It has been shown that the hydrogen incorporated into the product of reduction of diazotized diaminobimesityl *(1)* to bimesityl by $NaBH_4$ in methanol does not originate from the hydride but from the OH group and to a slight extent from the CH_3 group of the solvent. This indicates that hydride ions attack the terminal nitrogen of the diazo group, as has also been established for many nucleophiles ($CN^{\ominus}$, $N_3^{\ominus}$, $OH^{\ominus}$, *etc.*), and that a phenyldiimine is formed as an unstable intermediate[1].

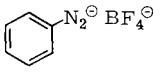
Since this mechanism has recently also been studied by other workers and discussed in some cases in different terms[2–4] we here wish to report experiments designed to demonstrate the presence of phenyldiimine for the simplest example of this reaction.

[*] Dipl.-Chem. E. König, Prof. Dr. H. Musso, and Dr. U.-I. Záhorszky
Institut für Organische Chemie der Universität
75 Karlsruhe, Richard-Willstätter-Allee (Germany)

[*] Dipl.-Chem. E. König, Prof. Dr. H. Musso, and Dr. U.-I. Záhorszky
Institut für Organische Chemie der Universität
75 Karlsruhe, Richard-Willstätter-Allee (Germany)



(1)



(2)

Reaction of phenyldiazonium tetrafluoroborate *(2)* in methanol with copper powder at 0°C affords benzene in 62% yield. In CH_3OD the benzene contains 1.6% deuterium, in CD_3OH 54%, and in CD_3OD 81% (see Table). These values are characteristic for free phenyl radicals[5]; it has been calculated that the radicals abstract hydrogen to the extent of 90% from the CH_3 group and 10% from the OH group[5]. In the absence of copper powder the diazonium salt is stable under these conditions; less than 0.3% of benzene is formed in 2 h.

If compound *(2)* is reduced by $NaBD_4$ in methanol at 0°C a 48% yield of benzene is obtained and the incorporation of deuterium amounts to only about 1%; in CH_3OD, however, 60% of deuterium is incorporated, in CD_3OH 26%, and in CD_3OD 88%. Reaction of the potassium salt of phenylazocarboxylic acid *(3)* under analogous conditions in CH_3OD, CD_3OH, and CD_3OD furnishes benzene containing 40, 14, and 94% of deuterium (see Table).

Table. (Yields) and degrees of deuteration of benzene (both given as percentages).

Source of radicals	Conc. (mol/l)	CH_3OH	CH_3OD	CD_3OH	CD_3OD
$C_6H_5-N=N^{\oplus}BF_4^{\ominus}$		(62)	(57)	(15)	(8)
+ Cu	0.6	0.0	1.6	54	81
	1.0		1.6	53	
$C_6H_5-N=N^{\oplus}BF_4^{\ominus}$		(48)	(33)	(45)	(28)
+ $NaBD_4$	0.6	0.7	60	26	88
	1.0	1.3	67	20	
$C_6H_5-N=N-CO_2K$		(28)	(23)	(32)	(25)
(3)	0.27	0.0	28	17	94
	0.82		40	14	

Studies by *Bunnett*[6], *Kosower*[7], *Hoffmann*[8], and *Heesing*[9] have established the formation of phenyldiimine on decomposition of the salt *(3)*, its esters, and other derivatives. Numerical data for the decomposition of *(3)* are in reasonable agreement with those for the reduction of *(2)* but differ widely from those obtained for reactions known to proceed by way of phenyl radicals. It is thus demonstrated that reduction of diazonium salts with $NaBH_4$ involves an intermediate that reacts with methanol in the same manner as phenyldiimine. In the meantime, UV maxima characteristic of phenyldiimine have also been found in the reaction solution[3].

The degrees of deuteration in lines 2 and 3 of the Table also provide some information about the further fate of the phenyldiimine. 20—30% decomposes into free phenyl radicals that abstract hydrogen from the CH_3 and OH group of the methanol (9:1). Some 65—80% of the phenyldiimine seems to decompose to give the phenyl anion which removes the acidic proton from the OH group. This ratio (20—30%/65—80%) is only valid, however, when approximately equal isotope effects are assumed for both pathways. The preceding communication[5] shows that this ratio will not be significantly falsified by the low proportion of OH abstraction by the free phenyl radicals.

As in the formation of phenyl radicals, the degree of deuteration of the benzene formed on decomposition of phenyldiimine by H abstraction from the CH_3 group of methanol also increases with increasing dilution. By way of contrast, the degree of deuteration of the benzene from phenyldiimine decomposition increases with increasing concentration when the OH proton is incorporated. There are two possible reasons for this behavior: Either the concentration of the diimine anion increases with the concentration of reactants, or a third decomposition pathway is available, *e.g. via* dimeric associates of phenyldiimine such as have been discussed by *Kosower* in acetonitrile[7] and by *Heesing* for acid solutions[9] in the formation of hydrazobenzene.

Reduction of the diazonium salt by $NaBD_4$ in methanol gives biphenyl (2—4%), hydrazobenzene, azobenzene, and phenyl azide as by-products. The deuterium content of the biphenyl (in CH_3OD, 56%; in CD_3OH, 14%; in CD_3OD, 88%) is similar to that of the benzene obtained from the same reaction solution (Table). The same applies to the decomposition of the salt *(3)* in deuterated methanol (biphenyl: 17, 12, and 40% D_1 resp.). The above constitutes a fairly rigorous proof that the major part of the biphenyl formed on decomposition of phenyldiimine arises by radical substitution of the incipient benzene and not by combination of two phenyl radicals.

The yields of benzene were determined by gas chromatography (±2%), and the degrees of deuteration by mass spectrometry (±0.3%). The methanol employed was at least 98% deuterated, the salts were dried at room temperature in high vacuum for about 1—2 h and certainly still contained traces of water that were not determined.

Received: September 1, 1971 [Z 521 b IE]
German version: Angew. Chem. *84*, 33 (1972)

[1] *M. Bloch, H. Musso,* and *U.-I. Záhorszky,* Angew. Chem. *81*, 392 (1969); Angew. Chem. internat. Edit. *8*, 370 (1969).

[2] *A. Rieker, P. Niederer,* and *D. Leibfritz,* Tetrahedron Lett. *1969*, 4287.

[3] *C. E. McKenna* and *T. G. Traylor,* J. Amer. Chem. Soc. *93*, 2313 (1971).

[4] *T. Severin, R. Schmitz, J. Loske,* and *J. Hufnagel,* Chem. Ber. *102*, 4152 (1969).

[5] *E. König, H. Musso,* and *U.-I. Záhorszky,* Angew. Chem. *84*, 33 (1972); Angew. Chem. internat. Edit. *11*, 45 (1972).

[6] *J. F. Bunnett* and *H. Takayama,* J. Amer. Chem. Soc. *90*, 5173 (1968).

[7] *P. C. Huang* and *E. M. Kosower,* J. Amer. Chem. Soc. *90*, 2354, 2362 (1968); *E. M. Kosower, P. C. Huang,* and *T. Tsuji, ibid. 91*, 2325 (1969).

[8] *R. W. Hoffmann* and *G. Guhn,* Chem. Ber. *100*, 1474 (1967).

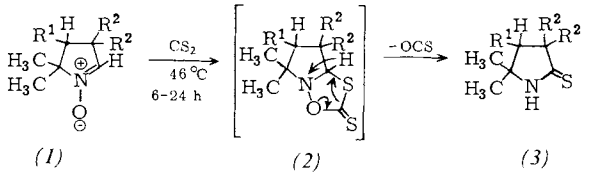
[9] *A. Heesing* and *B. U. Kaiser,* Tetrahedron Lett. *1970*, 2845; *1971*, 1307.

Conversion of Cyclic Nitrones to Thiolactams by Reaction with Carbon Disulfide

By *David St. Clair Black* and *Keith G. Watson*[*]

We report that the cyclic aldonitrones *(1a)*—*(1c)*[1] are converted into the related thiolactams *(3a)*—*(3c)*, simply by heating under reflux in carbon disulfide. The conversion is spectroscopically quantitative and the pure thiolactams can be isolated easily in high yields. The reaction presumably depends upon the loss of carbon oxysulfide from the intermediates *(2)*, which are the expected products of the cycloaddition of carbon disulfide to the nitrones *(1)*. A similar reaction[2] involves loss of sulfur dioxide from the cycloadduct of a nitrone and *N*-sulfinylaniline; related fragmentation reactions[3,4] often occur if aromatic products can be formed.

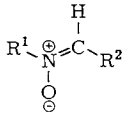
We have been unable to detect the presence of the cycloadducts *(2)*, even though reactions can be followed carefully by nuclear magnetic resonance spectroscopy. The previously unknown thiolactams 5,5-dimethylpyrrolidine-2-thione *(3a)*, 3,3,5,5-tetramethylpyrrolidine-2-thione *(3b)*, and 5,5-dimethyl-4-phenylpyrrolidine-2-thione *(3c)* have been characterized fully.



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

(a), $R^1 = R^2 = H$
(b), $R^1 = H$, $R^2 = CH_3$
(c), $R^1 = C_6H_5$, $R^2 = H$

Reports of cycloaddition reactions between carbon disulfide and nitrones or *N*-oxides are rare. In one special case[5], a stable adduct is reported. On the other hand, isoquinoline *N*-oxide[4] and the diphenyl nitrone *(4a)*[6] are deoxygenated, supposedly *via* their respective cycloadducts. This competing deoxygenation reaction is apparently successful when it can afford a highly conjugated product.



(4a), $R^1 = R^2 = C_6H_5$
(4b), $R^1 = C(CH_3)_3$; $R^2 = C_6H_5$

We have also observed that the *C*-phenyl nitrone *(4b)* undergoes thermal rearrangement and decomposition in preference to any reaction with carbon disulfide.

Thus the conversion of aldonitrones to thioamides does not hold for all nitrones and appears to require a nitrone configuration which allows a reasonable rate[7] of cycloaddition.

The Willgerodt-Kindler reaction[8] already provides a method for the conversion of simple aldehydes into thioamides, but is not readily applicable to the preparation of thiolactams. The method described in this communication compares very favorably with the main existing alternative, which is the reaction[9] of a lactam with phosphorus pentasulfide.

Received: September 3, 1971 [Z 522 IE]
German version: Angew. Chem. *84*, 34 (1972)

[*] Dr. D. St. C. Black and Mr. K. G. Watson
Department of Chemistry, Monash University,
Clayton, Victoria, 3168 (Australia)

[1] *R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland*, and *A. Todd*, J. Chem. Soc. *1959*, 2094; *J. B. Bapat* and *D. St. C. Black*, Austral. J. Chem. *21*, 2483 (1968).

[2] *O. Tsuge, M. Tashiro*, and *S. Mataka*, Tetrahedron Lett. *1968*, 3877.

[3] *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. internat. Edit. *2*, 565 (1963).

[4] *H. Seidl, R. Huisgen*, and *R. Grashey*, Chem. Ber. *102*, 926 (1969).

[5] *T. Sasaki* and *M. Ando*, Bull. Chem. Soc. Japan *41*, 2960 (1968).

[6] *M. Hamana, B. Umezawa*, and *S. Nakashima*, Chem. Pharmac. Bull. (Tokyo) *10*, 969 (1962).

[7] *R. Huisgen, H. Seidl*, and *I. Brüning*, Chem. Ber. *102*, 1102 (1969).

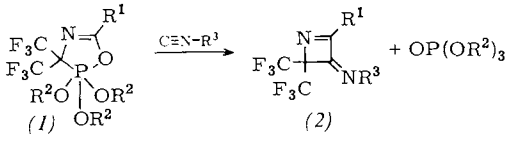
[8] *R. Guépet, R. Piganiol, A. Carayon-Gentil*, and *P. Chabrier*, Bull. Soc. Chim. France *1965*, 224.

[9] *W. Walter* and *K. D. Bode*, Angew. Chem. *78*, 517 (1966); Angew. Chem. internat. Edit. *5*, 447 (1966).

Cycloaddition of Isocyanides to 4,5-Dihydro-1,3,5-oxazaphosph(v)oles[**][1]

By *Klaus Burger* and *Josef Fehn*[*]

We recently reported [3+2]cycloadditions of 4,5-dihydro-1,3,5-oxazaphosph(v)oles *(1)*[2] to alkynes and alkenes[3]. We have now found an example of the very rare [3+1]-cycloaddition type[4]: Compounds *(1)* react with isocyanides in boiling benzene with elimination of phosphoric acid esters to give 1:1 adducts to which we ascribe the structures of substituted azetines *(2)* on the basis of spectroscopic data. The reaction could involve a nitrile ylide intermediate.



(1) *(2)*

Cpd.	Groups R $R^2 = CH_3$	M.p. (°C) B.p. (°C/torr)	Yield (%)	IR (cm^{-1})
(2a)	$R^1 = C(CH_3)_3$ $R^3 = C_6H_{11}$	58/0.2	80	1705, 1645 [a]
(2b)	$R^1 = C(CH_3)_3$ $R^3 = CH(CH_3)C_6H_5$	58/0.2	75	1705, 1645 [a]
(2c)	$R^1 = C_6H_5$ $R^3 = C_6H_{11}$	61	82	1705 [b]
(2d)	$R^1 = C_6H_5$ $R^3 = CH(CH_3)C_6H_5$	110/0.3	45	1700, 1630 [a]

Recorded [a] as films, [b] in KBr with a Perkin-Elmer Infracord.

Supporting evidence for structure *(2)* comes from the acid hydrolysis of *(2c)* to phenylglyoxylic acid as well as from the hydrogenation of the endocyclic double bond of *(2c)* with $LiAlH_4$ and acid hydrolysis of the resulting azetidine to *N*-(2,2,2-trifluoro-1-trifluoromethylethyl)phenylglycine cyclohexylamide.

2-Alkyl- and 2-aryl-1-azetines have become accessible only very recently by pyrolysis of cyclopropylazides[5]; hitherto only a few 2-alkoxy-, 2-alkylthio-, and 2-chloro-1-azetines derived from β-lactams were known[6].

[*] Dr. K. Burger and Dipl.-Chem. J. Fehn
Organisch-chemisches Institut der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

2-Phenyl-3-cyclohexylimino-4,4-bis(trifluoromethyl)-1-azetine (2c):

2-Phenyl-4,4-bis(trifluoromethyl)-5,5,5-trimethoxy-4,5-dihydro-1,3,5-oxazaphosph(v)ole *(1c)* (4.32 g, 11 mmol) and cyclohexyl isocyanide (1.09 g, 10 mmol) are refluxed for 12—24 h in anhydrous benzene. Removal of solvent and phosphoric acid ester by vacuum distillation gives a crystalline residue; yield after recrystallization from methanol/water: 2.95 g (82%) of *(2c)*.

Received: September 3, 1971 [Z 523 IE]
German version: Angew. Chem. *84*, 35 (1972)

[1] Reactions of 4,5-dihydro-1,3,5-oxazaphosph(v)oles, Part 3. — Part 2: [3b].

[2] *K. Burger, J. Fehn,* and *E. Moll,* Chem. Ber. *104*, 1826 (1971).

[3] a) *K. Burger* and *J. Fehn,* Angew. Chem. *83*, 761 (1971); Angew. Chem. internat. Edit. *10*, 728 (1971); b) Angew. Chem. *83*, 762 (1971); Angew. Chem. internat. Edit. *10*, 729 (1971).

[4] *R. Huisgen,* Angew. Chem. *80*, 329 (1968); Angew. Chem. internat. Edit. *7*, 321 (1968); *J. A. Deyrup,* Tetrahedron Lett. *1971*, 2191.

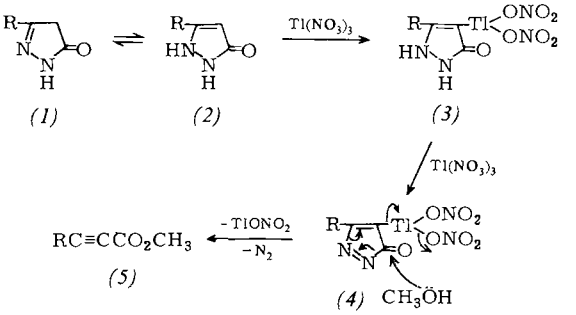
[5] *A. B. Levy* and *A. Hassner,* J. Amer. Chem. Soc. *93*, 2051 (1971).

[6] *G. Pifferi, P. Consonni, G. Pelizza,* and *E. Testa,* J. Heterocycl. Chem. *4*, 619 (1967); *D. Bormann,* Liebigs Ann. Chem. *725*, 124 (1969); *A. Hassner, J. O. Currie, A. S. Steinfeld,* and *R. F. Atkinson,* Angew. Chem. *82*, 772 (1970); Angew. Chem. internat. Edit. *9*, 731 (1970).

A Facile Synthesis of 2-Alkynoic Esters[1]

By *Edward C. Taylor, Roger L. Robey,* and *Alexander McKillop*[*]

We report a facile one-step synthesis of 2-alkynoic esters *(5)* from the readily available 5-pyrazolones *(1)* by treatment with two equivalents of thallium(III) nitrate[2] in methanol. Yields are high and reaction conditions are extremely mild. Since 5-pyrazolones may be prepared in quantitative yield by the reaction of hydrazine with β-keto esters[3], this conversion represents in a formal sense the dehydration of β-keto esters to 2-alkynoic esters[4]. In fact, the direct conversion of β-keto esters into 2-alkynoic esters *(5)* without isolation of the intermediate 5-pyrazolones *(1)* can be achieved by treatment in methanol solution first with hydrazine and then with thallium(III) nitrate; comparable overall yields are obtained. Representative conversions are summarized in the Table.



We suggest that this transformation involves initial electrophilic thallation of the 3-pyrazolin-5-one tautomer *(2)*[5] to give *(3)*, which undergoes a subsequent oxidation by the second equivalent of thallium(III) nitrate to give the oxopyrazole *(4)*. Solvolysis by methanol, with concomitant elimination of nitrogen and thallium(I), yields the 2-alkynoic ester *(5)* directly. Previous observations that 5-pyrazolones mercurate at position 4[6] and undergo oxidation to oxopyrazoles[7] support this interpretation.

Table. Synthesis of 2-alkynoic esters *(5)* from 5-pyrazolones *(1)* with thallium(III) nitrate in methanol. Products were identified by comparison with authentic material and/or spectral data and yields determined by GLPC.

R	Yield (%)
CH_3	78
CH_2CH_3	95
n-C_3H_7	85
$CH_2CH(CH_3)_2$	85
n-C_5H_{11}	90
C_6H_5	67

Experimental

A solution of thallium(III) nitrate (0.021 mol) in methanol (25 ml) is added to a suspension or solution of the 5-pyrazolone (0.010 mol) in methanol (25 ml), and the reaction mixture is stirred for 15 min at room temperature and then for an additional 15 min at reflux (water bath). The cooled reaction mixture is filtered to remove precipitated thallium(I) nitrate and the filtrate diluted with water and extracted with chloroform. The extracts are washed with water, dried over anhydrous Na_2SO_4, filtered through a short column of Florisil and evaporated to give the pure (GLPC) 2-alkynoic esters.

Received: August 30, 1971 [Z 524 IE]
German version: Angew. Chem. *84*, 60 (1971)

[1] Thallium in Organic Synthesis, Part 30. — Part 29: *E. C. Taylor, F. Kienzle,* and *A. McKillop,* Synthesis, in press.

[2] *A. McKillop, J. D. Hunt, E. C. Taylor,* and *F. Kienzle,* Tetrahedron Lett. *1970*, 5275.

[3] *R. H. Wiley* and *P. Wiley* in *A. Weissberger:* The Chemistry of Heterocyclic Compounds. Interscience, New York 1964, Vol. 20.

[4] Oxidation of 5-pyrazolones to 2-alkynoic esters with thallium(III) nitrate in methanol, as herein described, represents a considerable simplification over the only previously available procedure for effecting this type of overall conversion, which involves chlorination of the 5-pyrazolone to give a 4,4-dichloro-2-pyrazolin-5-one, which is subsequently treated with strong alkali to give a 2-alkynoic acid (*L. A. Carpino, P. H. Terry,* and *S. D. Thatte,* J. Org. Chem. *31*, 2867 (1966)).

[5] *A. R. Katritzky* and *J. M. Lagowski,* Advan. in Heterocycl. Chem. *2*, 28 (1963).

[6] See ref. [3], pp. 104—105.

[7] *B. T. Gillis* and *R. Weinkam,* J. Org. Chem. *32*, 3321 (1967).

[*] Prof. Dr. E. C. Taylor and R. L. Robey
Department of Chemistry
Princeton University
Princeton, N. J. 08540 (USA)
Dr. A. McKillop
School of Chemical Sciences
University of East Anglia
Norwich NOR 88C (England)

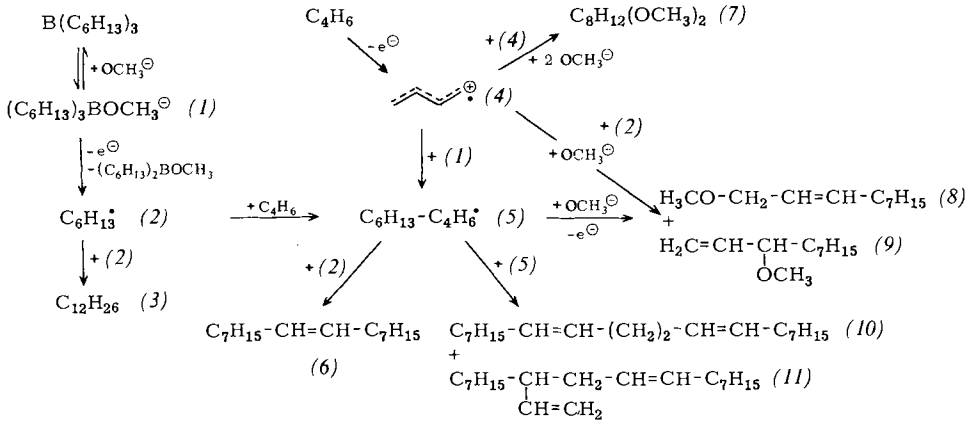
Anodic Oxidation of Trihexylmethoxyborate in Presence of Butadiene[1][**]

By *Hans Schäfer* and *Dietrich Koch*[*]

Alkyl groups in borates can be dimerized with Ag(I)[2] or made to give alkyl-metal compounds by reaction with active anodes[4]; aryl groups in borates can be dimerized electrochemically[3]. In the course of our work on the anodic bifunctionalization of olefins[5] we have now been

[*] Doz. Dr. H. Schäfer and Dipl.-Chem. D. Koch
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.



able to transfer anodically the hexyl group from trihexylborane to butadiene.

Voltammetric measurements on a 10^{-2} M solution of trihexylborane prepared *in situ* in the electrolyte 0.3 mol/l $NaClO_4$/0.5 mol/l $NaOCH_3$/methanol at a graphite disk anode[6] revealed the peak potentials: $E_p(1) = -0.04$ V and $E_p(2) = +0.3$ V (*vs.* Ag/AgCl). Comparison of the corresponding peak currents $i_p(1)$ and $i_p(2)$ with that of an aqueous solution of $K_4Fe(CN)_6$ shows that both oxidation steps involve transfer of a single electron.

The preparative electrolysis of hydroborated 1-hexene (50 mmol) and $NaOCH_3$ (80 mmol) in methanol employing a diaphragmless electrolysis cell with a graphite anode at an anode potential of $\leq +0.5$ V (*vs.* Ag/AgCl), a current density of 25 mA/cm^2, and a temperature of -5 °C affords dodecane *(3)* (25% current yield; 48% based on reacted borane). Under otherwise identical reaction conditions but at -20°C and in the presence of 0.63 mol/l of butadiene a 41% yield (based on reacted borane) of the following products is obtained: 9%[7] of dodecane *(3)*; 18% of 8-hexadecene *(6)*; 23% of 1-methoxy-2-decene *(8)*; 20% of 3-methoxy-1-decene *(9)*; 16% of 8,12-eicosadiene *(10)*; and 13% of 8-vinyl-10-octadecene *(11)*. Three isomeric dimethoxyoctadienes *(7)*, methoxy-substituted dimers of butadiene[8], are formed simultaneously in a current yield of 17%.

As a working hypothesis we assume that trihexylmethoxyborate *(1)*—and presumably also dihexylborate—and butadiene are oxidized simultaneously to the hexyl radical *(2)* and the butadiene radical cation *(4)*, respectively, which give *(3)* and *(7)* on dimerization and *(8)* and *(9)* on mixed coupling. The products *(6)*, *(10)*, and *(11)* could be formed by addition of *(2)* to butadiene and subsequent coupling of the primary adduct *(5)*; oxidation of *(5)* would give *(8)* and *(9)*. Formation of *(6)* and *(8)*—*(11)* by electrophilic attack of *(4)* on *(1)* is also conceivable.

The electrolysis of alkyl borates in the presence of olefins is of interest as a method for the alkylation of olefins. It complements the anodic addition of Grignard compounds[9] since it starts from alternative precursors and can be carried out in protic solvents. Owing to the lower anionic reactivity of the borates it should be possible to use boranes or olefins carrying substituents such as halogen, NO_2, COOR, or SO_2R.

Received: August, 27, 1971 [Z 519 IE]
German version: Angew. Chem. *84*, 32 (1972)

[1] Anodic oxidation of organic compounds, Part 8.—Part 7: *H. Schäfer* and *E. Steckhan*, Tetrahedron Lett. *1970*, 3835.

[2] *H. C. Brown* and *C. H. Snyder*, J. Amer. Chem. Soc. *83*, 1002 (1961).

[3] *D. H. Geske*, J. Phys. Chem. *66*, 1743 (1962); *W. R. Turner* and *P. J. Elving*, Anal. Chem. *37*, 207 (1965).

[4] *K. Ziegler* and *O. Steudel*, Liebigs Ann. Chem. *652*, 1 (1962).

[5] *H. Schäfer*, Chemie-Ing.-Techn. *42*, 164 (1970).

[6] Platinum is unsuitable as anode material because of pronounced passivation.

[7] Relative yields; all products were identified by IR, NMR, MS, and C,H analysis or by gas-chromatographic comparison with authentic substances.

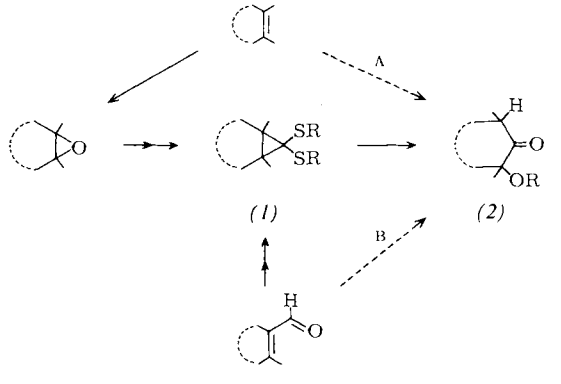
[8] *H. Schäfer* and *E. Steckhan*, Angew. Chem. *81*, 532 (1969); Angew. Chem. internat. Edit. *8*, 518 (1969).

[9] *H. Schäfer* and *H. Küntzel*, Tetrahedron Lett. *1970*, 3333.

Solvolysis of 7,7-Bis(alkylthio)norcaranes. A New Method of Homologation

By *Dieter Seebach* and *Manfred Braun*[*]

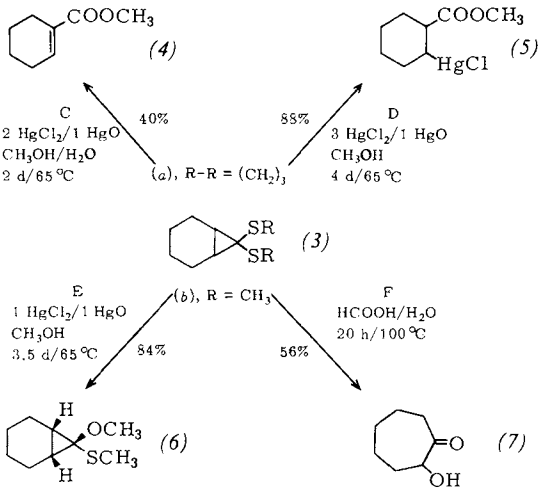
Bis(alkylthio)cyclopropanes (cyclopropanone dithioacetals) *(1)* are readily available either from epoxides[1,2] (with extension by one carbon atom) or from α,β-unsaturated aldehydes[1,3] (with conservation of the carbon skeleton). Their solvolysis should produce derivatives *(2)* of acyloins[4]. Effectively, this would provide a means of "intermolecular"—route A—or "intramolecular"—route B—insertion of a carbonyl group between the carbons of a double bond.



Because of the potential synthetic value of such transformations we investigated the solvolytic behavior of the norcaranes *(3a)* and *(3b)* obtained from cyclohexene oxide

[*] Prof. Dr. D. Seebach and Dipl.-Chem. M. Braun
Institut für Organische Chemie der Universität Karlsruhe
Present address:
Institut für Organische Chemie der Universität
63 Giessen, Ludwigstrasse 21 (Germany)

by a simplified procedure (see below). It turns out that the three-membered ring of these compounds, when subjected to the usual conditions[1] of neutral thioacetal hydrolysis or methanolysis, opens up (very slowly) either on the "wrong side" (reactions C and D) or not at all (reaction E), while the expected process takes place when the methylthio derivative is heated with aqueous formic acid (reaction F).



The structures of *(4)*—*(7)* were established as follows: *(4)* by comparison with an authentic sample; *(5)* (m.p. 88.5—89.0 °C) by $NaBH_4$ reduction to methyl cyclohexanecarboxylate; *(6)* (m.p. of sulfone 68.8—69.4 °C) by elemental analysis and spectroscopic data; and *(7)* by removal of the hydroxyl group (Zn/acetic acid) to give cycloheptanone, identical in every respect (IR, NMR, VPC, DNPH) with authentic material.

The cleavages C and D are caused by attack of $ClHg^{\oplus}$ at a cyclopropane C—C bond[5,6] of *(3)* rather than at sulfur, suggesting that compounds of type *(1)* might also, under certain conditions, serve as protective groups for "future" ester groups. The reaction leading to the formation of *(6)* is a rare[7] example of nucleophilic displacements at a cyclopropyl carbon atom.

The conditions of reaction F have not yet been optimized. Preliminary experiments show that the conversions of *(3)* described here are typical of other mono- and bicyclic cyclopropanes *(1)*.

α-Hydroxycycloheptanone (7) from cyclohexene oxide:

To a solution of bis(methylthio)methane (10.8 g, 100 mmol) in THF (120 ml) are added successively (inert atmosphere, stirring) *n*-butyllithium (110 mmol, 2 M in *n*-hexane; addition at −50 °C, reaction time 2.5 h at −25 °C), cyclohexene oxide (11.0 ml, 108 mmol; −78 °C, 15 h, 0 °C), toluenesulfonyl chloride (19.0 g, 100 mmol in 100 ml of THF; −78 °C, 6 h, 0 °C), and again *n*-butyllithium (110 mmol; −78 °C to −30 °C in 2 h, 20 h, 0 °C). Workup with pentane furnishes 15.2 g (81%) of *(3b)*, b.p. 65 °C/1 torr, m.p. of disulfone 87.8—88.4 °C.

A stirred mixture of *(3b)* (5.64 g, 30 mmol), formic acid (25 ml), and water (5 ml) is heated at reflux in a hood for 20—30 h. Pouring into water, extracting with dichloromethane, neutralizing with bicarbonate solution, and distilling gives 3.52 g of crude product, b.p. 91—94 °C/13 torr. 2.10 g [56% based on *(3b)*] of *(7)* are separated from the distillate by VPC (2 m, silicone on chromosorb, WAW-DMCS 60/70, 150 °C, 200 ml H_2/min, retention time 16 min), IR spectrum (neat): 3460, 2930, 2850, 1695, 1450, 1400, 1340, 1265, 1190, 1150, 1100, 1075, 1040, 1015, 1000, 930, 800 cm^{-1}.

Received: September 6, 1971 [Z 525 IE]
German version: Angew. Chem. *84*, 60 (1972)

[1] *D. Seebach*, Synthesis *1969*, 17, and literature cited therein.

[2] Compare also *J. B. Jones* and *R. Grayshan*, Chem. Commun. *1970*, 141, 741.

[3] *J. P. O'Brien*, *A. I. Rachlin*, and *S. Teitel*, J. med. Chem. *12*, 1112 (1969); *C. Feugeas* and *J. P. Galy*, C.R. Acad. Sci. Paris *C 270*, 2157 (1970).

[4] Analogous ring openings of dihalocarbene adducts to give halogen-free products are difficult: see *C. D. Gutsche* and *D. Redmore*: Carbocyclic Ring Expansion Reactions. Academic Press, New York 1968.

[5] Norcarane gives acetoxy-(2-hydroxy- or acetoxy-(2-acetoxy-cyclohexylmethyl)mercury(II) under these conditions: *R. Y. Levina*, *B. N. Kostin*, and *T. K. Ustynyuk*, Zh. Obshch. Khim. *30*, 359 (1960); Chem. Abstr. *54*, 54457 (1960); cf. *A. De Boer* and *C. H. De Puy*, J. Amer. Chem. Soc. *92*, 4008 (1970).

[6] *(4)* is probably formed from *(5)* through a carbonium ion [*F. R. Jensen* and *R. J. Oulette*, J. Amer. Chem. Soc. *83*, 4477, 4478 (1961); *85*, 363, 367 (1963)].

[7] *U. Schöllkopf*, Angew. Chem. *80*, 603 (1968); Angew. Chem. internat. Edit. *7*, 588 (1968); *U. Schöllkopf et al.* Tetrahedron Lett. *1970*, 5077; *J. A. Landgrebe* and *L. W. Becker*, J. Amer. Chem. Soc. *90*, 395 (1968), and literature cited therein.

Aminopentalenecarbonitriles, a Group of Stable Pentalenes[**]

By *Klaus Hartke* and *Rudolf Matusch*[*]

Knoevenagel condensation of 2 mol. equiv. of malononitrile *(1)* with 1 mol. equiv. of 2,5-hexanedione *(2)* in the presence of NH_4Ac/HAc as catalyst in boiling benzene with constant removal of water yields the cyclopentadiene derivative *(4)* as a precipitate of yellow needles in 62% yield [*(4)*, m.p. 285 °C (decomp.); IR (KBr): 3425, 3344, 3257 (NH_2); 2222, 2208, 2188 (C≡N); 1661 (NH_2); 1613, 1534 cm^{-1} (C=C); NMR [D_6-acetone, δ (ppm)]: 2.43 (CH_3/s); 2.53 (CH_3/s); 3.87 (CH_2/s); 6.5—7.5 (NH_2/s)]. Shaking of the benzene phase several times with NaCl solution followed by removal of the organic solvent under mild conditions yields 8% of tetracyanohexadiene *(3)* [*(3)*, m.p. 127 °C; IR(KBr): 2232 (C≡N); 1577 cm^{-1} (C=C); NMR [D_6-acetone, δ(ppm)]: 2.43 (CH_3/s); 3.00 (CH_2/s)].

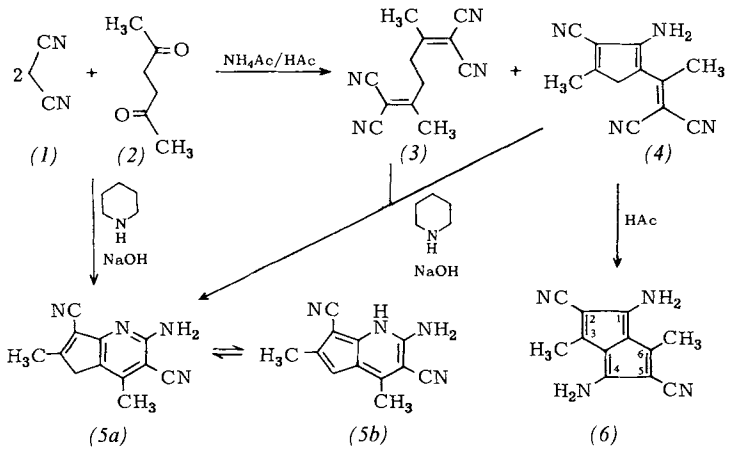
Brief boiling of *(3)* or *(4)* in ethanol in the presence of a few drops of alkali hydroxide solution or another base (*e.g.* piperidine, morpholine) converts it into the 1-pyrindine *(5a)*[1] for which we have been able to detect a solvent-dependent equilibrium with the tautomeric azalene *(5b)* by NMR spectroscopy.

Six hours' boiling of *(4)* in glacial acetic acid followed by removal of the solvent and sublimation of the residue (215 °C/0.1 torr) or chromatography on acidic alumina [first acetone/methylene chloride (1:1), then methanol] furnishes 1,4-diamino-3,6-dimethylpentalene-2,5-dicarbonitrile *(6)* in 40% yield. We deduce the pentalene structure

[*] Prof. Dr. K. Hartke and Dr. R. Matusch
Institut für Pharmazeutische Chemie and Lebensmittelchemie der Universität
355 Marburg, Marbacher Weg 6 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

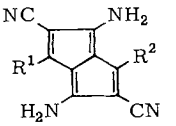
from the following information: Correct elemental analysis; M. W. 210 (mass spectrum); IR (KBr) 3436, 3413, 3356, 3311, 3257, 3236 (NH_2); 2193 (shoulder), 2179 (C≡N); 1667, 1647 (NH_2); 1587, 1550 cm^{-1} (C=C); [D_6-DMSO, δ(ppm)]: 2.07 (CH_3/s); 7.67 (NH_2/s, broad); UV [CH_3OH, $\lambda_{max}(\log\varepsilon)$][2]: 656 (3.55); 434 (4.18); 319 (4.39); 278 nm (4.86).



(1) (2) (3) (4) (5a) (5b) (6)

Compound *(6)* is the third example in the series of non-annelated pentalenes[5] that are stable at room temperature, *viz.* hexaphenylpentalene[3] and 1,3-bis(dimethylamino)-pentalene[4]. The unusual chemical and thermal stability of the pentalene *(6)*[6] probably arises from the push-pull effect of a strong electron acceptor and a strong electron donor attached to the ends of the two diene structures. In this respect compound *(6)* resembles the similarly stable 2,4-bis(dialkylamino)cyclobutadiene-1,3-dicarboxylic esters[7].

The condensation of other aliphatic 1,4-diketones (*e.g.* 2,5-heptanedione) with malononitrile also proceeds in accord with the reaction scheme shown. Cyclization of the cyclopentadiene precursor corresponding to *(4)* in glacial acetic acid gives 1,4-diamino-3-ethyl-6-methylpentalene-2,5-dicarbonitrile *(7a)* [blue-black needles, decomp. >330 °C]. Knoevenagel condensation of a typical aromatically substituted 1,4-diketone, dibenzoylethane, with malononitrile directly gives the 1-pyrindine derivative corresponding to *(5)*; we were not able to isolate a cyclopentadiene intermediate. However, if dibenzoylethane is refluxed for 24 h with malononitrile and piperidinium



(7a), $R^1 = CH_3$, $R^2 = C_2H_5$
(7b), $R^1 = R^2 = C_6H_5$

acetate in ethanol, chromatography of the residue left on evaporation of solvent on basic alumina with acetone under nitrogen yields about 2—3% of *(7b)* [blue-black crystals, decomp. >300 °C].

Received: September 10, 1971 [Z 527 IE]
German version: Angew. Chem. *84*, 61 (1972)

Simple Synthesis and NMR Spectroscopic Behavior of 1,2-Dihalo[18]annulene[1]

By *Gerhard Schröder*, *Rainer Neuberg*, and *Jean F. M. Oth*[*]

[18]Annulene, which was first prepared by *Sondheimer et al.*[2], exhibits temperature-dependent NMR spectra. At 60 MHz and −60 °C the spectrum corresponds to the structure (12 outer H at τ = 0.75, 6 inner H at τ = 12.9). At 120 °C (18 H as singlet at τ = 4.55) it reflects the prevailing dynamic situation[2]. The 17 protons of monosubstituted [18]annulenes exhibit less mobility[3]; in this case the 6 outer and the 6 inner protons are undergoing exchange while 5 outer protons retain their positions[3].

This dynamic situation, which may appear surprising at first glance, can be explained in the following way: In the case of [18]annulene three conformers of equal energy are in equilibrium with one another[2c, 3]. This number of conformers is reduced to two for monosubstituted[3] and 1,4-, 1,7-, and 1,10-disubstituted [18]annulenes[4]. For 1,2-, 1,3-, 1,5-, 1,8-, and 1,9-disubstituted annulenes the equilibrium is dominated by only one conformer, *i. e.* that having two outwardly directed substituents. Such disubstituted [18]-annulenes should exhibit NMR spectra *independent* of temperature[5].

We wish to report the synthesis of two 1,2-disubstituted [18]annulenes and their *temperature-independent* NMR spectra.

Dimeric cyclooctatetraene[6] *(1)* *(5g)* is heated with 1,1-difluoro-2,2-dichloroethylene (100 g) to 115 °C in an ampoule for *ca.* 70 h. Colorless crystalline *(3)*, m. p. 136 °C (from ethanol)[7], is formed in 21% yield (1.7 g) by way of a [2+2]cycloaddition of difluorodichloroethylene to a double bond of the cyclohexadiene system of *(2)*. *(2)* is a valence isomer of *(1)* and cannot be detected by spectroscopy in the presence of *(1)*. The double bonds of the six-membered ring system in *(2)* are thus considerably more reactive towards difluorodichloroethylene than those of the eight-membered ring in *(1)*. Compound *(3)* is dehalogenated to colorless crystalline *(4)* [yield 80%, m. p. 95 °C (from ethanol)[7]] on treatment with zinc powder in boiling ethanol. Irradiation of *(4)* (1.5 g) in ether (1.5 l) with a low-pressure UV lamp (2537 nm, quartz glass, 200 mA/500 V *ex* Gräntzel, Karlsruhe) at −70 °C ruptures the four "*endo*" σ bonds, probably successively, and a greenish-yellow ethereal solution results. After removal of the ether in a rotary evaporator the residue is taken up in a little chloroform. On standing in a refrigerator 1-chloro-

[1] Compound *(5)*, which was unknown at the outset of our investigations, has since been prepared by condensation of malononitrile and 2,5-hexanedione with piperidine or NaOH without isolation of intermediates: *H. Junek* and *R. J. Schaur*, Monatsh. Chem. *99*, 89 (1968).

[2] All the maxima found except that at 434 nm are in good agreement with recently published NNDO MO calculations for unsubstituted pentalene: 659, 335, 273, and 232 nm; cf. *N. C. Baird* and *R. M. West*, J. Amer. Chem. Soc. *93*, 3072 (1971).

[3] *E. Le Goff*, J. Amer. Chem. Soc. *84*, 3975 (1962).

[4] *K. Hafner*, *K. F. Bangert*, and *V. Orfanos*, Angew. Chem. *79*, 414 (1967); Angew. Chem. internat. Edit. *6*, 451 (1967).

[5] *R. Bloch*, *R. A. Marty*, and *P. de Mayo*, J. Amer. Chem. Soc. *93*, 3071 (1971), have recently been able to establish the existence of methylpentalene at −196 °C by spectroscopy; it dimerizes at as low a temperature as −140 °C.

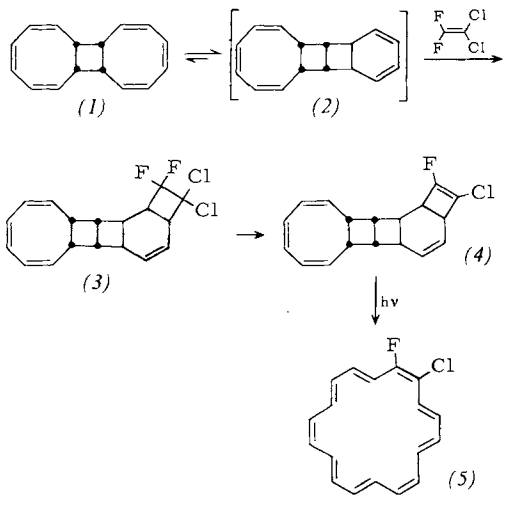
[6] Pure samples of *(6)* remained unchanged after two years' storage at room temperature.

[7] *R. Gompper* and *G. Seybold*, Angew. Chem. *80*, 804 (1968); Angew. Chem. internat. Edit. *7*, 824 (1968); *M. Neuenschwander* and *A. Niederhauser*, Chimia *22*, 491 (1968); Helv. Chim. Acta *53*, 519 (1970).

[*] Prof. Dr. G. Schröder und Dipl.-Chem. R. Neuberg
Institut für Organische Chemie der Universität
75 Karlsruhe, Richard-Willstätter-Allee (Germany)

Prof. Dr. J. F. M. Oth,
Eidgenössische Technische Hochschule, CH-8006 Zürich (Switzerland)

2-fluoro[18]annulene *(5)*[7] crystallizes as reddish violet needles [330 mg, 22%; m. p. 210 °C (from $CHCl_3$; decomp.)]. The three-step synthesis of *(5)* from *(1)* is not only simple but also makes *(5)* accessible in gram quantities (overall yield 3.7%).



UV spectrum (in methanol) of *(5)*: $\lambda_{max} = 279$ (8600), 373 (210000), 453 nm (15000); $\lambda_{sh} = 410$ nm (8000).

The NMR spectrum of *(5)* at 35 °C exhibits a narrow multiplet centered at $\tau = 1.40$ (10 outer H) and several multiplets between $\tau = 11.66$ and 13.03 (6 inner H). At 100 °C the multiplets have neither lost their fine structure nor have they undergone broadening. The signal at low field is shifted slightly upfield ($\tau = 1.87$), those at high field are shifted slightly downfield (between $\tau = 10.0$ and 11.7). This temperature effect of the chemical shift was also observed for [18]annulene in the temperature range in which no exchange of resonance signals is visible (below −20 °C)[8].

If 1,1-difluoro-2,2-dichloroethylene is replaced by trifluorochloroethylene then the reaction yields 1,2-difluoro-[18]annulene, m. p. 200 °C (from $CHCl_3$; decomp.)[7], albeit in much poorer overall yield (≈0.8%); the compound also exhibits NMR spectra that are independent of temperature.

Received: September 20, 1971 [Z 528 IE]
German version: Angew. Chem. *84*, 36 (1972)

[1] Annulenes, Part 14.—Part 13: *G. Schröder, U. Prange, B. Putze, J. Thio*, and *J. F. M. Oth*, Chem. Ber. *104*, 3406 (1971).

[2] a) *F. Sondheimer* and *R. Wolovsky*, Tetrahedron Lett. *1959*, 3; b) *F. Sondheimer, R. Wolovsky*, and *Y. Amiel*, J. Amer. Chem. Soc. *84*, 274 (1962); c) *R. Wolovsky, E. P. Woo*, and *F. Sondheimer*, Tetrahedron *26*, 2133 (1970).

[3] *I. C. Calder, P. J. Garratt, H. C. Longuet-Higgins, F. Sondheimer*, and *R. Wolovsky*, J. Chem. Soc. *C 1967*, 1041; *E. P. Woo* and *F. Sondheimer*, Tetrahedron *26*, 3933 (1970).

[4] This is a logical extension of the concepts presented in ref. [3].

[5] We have already discussed a possible mechanism for the interconversion of identical conformers of [18]annulenes: *G. Schröder* in: 20 Jahre Fonds der Chemischen Industrie. Published by Verband der Chemischen Industrie e. V., Fonds der Chemischen Industrie, Frankfurt 1970, p. 75; *J. F. M. Oth*, Lecture to the IUPAC Conference at Boston, July 29, 1971.

[6] *G. Schröder* and *W. Martin*, Angew. Chem. *78*, 117 (1966); Angew. Chem. internat. Edit. *5*, 130 (1966).

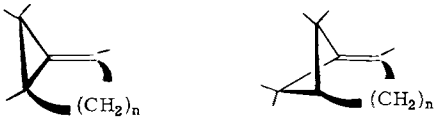
[7] NMR, IR, and UV spectra all agree with the proposed structure, as do C,H analyses and molecular-weight determinations.

[8] *F. Sondheimer*, Proc. Roy. Soc. (London) *A 297*, 173 (1967); *Y. Gaoni, A. Melera, F. Sondheimer*, and *R. Wolovsky*, Proc. Chem. Soc. (London) *1964*, 394.

Bridged Methylenecyclopropanes as Test Cases for Bredt's Rule: 2,5,5,7,7-Pentamethylbicyclo[4.1.0]-hept-1-ene[**]

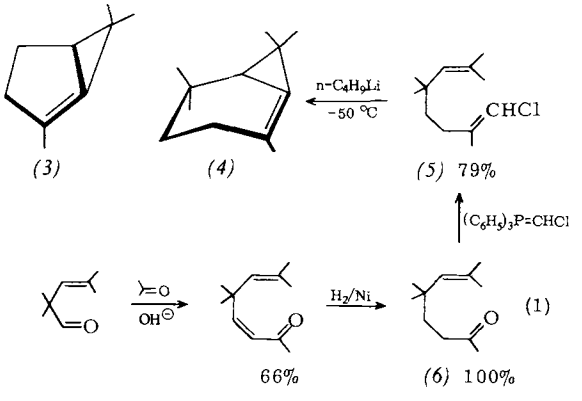
By *Gert Köbrich* and *Manfred Baumann*[*]

According to studies on molecular models, methylenecyclopropanes of type *(1)* ($n < 5$) having short-chain bridges are subject not only to the ring strain inherent in methylenecyclopropanes (41 kcal/mol[11]) but also to strong additional strain forces arising a) from planar and non-planar bond angle deformations of the σ skeleton and b) from the twisting of the π bond about the longitudinal axis of the double bond at the bridgehead. The same strain forces also operate in bicycloolefins such as *(2)*, whose behavior is described by Bredt's rule[2], and which were formerly not considered to include compounds *(1)* owing to the latters' "zero bridge"[3].



According to model considerations, the bicyclic compounds *(1)* and *(2)* having the same value of *n* should exhibit comparable overall strain [with different individual contributions from a) and b)]. The results obtained for the bicyclic compounds *(1)* should therefore provide information about the range of validity of Bredt's rule.

The hydrocarbon *(3)* [a trimethyl derivative of *(1)* with $n = 2$] has recently been detected as a short-lived intermediate[4]. We have now prepared the homolog *(4)* [a pentamethyl derivative of *(1)* with $n = 3$]. It is formed in 20 to 30% yield on carbenoid cyclization of the chloro



olefin *(5)* [prepared according to eq. (1)] with *n*-butyllithium in THF at −50 °C. The compound, which has not yet been isolated, decomposes in solution at room temperature with a half-life of about 70 h (gas chromatography) and is thus considerably more stable than *(3)*.

To establish the structure of *(4)* we converted it into the saturated bicyclic compound *(7)* ($n_D^{20} = 1.4585$) by treatment with diimine[5]; *(7)* was isolated by gas chromatog-

[*] Prof. Dr. G. Köbrich and Dipl.-Chem. M. Baumann
Institut für Organische Chemie der Technischen Universität
3 Hannover, Schneiderberg 1 B (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

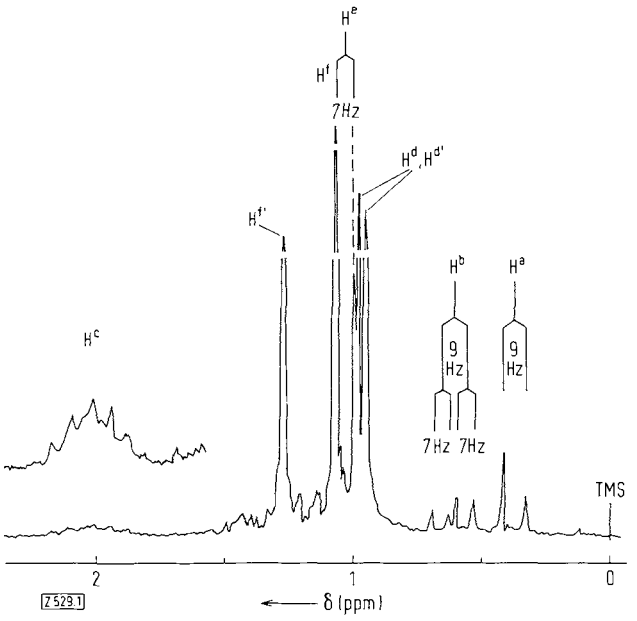
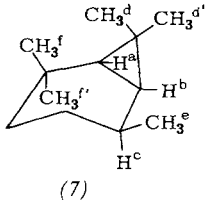
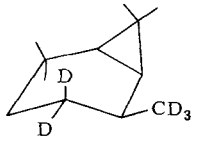


Fig. 100-MHz ^{1}H-NMR spectrum of 2,5,5,7,7-pentamethylbicyclo-[4.1.0]heptane *(7)* (in $CDCl_3$, chemical shifts referred to TMS).

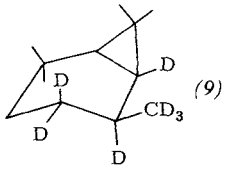
raphy and its empirical formula determined by analysis and mass spectrometry. In the NMR spectrum the protons H^a and H^b combined with H^c give a characteristic line system (Figure) with $J_{ab}=9.0$ Hz and $J_{bc}=7.0$ Hz which, as expected, simplifies to an unresolved triplet (D coupling) for H^a at 0.35 ppm in the case of the 1,2-dideuterio derivative [from *(4)* with $[D_2]$diimine]; moreover, the H^c multiplet at 2.0 ppm disappears. The position of the double bond at the bridgehead is thus clearly established.



(7)

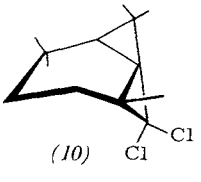


(8)



(9)

Starting from the ketone $[D_5]$-*(6)* bearing deuterium labels at the α and α′ positions we prepared $[D_5]$-*(4)*, which gave *(8)* and *(9)* on treatment with diimine and with dideuteriodiimine respectively. The CH_3^e doublet of *(7)* at 1.03 ppm ($J=7$ Hz; the peak at lower field is masked by the CH_3^f singlet at 1.07 ppm; these signals are resolved in the 60 MHz spectrum) is absent in the NMR spectrum of *(8)*; the H^c multiplet of *(7)* appears as a broad doublet for *(8)*. *(9)* shows the same H^a signal as *(8)*; the four different



(10)

methyl groups are seen as four singlets at 0.96 and 0.98 (CH_3^d, $CH_3^{d'}$)[6], 1.07 (CH_3^f), and 1.28 ppm ($CH_3^{f'}$).

In spite of its strained double bond, compound *(4)* exhibits only a slight tendency to undergo cycloadditions; it either fails to react or gives undefined products with phenyl azide, furan, and diazomethane—presumably owing to the strong repulsion between the methyl groups CH_3^d and CH_3^f in the hypothetical cycloadducts. Dichlorocarbene (from $LiCCl_3$), however, reacts readily to give the bridged spirane *(10)* whose structure is supported by spectroscopy.

Our findings suggest that the hitherto unknown bicyclic compounds *(2)*, $n=2$ and 3, have finite though limited lifetimes.

Received: September 22, 1971 [Z 529 IE]
German version: Angew. Chem. *84*, 62 (1972)

[1] *K. B. Wiberg* and *R. A. Fenoglio*, J. Amer. Chem. Soc. *90*, 3395 (1968).

[2] *J. Bredt*, Liebigs Ann. Chem. *437*, 1 (1924).

[3] *F. S. Fawcett*, Chem. Rev. *47*, 219 (1950).

[4] *G. Köbrich* and *H. Heinemann*, Chem. Commun. *1969*, 2181.

[5] *S. Hünig, H. R. Müller*, and *W. Thier*, Angew. Chem. *77*, 368 (1965); Angew. Chem. internat. Edit. *4*, 271 (1965).

[6] Methyl groups in 7,7-dimethylnorcarane: 0.97 ppm; *E. D. Andrews* and *W. E. Harvey*, J. Chem. Soc. *1964*, 4636.

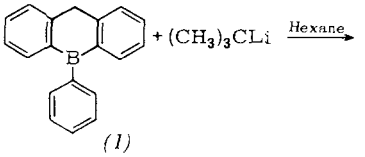
Preparation of the 9-Phenyl-9-boraanthracene Anion[**]

By *Peter Jutzi*[*]

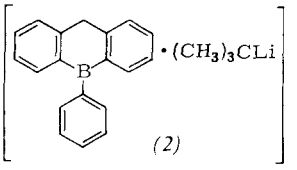
π-Bonds between boron and carbon, which command considerable theoretical interest, are hardly known: The preparation of a highly unstable 9-boraanthracene-dimethylsulfane adduct[1] and of the free[2] and complexed[3] 1-phenyl-1-borabenzene anion have only been accomplished very recently[11].

Depending on the reaction conditions the reaction of 9-phenyl-9,10-dihydro-9-boraanthracene *(1)*[4] with *tert*-butyllithium can yield different products:

In hexane as solvent the reactants form the Lewis acid-base pair *(2)* almost quantitatively; *(2)* can be isolated as a very reactive crystalline substance[5].



(1)



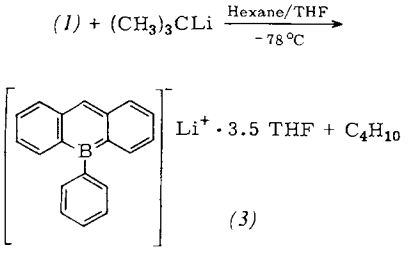
(2)

In hexane/tetrahydrofuran (1:1) compound *(1)* is metalated in position 10; the orange-red ion pair *(3)* containing the 9-phenyl-9-boraanthracene anion crystallizes from the initial oily product.

[*] Dr. P. Jutzi
Institut für Anorganische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

(3) is stable when stored in an inert gas but decomposes when exposed to air and moisture. The coordinated THF molecules cannot be removed by reduction of pressure (1 torr) for several hours: the ratio THF/Li remains constant at 3.5:1. The structure of *(3)* follows from spectro-



scopic data. Thus the ^{1}H-NMR spectrum gives the required ratios for the various protons (Table). An expected upfield shift for C_{10}-H in *(3)* is largely compensated by anisotropic or weak ring-current effects. The diamagnetic shift of the THF protons in *(3)* can also be interpreted in terms of anisotropic and ring-current effects. The enhanced electron density on the sp^2-hybridized boron atom in *(3)* due to the π-bond—and the resulting partial negative charge—become clearly apparent on comparison of the ^{11}B-NMR spectra[6] of *(1)* and *(3)* (Table): In the anion the resonance signal is shifted upfield by 68 ppm.

Table. ^{1}H- and ^{11}B-NMR spectra of tetrahydrofuran, *(1)*, and *(3)*.

Cpd.	Phenyl-H	C_{10}-H	THF protons α	THF protons β	^{11}B
THF	—	—	−3.52	−1.43	—
(1)	−(8.10–6.91)	−4.14	— [7]	—	−58
(3)	−(7.83–6.89)	−4.05	−3.10	−1.28	+10

Ca. 30% solution in C_6D_6; chemical shifts in ppm relative to TMS as internal standard and $BF_3 \cdot OEt_2$; a negative sign indicates a downfield shift.

The electronic spectra of the 9-boraanthracene-dimethylsulfane complex[11] and of *(3)* are reproduced in Fig. 1. The characteristic form of the curve is almost identical in both cases, though it is shifted to longer wavelengths in the case of *(3)*.

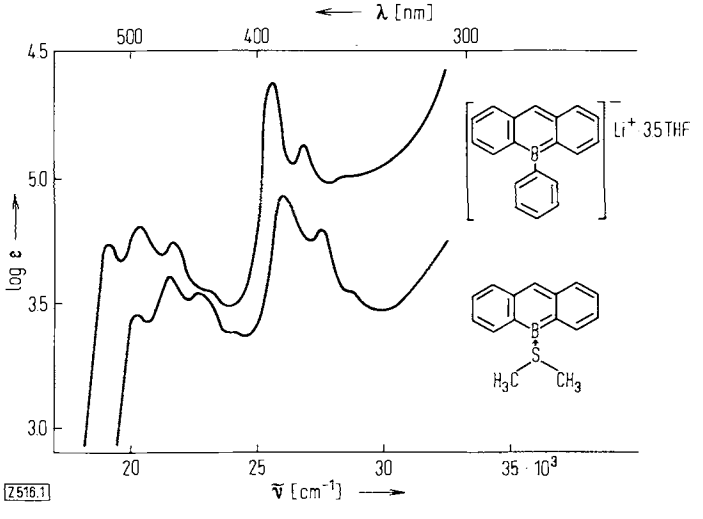


Fig. 1. Electronic spectra of the 9-boraanthracene-dimethylsulfane complex and of compound *(3)* recorded in tetrahydrofuran [8].

The structures of the long-wave absorption maxima in the spectra of anthracene (^{1}La band), 9-phosphaanthracene[9], 9-arsaanthracene[10], and 9-boraanthracene are very similar and provide a clear indication of comparable 14 π-electron systems. The bathochromic shifts of the curves, which increase in the above order, are presumably due to the decreasing electronegativity of the hetero atoms in position 9.

Received: August 24, 1971 [Z 516 IE]
German version: Angew. Chem. *84*, 28 (1972)

[1] *P. Jutzi*, Int. Symp. Chem. Nonbenzenoid Aromatic Compounds, Sendai (Japan) 1970, Abstr. p. 147.

[2] *A.J. Ashe, III* and *P. Shu*, J. Amer. Chem. Soc. *93*, 1804 (1971).

[3] *G.E. Herberich, G. Greiss*, and *H.F. Heil*, Angew. Chem. *82*, 838 (1970); Angew. Chem. internat. Edit. *9*, 805 (1970).

[4] *P. Jutzi*, Chem. Ber. *104*, 1455 (1971).

[5] The structure of *(2)* was proved by elemental analysis, the ^{1}H-NMR spectrum, and chemical reactions.

[6] I am indebted to Dipl.-Chem. *B. Wrackmeyer*, Universität München, for recording the ^{11}B-NMR spectra.

[7] An adduct from *(1)* and THF could neither be isolated nor detected by spectroscopy.

[8] Owing to the extreme sensitivity of *(3)*, particularly in dilute solution, a parallel shift of the extinction curve along the ordinate cannot be ruled out.

[9] *P. de Koe* and *F. Bickelhaupt*, Angew. Chem. *79*, 533 (1967); Angew. Chem. internat. Edit. *6*, 567 (1967).

[10] *P. Jutzi* and *K. Deuchert*, Angew. Chem. *81*, 1051 (1969); Angew. Chem. internat. Edit. *8*, 991 (1969); *H. Vermeer* and *F. Bickelhaupt*, Angew. Chem. *81*, 1052 (1969); Angew. Chem. internat. Edit. *8*, 992 (1969).

[11] Meanwhile the existence of a 9-mesityl-9-boraanthracene anion in solution has been proved by UV spectroscopy: *R. Van Veen* and *F. Bickelhaupt*, J. Organometal. Chem. *30*, C 51 (1971).

7-Isopropylidenenorbornadiene

By *Hans-Dieter Martin* and *Dieter Forster*[*]

In the present communication we report a bicyclic triene having formally isolated double bonds whose spectroscopic properties indicate a considerable measure of homoconjugation[1].

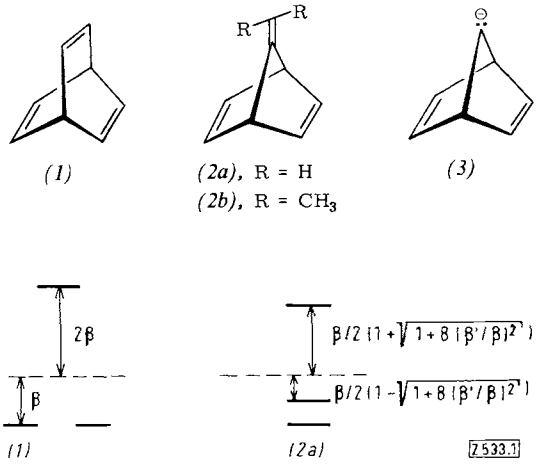
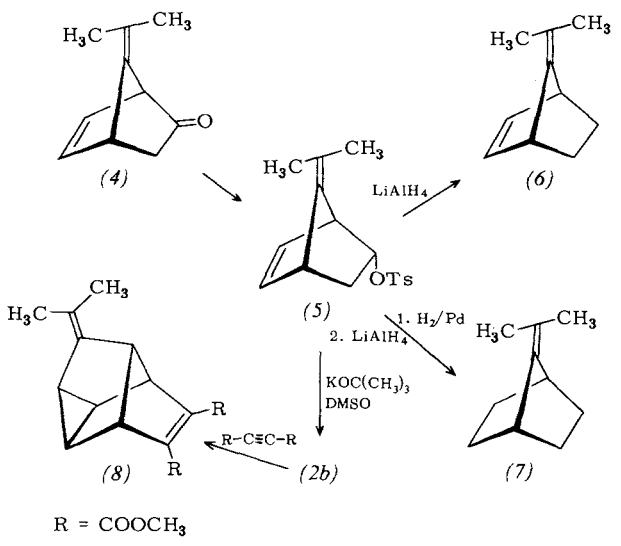


Fig. 1. Hückel eigenvalue schemes of *(1)* and *(2a)*. β is the resonance integral for homoconjugation in barrelene *(1)* and in the norbornadiene part of *(2a)*; β' refers to the interaction of the 7-methylene double bond with the two endocyclic π bonds in *(2a)*. Equal energies have been assumed for all three basis orbitals.

[*] Dr. H.-D. Martin and D. Forster
Institut für Organische Chemie der Universität
78 Freiburg, Albertstrasse 21 (Germany)



The tosylate *(5)* was prepared by way of the ketone *(4)*[6]; dehydrotosylation of *(5)* to *(2b)* (15–20% yield) with potassium *tert*-butoxide was carried out in dimethyl sulfoxide at 70 °C. *(5)* could also be reduced directly to *(6)* (74% yield) by $LiAlH_4$ in ether; if reduction is performed after prior hydrogenation[6] of *(5)* then *(7)* is obtained in 82% yield.

The most important data for these compounds are collected in the Table. *(2b)* is a weakly yellow liquid[8] which has a peculiar odor and survives 24 hours' heating at 100 °C. Together with dimethyl acetylenedicarboxylate at 100 °C it gives the adduct *(8)* in a kind of homo-Diels-Alder reaction [NMR data of *(8)* (see also footnote [b] to the Table): $\tau = 6.15$ (s), 7.05 (m), 7.35 (m), 7.75 (t), 8.15 (m), 8.27 (s), 8.35 (s)].

Photoelectron spectroscopic studies[9] on *(2b)* revealed a high degree of cyclic homoconjugation. If the *exo*-isopropylidene bond in *(2b)* is assumed to have a basis

Cpd. b.p. (C/torr)	UV [a]	^{1}H-NMR [b]	Gas chromatography [c]	Mass spectrum
(2b) 64/20	300 (S, 30) [d] 260 (S, 184)	3.21 (4 H/"t") 6.02 (2 H/m) 8.59 (6 H/s)	10% SE 30 on 45/60 Chromosorb W 10′ × ⅜″, 90 °C, 16 min	132 (M^+, 82%) 117 (100%) 91 (69%)
(6) 70/20		3.89 (2 H/"t") 6.80 (2 H/m) 8.15 to 9.20 (4 H/m) 8.49 (6 H/s)	10% Carbowax 20 M on 45/60 Chromosorb W 10′ × ⅜″, 88 °C, 9 min	134 (M^+, 11%) 119 (15%) 106 (100%) 91 (88%)
(7) 58/14		7.48 (2 H/m) 8.20 to 8.95 (8 H/m) 8.39 (6 H/s)	10% SE 30 on 45/60 Chromosorb W 10′ × ⅜″, 103 °C, 14 min	136 (M^+, 38%) 121 (30%) 108 (66%) 107 (74%) 93 (100%) 91 (55%) 79 (66%)

[a] λ_{max} nm (ε), S = shoulder. For comparison: *(1)*, $\lambda_{max} = 239$ nm (ε = 302), 208 (1120) (in ethanol) [7]. Norbornadiene: $\lambda_{max} = 230$ nm (ε = 200), 220 (870), 214 (1480), 205 (2100) (in ethanol) [7].
[b] 60 MHz, CCl_4, TMS internal reference, τ scale, "t" = pseudotriplet, m = multiplet, s = singlet.
[c] Column, temperature, retention time (helium, 170 ml/min).
[d] In ether.

If a further double bond approaches a 1,4-cyclohexadiene system then the possible arrangements include two particularly significant ones: Barrelene *(1)* and 7-methylenenorbornadiene *(2a)*, which is iso-π-electronic with the hitherto unknown longicyclic[2] anion *(3)*. The Hückel eigenvalue schemes of *(1)* and *(2a)* are depicted in Figure 1.

Whereas adequate information is available regarding the electronic system of *(1)*[3], there is a dearth of comparable data for system *(2)*. Hitherto reference has been made only to the interesting electron-spectroscopic properties of various substituted methylenenorbornadienes that are readily available by diene synthesis[4]. The vapor pressure of these compounds was too low, however, for gas phase spectroscopic studies.

Attempted syntheses of the more symmetrical and relatively volatile 7-isopropylidenenorbornadiene *(2b)* by oxidative decarboxylation of the maleic acid/dimethylfulvene adduct (electrochemically and with lead(IV) acetate) have so far been unsuccessful[5]. We chose a synthetic pathway leading *via* the tosylate *(5)*, from which the partially hydrogenated derivatives *(6)* and *(7)* (essential for detailed spectroscopic analysis) could also be obtained.

energy ($E = -3\beta/2$) differing from that of the two other double bonds ($E = 0$), more in line with the actual conditions prevailing, then the expression for the energy of the highest

[1] *P. Bischof*, *R. Gleiter*, and *E. Heilbronner*, Helv. Chim. Acta *53*, 1425 (1970); *S. Winstein* in: Aromaticity. Spec. Publ. No. 21, Chem. Soc., London 1967; *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971); *P. Bischof*, *E. Heilbronner*, *H. Prinzbach*, and *H.-D. Martin*, Helv. Chim. Acta *54*, 1072 (1971).

[2] *M. J. Goldstein* and *R. Hoffmann*, Symmetry, Topology and Aromaticity, Internat. Symposium on the Chemistry of Nonbenzenoid Aromatic Compounds, Sendai, August 1970.

[3] *E. Haselbach*, *E. Heilbronner*, and *G. Schröder*, Helv. Chim. Acta *54*, 153 (1971).

[4] *H. Prinzbach* and *J. Rivier*, Helv. Chim. Acta *53*, 2201 (1970).

[5] *H. Prinzbach*, *T. Hink*, and *D. Stusche*, unpublished.

[6] *C. H. DePuy* and *P. R. Story*, J. Amer. Chem. Soc. *82*, 627 (1960).

[7] *C. F. Wilcox*, *S. Winstein*, and *W. G. McMillan*, J. Amer. Chem. Soc. *82*, 5450 (1960); *H. E. Zimmermann* and *R. M. Paufler*, *ibid.* *82*, 1514 (1960).

[8] Compound *(2b)* appears to be homogeneous after purification by preparative scale gas chromatography. Contamination by a compound having the same retention time, however, cannot be ruled out; the NMR spectrum shows that its concentration must be under 1%.

[9] *E. Heilbronner* and *H.-D. Martin*, to be published; *E. Heilbronner*, Pure and Appl. Chem. *7*, 9 (1971).

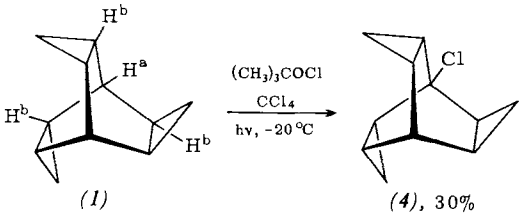
occupied molecular orbitals becomes $E=\beta/4\times(-5\pm\sqrt{1+32(\beta'/\beta)^2})$. Qualitatively the orbital scheme given for *(2a)* in Figure 1 is retained, *i.e.* $\Delta E_{1,2}\approx 4\Delta E_{2,3}$ is valid for the energy differences $\Delta E_{1,2}$ and $\Delta E_{2,3}$ between the three highest occupied orbitals. β and β' are of the same order. The energy level diagram for the ion *(3)* should be similar.

Received: August 10, 1971;
supplemented: November 22, 1971 [Z 533 IE]
German version: Angew. Chem. *84*, 65 (1972)

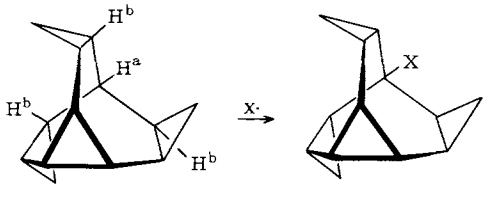
Bridgehead Reactivities of Trishomobarrelene and Trishomobullvalene[**]

By *Armin de Meijere, Otto Schallner*, and *Christian Weitemeyer*[*]

The extent to which a carbonium ion is stabilized by α-cyclopropyl substituents depends upon the orientation of the cyclopropane rings relative to the axis of the adjacent vacant p orbital of the carbonium ion[1]. Whereas the tricyclopropylmethyl cation is about as stable as the triphenylmethyl cation[2], destabilization is observed in a



(1) *(4)*, 30%



(2)

(3a), X = O-OH
(3b), X = OH 10%
(3c), X = CCl_2H 60%
(3d), X = Cl 30%

case in which the plane of the cyclopropane ring and the axis of the vacant p orbital are held perpendicular to each other[3]. In "trishomobarrelene" *(1)* and "trishomobullvalene" *(2)*[4] the "propeller"-cyclopropane rings are arranged in such a way that a partial stabilization of the corresponding bridgehead carbonium ions should result.

Bridgehead substituted derivatives of *(1)* and *(2)* are accessible by radical substitution reactions. *(2)* is readily autoxidized; upon standing in the presence of air the hydroperoxide *(3a)* is formed. *(3a)* decomposes upon heating to 100 °C to give the alcohol *(3b)*, m.p. 183 to 186 °C, which could be isolated in 10—15% yield by gas chromatography. The reaction of *(2)* with dichlorocarbene, generated by the method of *Makosza* and *Wawrzyniewicz*[5, 6], gave a 60% yield of the dichloromethyl derivative *(3c)*, m.p. 91 °C. Photochlorination of *(2)* in carbon tetrachloride with *tert*-butyl hypochlorite at −20 °C yielded 30% of pure 1-chlorotrishomobullvalene *(3d)*, m.p. 128—129 °C. 1-Chlorotrishomobarrelene *(4)*, m.p. 114 to 116 °C, could be obtained analogously in the same yield.

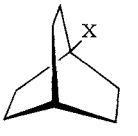
The NMR- and mass spectra as well as elemental analyses of compounds *(3b)*—*(3d)* and *(4)* are in accord with the proposed structures.

The exclusive substitution at the bridgehead positions in *(1)* and *(2)* observed in the reported reactions suggests a special reactivity of these positions. In order to obtain some information about the stabilization of the bridgehead carbonium ions of *(1)* and *(2)*, we measured the half-reaction times of the solvolysis of *(3d)* and *(4)* in 90% aqueous ethanol[7]. The rate constants which were estimated from these data (see Table 1) indicate that at 25 °C *(4)* reacts about 300 times faster than *tert*-butyl chloride *(5a)* and more than 10^9 times faster than 1-chlorobicyclo[2.2.2]octane *(6a)*[8].

(3d) is so reactive that it is readily hydrolyzed to the alcohol *(3b)* upon exposure to moist air; in 90% aqueous ethanol even at 0 °C it is solvolyzed so rapidly that the half-reaction time could not be measured very accurately. At 0 °C *(3d)* reacts more than 10^{11} times faster than *(6a)* at 25 °C.

The geometry of *(1)* and *(2)* which is pertinent to this reactivity may be estimated from NMR-spectroscopic data (see Table 2). The $^{13}C,H$ coupling constants indicate that the bridgehead carbon in *(2)* is sp^3 hybridized whereas the bridgehead C—H bond in *(1)* exhibits a slightly higher

$(CH_3)_3C$-X
(5a), X = Cl
(5b), X = Br



(6a), X = Cl
(6b), X = Br

Table 1. Relative solvolysis rate constants of some tertiary halides in 90% aqueous ethanol.

Cpd.	t (°C)	k (sec^{-1})	k_{rel}	k_{rel}	Ref.
(4)	25	5.5×10^{-4} [a]	3×10^{2}	$>10^{9}$	
(3d)	0	(7×10^{-2}) [a]	(4×10^{4})	$>10^{11}$	
(5a)	25	1.73×10^{-6}	1.0	5×10^{6}	[10]
(5b)	25	7.14×10^{-5}	41	5×10^{7}	[10]
(6a)	25	$<4\times10^{-13}$	$<2.3\times10^{-7}$	1.0	[8]
(6b)	25	4.05×10^{-12}	2.34×10^{-6}	>10	[9]

[a] Estimated from the measured half-reaction time.

s character, *i.e.* the C—C—C angles at the bridgehead in *(1)* are smaller than in *(2)*. The dihedral angles (φ_{HH}) between the bridgehead protons (H^a) and the adjacent tertiary cyclopropyl protons (H^b) can be estimated from the vicinal coupling constants ($^3J_{HH}$) between the two[11] (see Table 2). The angle between the plane of a cyclopropane ring and a vacant bridgehead p orbital ($\varphi_{p-\pi}$) is approximately $90°-\varphi_{HH}$. Since the energy of interaction between two π-electron systems is proportional to $\cos^2\varphi$ of the torsional angle φ between the two[12], one may derive the crude approximation that the stabilization of the bridgehead carbonium ion per α-cyclopropyl group in *(1)* should be about 67% and in *(2)* about 45% of the greatest possible stabilization.

The experimentally determined reactivities of *(3d)* and *(4)* are in satisfactory agreement with these estimates.

[*] Dr. A. de Meijere, Dipl.-Chem. O. Schallner, and Dipl.-Chem. C. Weitemeyer
Organisch-chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

[**] Presented at the "International Symposium on the Chemistry of Small Ring Compounds and Activated Multiple Bonds", Louvain, Belgium, Sept. 13—16, 1971.

Table 2. $^{13}C,H$- and vicinal H,H-coupling constants of the bridgehead protons in *(1)* and *(2)*.

Cpd.	$J_{^{13}C,H}$ (Hz)	s character (%)	$^3J_{HH}$ (Hz)	φ_{HH} (°)	$\varphi_{p-\pi}$ (°)	E_φ E_0
(1)	137	27 [a]	4.24	55	35	0.67
(2)	127	25 [a]	5.44	42	48 [14]	0.45

[a] Calculated from the equation $\% s = J_{^{13}C,H}/500$ [13].

Although the effect of stabilization in *(4)* is predicted to be larger than in *(3d)*, the latter reacts about 10^2 to 10^3 times faster than *(4)* because the bridgehead in *(3d)* is less strained and therefore the corresponding carbonium ion should more readily attain planarity.

Received: September 24, 1971 [Z 530 IE]
German version: Angew. Chem. *84*, 63 (1972)

[1] For references see [3a].

[2] *H. A. Hart* and *J. M. Sandri*, J. Amer. Chem. Soc. *81*, 320 (1959); *H. A. Hart* and *P. A. Law*, *ibid. 84*, 2462 (1962); *86*, 2959 (1964).

[3] a) *P. von R. Schleyer* and *V. Buss*, J. Amer. Chem. Soc. *91*, 5880 (1969); b) *J. C. Martin* and *B. R. Ree*, *ibid. 91*, 5882 (1969).

[4] *A. de Meijere* and *C. Weitemeyer*, Angew. Chem. *82*, 359 (1970); Angew. Chem. internat. Edit. *5*, 376 (1970).

[5] *M. Makosza* and *M. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659.

[6] Cf. *I. Tabushi*, *Z. Yoshida*, and *T. Takahashi*, J. Amer. Chem. Soc. *92*, 6670 (1970).

[7] Exact kinetic determinations are in progress.

[8] The solvolysis rate constant of *(6a)* is unknown, therefore it was estimated from the value for *(6b)* [9] and the known difference between the rates of *(5a)* and *(5b)*.

[9] Calculated from the measured value for 80% aqueous ethanol; *P. Brenneisen*, *C. A. Grob*, *R. A. Jackson*, and *M. Ohta*, Helv. Chim. Acta *48*, 146 (1965).

[10] *E. Grunwald* and *S. Winstein*, J. Amer. Chem. Soc. *70*, 846 (1948).

[11] *M. Karplus*, J. Chem. Phys. *30*, 11 (1959); in the present case a Karplus equation was used which was fitted for the vinylcyclopropane system with empirical constants: *H. Klose*, Dissertation, Universität Köln 1969.

[12] *I. Fischer-Hjalmars*, Tetrahedron *19*, 1805 (1963).

[13] *D. Seebach*, Angew. Chem. *77*, 119 (1965); Angew. Chem. internat. Edit. *4*, 121 (1965).

[14] *Note added in proof* (Dec. 5, 1971): An electron diffraction structure analysis of *(2)* has indicated that the angle $\varphi_{p-\pi}$ is actually about 65°, *i.e.* larger than the crude estimate obtained from the H,H-coupling constant. This will probably also apply to *(1)* (*B. Andersen*, *A. de Meijere*, and *O. Schallner*, unpublished results).

Mössbauer Measurements on Neptunium(VII) Compounds[**]

By *Klaus Fröhlich*, *Philipp Gütlich*, and *Cornelius Keller*[*]

Until a few years ago neptunium(VII) compounds were unknown. Recently, a number of neptunium compounds were prepared, which, on the basis of the preparation method and stoichiometric composition, are supposed to contain heptavalent neptunium (nominal valency with electronic configuration $[Rn]5f^0 6d^0 7s^0$)[1-6]. We have carried out Mössbauer measurements on a few of these compounds, namely Li_5NpO_6 *(1)*, $[Co(en)_3]NpO_5 \cdot xH_2O$[7] *(2)*, $Ba_3(NpO_5)_2 \cdot xH_2O$ *(3)*, and $Ca_3(NpO_5)_2 \cdot xH_2O$ *(4)*, to prove the oxidation state of the neptunium and to learn more about the structural and bond properties[8].

All measurements were made with source and absorber at 4.2 K. The compounds were used as absorber and the source was an alloy of ^{241}Am (5%) in thorium metal.

A more negative isomer shift (δ) than that for NpF_6 was obtained for all the materials studied (see Table). [According to previous Mössbauer spectroscopic investigations of neptunium(VI) compounds, NpF_6 is the most ionic in character and consequently exhibits the most negative isomer shift: its value, $\delta = -58$ mm/s (relative to NpO_2)[9], is the lower limit of the assumed characteristic isomer-shift range for Np^{VI} compounds.] Since $\Delta\langle r^2\rangle/\langle r^2\rangle$ for ^{237}Np is negative[10], it follows from the δ values that the electron density at the neptunium nucleus of the compounds under investigation is greater than in the case of NpF_6. In the oxygen-bonded compounds the valence electrons of the oxygen, which tends to be more covalent than fluorine, mainly occupy orbitals of the neptunium atom which shield s electrons from the nucleus. The covalent contribution to the Np—O bonding must introduce additional shielding to the s electrons of the central neptunium atom and thus lead to a lower electron density at the Np nucleus in Np—O compounds compared to Np—F compounds. The higher electron densities following from the measured δ values can be adequately explained only by the presence of heptavalent neptunium. The absence of the last 5f electron in Np(VII)—compared to Np(VI)—results in a weaker shielding of the s electrons (mainly on the 6s shell) and thus leads to the observed increase in electron density at the Np nucleus.

Table. Isomer shift (δ), quadrupole splitting (ΔE_Q), and asymmetry parameter (η) of neptunium compounds *(1)*—*(4)*. Source ($^{241}Am/Th$) and absorber at 4.2 K.

Absorber	δ [a] [mm s^{-1}]	ΔE_Q [mm s^{-1}]	η
(1)	-68.7 ± 2.9	15.3 ± 0.5	0.33 ± 0.01
(2)	-61.1 ± 2.6	44.6 ± 1.0	0.23 ± 0.02
(3)	-60.2 ± 2.8	43.2 ± 1.0	0.40 ± 0.03
(4)	-60.7 ± 3.0	33.7 ± 1.0	0.38 ± 0.03

[a] Isomer shift relative to NpO_2.

The occurrence of quadrupole splitting ΔE_Q (see Table) in the case of Li_5NpO_6 *(1)* disproves the previously presumed O_h symmetry of the NpO_6^{5-} ion[5,6]. Present findings are more consistent with a compressed octahedron (neptunyl group in the *z* direction). The deviation of the asymmetry parameter η from zero (see Table) indicates that the central Np atom is not situated at the symmetry center (*e.g.* due to presence of a non-linear neptunyl group) or that the *xy* plane formed by oxygen atoms is rhombically distorted.

The ΔE_Q values for compounds *(2)*, *(3)*, and *(4)* are two to three times greater than the value for *(1)*. This is explained as being due to the Np—O bond lengths of the neptunyl group in these compounds being shorter than in Li_5NpO_6. The more positive δ values measured for these three compounds support this explanation. The deviations of the η values from zero suggest that the common anion formed by all three compounds is $[NpO_4(OH)_2]^{3-}$ and not NpO_5^{3-}. The presence of both *trans*-O atoms and *trans*-OH groups in this anion in addition to the neptunyl group readily explains the observed values of the quadrupole splitting and asymmetry parameters (the two Np—O bond lengths in the *xy* plane are smaller than the Np—OH dis-

[*] Prof. Dr. P. Gütlich and Dr. K. Fröhlich
Eduard-Zintl-Institut für Anorganische und Physikalische Chemie der Technischen Hochschule
61 Darmstadt, Hochschulstrasse 4 (Germany)
Prof. Dr. C. Keller
Kernforschungszentrum
75 Karlsruhe, Postfach 3640 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Bundesministerium für Bildung und Wissenschaft.

tances). Such a tetragonal-bipyramidal configuration with compression in the z direction and rhombic distortion in the xy plane is the simplest structure consistent with the Mössbauer measurements.

Received: August 20, 1971 [Z 514 IE]
German version: Angew. Chem. *84*, 26 (1972)

[1] *N. N. Krot* and *A. D. Gel'man*, Dokl. Akad. Nauk SSSR *177*, 124 (1967).

[2] *N. N. Krot, M. P. Mefod'eva, I. V. Smirnova*, and *A. D. Gel'man*, Radiokhimiya *10*, 412 (1968).

[3] *V. I. Spitsyn, N. N. Krot, M. P. Mefod'eva*, and *A. D. Gel'man*, Dokl. Akad. Nauk SSSR *181*, 128 (1968).

[4] *V. I. Spitsyn, A. D. Gel'man, N. N. Krot, M. P. Mefod'eva, F. A. Zakharova, Y. A. Komkov, V. P. Shilov*, and *I. V. Smirnova*, J. Inorg. Nucl. Chem. *31*, 2733 (1969).

[5] *C. Keller* and *H. Seiffert*, Inorg. Nucl. Chem. Lett. *5*, 51 (1969).

[6] *S. K. Awasthi, L. Martinot, J. Fuger*, and *G. Duyckaerts*, Inorg. Nucl. Chem. Lett. *7*, 145 (1971).

[7] en = Ethylenediamine.

[8] Compounds *(1)*—*(4)* were prepared by *J. Gross* and *H. Seiffert* at the Kernforschungszentrum, Karlsruhe; see also *J. Gross*, Dissertation, Universität Stuttgart 1970; Report KFK 1339 (1970).

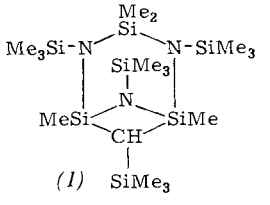
[9] *G. M. Kalvius*, private communication.

[10] *B. D. Dunlap, G. M. Kalvius, S. L. Ruby, M. B. Brodsky*, and *D. Cohen*, Phys. Rev. *171*, 316 (1968).

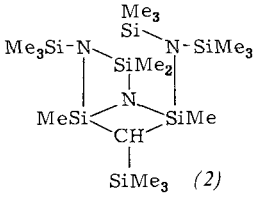
Two Crystal Structures of Cyclic Silicon-Nitrogen Compounds with Different Disorder[**]

By *Dietrich Mootz, José Fayos*, and *Annette Zinnius*[*]

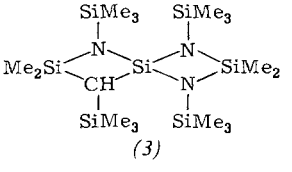
Dropwise addition of silicon tetrachloride to sodium bis(trimethylsilyl)amide at 200 °C gives the compound $C_{17}H_{49}N_3Si_7$, whose structure could not for a long time be determined unequivocally by chemical and spectroscopic methods[1]. We have carried out an X-ray crystal structure analysis of this substance in an attempt to decide between the formulas *(1)* and *(2)*, proposed to be equally probable. The results indicate that both these formulations can be ruled out in favor of a four-ring spirane structure *(3)*.



(1)



(2)



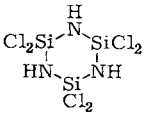
(3)

[*] Prof. Dr. D. Mootz
Max-Planck-Institut für Festkörperforschung
7 Stuttgart 1, Heilbronner Strasse 69 (Germany)
Dr. J. Fayos
Instituto de Química Física Rocasolano
Madrid 6, Serrano 119 (Spain)
Dr. A. Zinnius
Institut für Kristallographie
der Technischen Hochschule
51 Aachen, Templergraben 55 (Germany)

[**] These investigations were supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. They were carried out at the Institut für Anorganische Chemie der Technischen Universität Braunschweig. We are indebted to Prof. Dr. *U. Wannagat* for posing the problems and supplying the crystals.

The substance crystallizes in the orthorhombic system with $a = 19.552$, $b = 33.518$, and $c = 10.196$ Å; $d = 0.97$ g cm^{-3}. Hence, by calculation, the unit cell contains $Z = 8$ (7.93) $C_{17}H_{49}N_3Si_7$ molecules. This number and the observed space group Fddd-D_{2h}^{24} as lowest symmetry of the molecule in the crystal necessitate the point group 222-D_2, which, in principle, is not realized by formulas *(1)* and *(2)*, but very closely approached by formulation *(3)*. Consequently, the further structural analysis had to be carried out on the basis of a four-fold superposition of structure *(3)*, which leads to statistical equivalence of the three N atoms and the CH group of the spiro system. However, because of the different stereochemistry of N and CH, such a superposition does not give *exact* coincidence of these and all other, especially the outer, atoms. As a consequence of this, and of a further disorder in the orientation of the trimethylsilyl group, the accuracy of the analysis is limited.

Reflection intensities were measured on an automatic single crystal diffractometer fitted with punched-tape control (AED, *W. Hoppe*, *ex* Siemens) using $Cu_{K\alpha}$ radiation and the θ:2θ scan technique ($\theta_{max} = 50°$). Conventional methods were used for solving the structure. Refinement with anisotropic thermal parameters led to R factors of 0.071 for 591 observed reflections alone, and 0.088 on inclusion of 236 "unobserved" data. The bond lengths and angles thus obtained [bond lengths: Si—N(C) = 1.74 Å (in and at the spirosystem; three independent measurements) and Si—C = 1.82 Å; bond angles: N(C)—Si—N(C) = 88° (two independent measurements in the four-membered ring), Si—N(C)—Si = 92° in the ring and 130 and 138° at the ring, and C—Si—C = 104° at the ring] support this structure and disorder model (standard deviations *ca.* 0.01 Å and 1°).



(4)

Hexachlorocyclotrisilazane *(4)* can be prepared by controlled ammonolysis of silicon tetrachloride[2]. Its IR spectrum indicated a planar six-membered ring structure with point group $\bar{6}m2$-D_{3h}[3]. A crystal structure analysis carried out by us in an attempt to gain further information about the architecture of this purely inorganic Si—N compound once again led to a disordered structure adversely affecting accuracy of analysis.

The X-ray photographs show diffuse ($h - k \neq 3n$) reflections as well as sharp ($h - k = 3n$) reflections, indicating an order-disorder (OD) structure. The symmetry is hexagonal (Laue group 6/mmm). Only the sharp reflections were used for determination of structure (102 data, $Cu_{K\alpha}$, $\theta_{max} = 70°$, diffractometer). The superimposed structure defined by this data has the lattice constants $A = 4.554$ and $C = 11.766$ Å and contains 2/3 molecules in the unit cell. Of the three space groups $P6_3mc$, $P\bar{6}2c$, and $P6_3/mmc$ that are possible on the grounds of the single extinction $0KL$ with $L = 2n$, the last, centrosymmetric one was assumed in order to provide the relatively best resolution for the superimposed structure. Thus, from the outset, the molecular symmetry was restricted to $\bar{6}m2$-D_{3h}. The determination and refinement of the atomic positions—which could be carried out by conventional methods—led to the following plausible bond lengths and angles: Si—N = 1.68, Si—Cl = 2.03 Å; Si—N—Si = 131°, N—Si—N = 109°, and Cl—Si—Cl = 103° (standard deviations *ca.* 0.01 Å and 1°; R-factor 0.093).

The molecules form layers perpendicular to the *c*-axis and rotated through 60° to one another. Thus, a layer B′ *or* a layer C′ can follow a layer A without influencing the interatomic distances and angles between adjacent layers (see Figure; the dash signifies rotation with respect to the start-

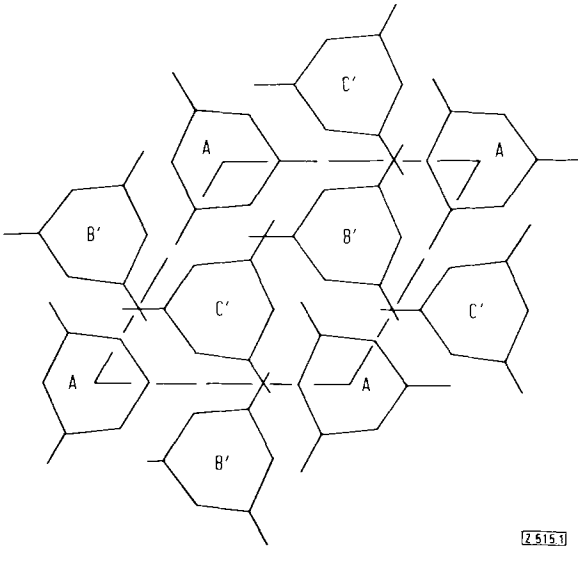


Fig. Disorder of hexachlorocyclotrisilazane.

ing layer; the outlined rhombus is the basal plane of the unit cell defined by *all* reflections). Stacking faults of this type give the structure its OD character.

Received: August 23, 1971 [Z 515 IE]
German version: Angew. Chem. *84*, 27 (1972)

[1] *U. Wannagat, J. Herzig,* and *H. Bürger,* J. Organometal. Chem. *23*, 373 (1970).

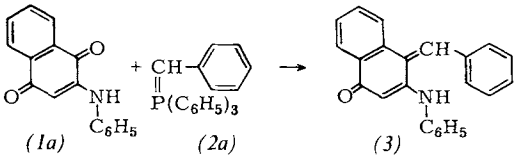
[2] *U. Wannagat, P. Schmidt,* and *M. Schulze,* Angew. Chem. *79*, 409 (1967); Angew. Chem. internat. Edit. *6*, 446 (1967).

[3] *H. Bürger,* Inorg. Nucl. Chem. Lett. *3*, 43 (1967).

A Novel Method for the Synthesis of Acridinium Betaines

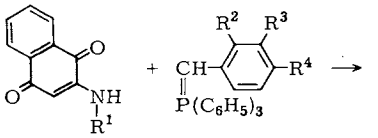
By *Hans-Jürgen Bestmann, Hans-Jochen Lang,* and *Werner Distler*[*]

During the course of our investigations on reactions of quinones with ylides we were able to isolate the red quinone methide *(3)* from the reaction of 2-anilino-1,4-naphthoquinone *(1a)* with benzylidenetriphenylphosphorane *(2a)*[1].

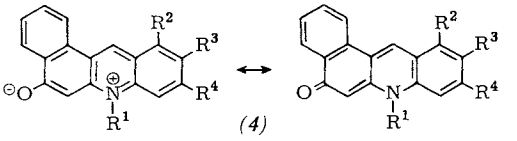


(1a) *(2a)* *(3)*

We have now found that reaction of naphthoquinones *(1a)*—*(1c)* with phosphoranes *(2a)*—*(2c)* leads, under more drastic conditions, to the new class of compounds of the benzo- or dibenzoacridinium betaines *(4)*. *(4)* can be described by two mesomeric limiting formulas.



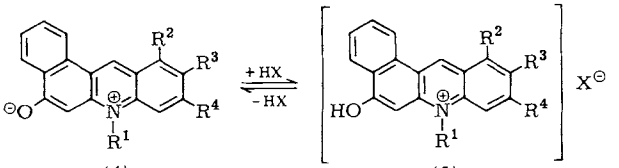
(1a), $R^1 = C_6H_5$ *(2a)*, $R^2 = R^3 = R^4 = H$
(1b), $R^1 = CH_3$ *(2b)*, $R^2 = R^3 = H$, $R^4 = OCH_3$
(1c), $R^1 = C_2H_5$ *(2c)*, $R^2, R^3 =$  , $R^4 = H$



(4)

On treatment with hydrochloric acid or trifluoroacetic acid, compounds *(4)* are converted into the acridinium salts *(5)*; the conversion is reversible.

All compounds of type *(4)* are orange to dark-red and fluoresce exceptionally strongly in polar solvents. Proof of structure for *(4)* followed from elemental analysis, IR



(4) *(5)*

and mass spectra, and from the fact that distillation of 10-phenylbenzo[*a*]acridinium-3-olate *(4aa)* in the presence of zinc dust gives benz[*a*]acridine, which is identical with authentic material[2].

Table. Acridinium betaines *(4)* from 2-amino-1,4-naphthoquinone *(1)* and benzylidenetriphenylphosphoranes *(2)*.

Cpd.	R^1	R^2	R^3	R^4	Yield (%)	M.p. (°C)	Color
(4aa)	C_6H_5	H	H	H	20	270	orange-red
(4ab)	C_6H_5	H	H	—O—CH_3	11	280	orange
(4ac)	C_6H_5	—$(CH)_4$—		H	42	293	red-brown, metallic luster
(4bc)	$-CH_3$	—$(CH)_4$—		H	46	285	red
(4cc)	$-C_2H_5$	—$(CH)_4$—		H	11	253	dark-red, metallic luster

Experimental:

(1a) (50 mmol; 12.5 g) is added portionwise with stirring under nitrogen to a salt-free solution of the ylide *(2a)* (50 mmol) in anhydrous xylene[3]. The reaction mixture is heated under reflux for five days. The solvent is then distilled off and the residue boiled in benzene (100 ml). On rubbing the benzene solution and allowing it to cool in the refrigerator, a crude crop of *(4aa)* is precipitated which is then purified by reprecipitation from chloroform/petroleum ether and recrystallization from ethyl acetate. All the compounds *(4)* mentioned above were prepared analogously.

The acridinium chlorides of type *(5)* are obtained in almost quantitative yields by treatment of compounds *(4)* with

[*] Prof. Dr. H. J. Bestmann and Dipl.-Chem. W. Distler
Institut für Organische Chemie
der Universität Erlangen-Nürnberg
852 Erlangen, Henkestrasse 42 (Germany)
Dr. H. J. Lang
Farbwerke Hoechst Pharmaforschung (Germany)

methanolic HCl and subsequent removal of solvent. The acridinium betaines *(4)* can be recovered again from these salts by reaction with 2N NaOH in methanolic solution and subsequent precipitation with water.

Received: September 28, 1971 [Z 531 IE]
German version: Angew. Chem. *84*, 65 (1972)

[1] *H. J. Bestmann* and *H. J. Lang*, Tetrahedron Lett. *1969*, 2101.

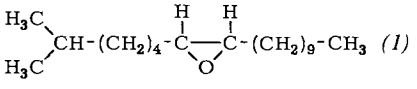
[2] *N. P. Buu-Hoi, R. Royer*, and *M. Hubert-Habart*, J. Chem. Soc. *1955*, 1082.

[3] Cf. also the review by *H. J. Bestmann*, Angew. Chem. *77*, 609, 651, 850 (1965); Angew. Chem. internat. Edit. *4*, 583, 645, 830 (1965).

Novel Total Synthesis of the Sex Attractant of *Porthetria dispar* (7,8-*cis*-Epoxy-2-methyloctadecane)

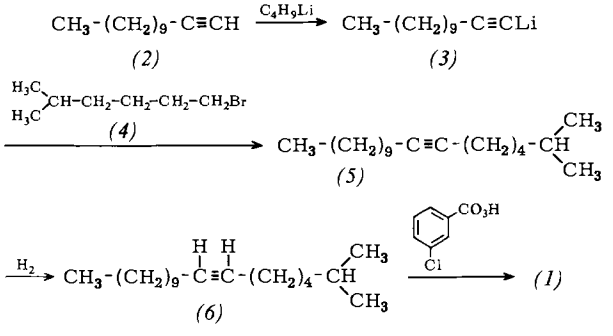
By *Karl Eiter*[*]

Bierl, Beroza, and *Collier*[1] isolated the sex attractant of the gypsy moth *(Porthetria dispar, Lymantria dispar)*, determined its structure and composition as 7,8-*cis*-epoxy-2-methyloctadecane *(1)*, and successfully carried out its total synthesis.



(1)

We have now tried to synthesize large amounts of this substance in a sterically homogeneous form in order to test its suitability as an attractant or decoy in combating this destructive insect. In view of the demands of modern environmental pollution control, this approach to the problem of pest control can be considered of utmost importance.

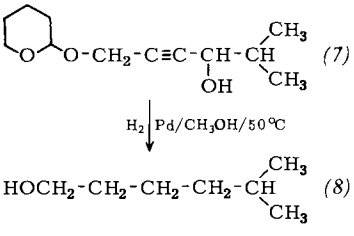


(2) *(3)* *(4)* *(5)* *(6)* *(1)*

For the synthesis of *(1)* we chose the following route:

$$C_{10} + C_2 = C_{12}, \qquad C_{12} + C_7 = C_{19}$$

A mixture containing small amounts of 1-dodecyne *(2)* has already been described[2]. We obtained pure, halogen-free 1-dodecyne in more than 70% yield by the following route: A molar amount of Na-acetylide, freshly prepared from a suspension of Na in anhydrous THF, was treated with an equal amount of 1-bromodecane dissolved in dimethyl formamide that had been distilled over CaH_2. THF was distilled off under pure N_2 until reaction at an internal temperature of 110°C proceeded exothermally. According to gas chromatography the distilled 1-dodecyne *(2)* was 96% pure. Under Zerewitinoff conditions, *(2)* gave only about 0.28% active hydrogen (calc. 0.605%). For the alkylation, *(2)* was treated in diethylene glycol dimethyl ether with an equimolar solution of *n*-butyllithium in *n*-hexane; the *n*-hexane was subsequently removed by distillation under pure N_2, and metalation to *(3)* brought to completion by eight hours' heating at 120—130°C. Introduction of isoheptyl bromide *(4)* and further reaction at 130°C (8 h) gave, after working-up, 96%[3] 2-methyl-7-octadecyne *(5)* in 50% yield. The molecular ion appears in the mass spectrum in only low intensity; the fragments occurring in the spectrum prove that degradation takes place from the unbranched end of the chain to the triple bond. The NMR spectrum shows a characteristic multiplet for $-C\equiv C-CH_2$ protons at $\delta = 2.1$ ppm (4H/m); the CH_3 protons appear at 0.80 (3 H/s) and 0.89 ppm (6 H/s), and the remaining 23 protons between 1.02 and 1.75 ppm. As is to be expected the IR spectrum [1460 (s), 1360, 1380, 1330, 760, and 725 cm^{-1}] shows no acetylene bonds in the region around 2100 cm^{-1}.



(7) *(8)*

The isoheptyl bromide *(4)* was prepared from 5-methyl-1-hexanol *(8)*, which we obtained directly in 50% yield by a novel reaction—hydrogenation of 6-(tetrahydropyran-2-yloxy)-2-methyl-4-hexyn-3-ol *(7)*. *(7)* is accessible in satisfactory yield from 3-(tetrahydropyran-2-yloxy)-1-propyne and isobutyraldehyde by organometallic reaction.

Specific *cis*-hydrogenation of the triple bond of 2-methyl-7-octadecyne *(5)* with a modified Lindlar catalyst (5 g 1%-$Pd/CaCO_3$ catalyst poisoned with 0.02 g lead acetate) proceeds exceptionally smoothly. In low-boiling petroleum ether as solvent, the calculated amount of hydrogen was taken up at about 25°C and hydrogenation terminated automatically; the 96%-pure 2-methyl-7-*cis*-octadecene *(6)*, which was obtained in quantitative yield, is an oil that is distillable under high vacuum and does not show any bands in the region of 960 cm^{-1} of its IR spectrum—proof that no symmetrically substituted *trans* ethylene bond is present. Since the olefinic protons are magnetically equivalent, no conclusions can be drawn from either the 60-MHz or the 220-MHz spectrum regarding symmetry. In the NMR spectrum three methyl groups are observable at $\delta = 0.91$ (s) and 0.81 ppm (s), and signals for 11 CH_2 groups and a C—H group occur as a multiplet in the region 1.06 to 1.07 ppm; signals for the two methylene groups adjacent to the *cis*-ethylene group appear as a doublet at 2.93 ppm and the triplet for the olefinic protons with $J = 5$ Hz occurs at 5.37 ppm. The IR spectra of *(5)* and *(6)* differ very little from each other; the mass spectrum of *(6)* contains the molecular ion.

[*] Priv.-Doz. Dr. K. Eiter
Farbenfabriken Bayer AG, Wissenschaftliches Hauptlaboratorium
509 Leverkusen (Germany)

[1] *B. A. Bierl, M. Beroza*, and *C. W. Collier*, Science *170*, 87 (1970); for a review see *K. Eiter* in *R. Wegler:* Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel, Vol. 1. Springer, Berlin 1970, p. 497; *K. Eiter*, Fortschr. Chem. Org. Naturstoffe *28*, 204 (1971), *29*, 235 (1971), and literature cited therein.

[2] *E. A. Bried* and *G. F. Hennion*, J. Amer. Chem. Soc. *60*, 1717 (1938).

[3] Determined gas-chromatographically.

[4] Unpublished work.

No problems were encountered in the epoxidation of 2-methyl-7-*cis*-octadecene *(6)* with *m*-chloroperbenzoic acid, which gave 97%[3] 7,8-*cis*-epoxy-2-methyloctadecane *(1)* in almost quantitative yield. The IR spectrum shows a band for the epoxide group at about 1270 cm^{-1}; the NMR spectrum contains a multiplet at 2.88 ppm due to the *cis*-protons of the three-membered ring. This data together with the results of an elemental analysis provided confirmatory evidence for the structure. The mass spectrum showed fragmentation under the conditions used.

7,8-*cis*-Epoxy-2-methyloctadecane *(1)* exhibits a remarkable degree of biological activity, both in the laboratory and in the field[4].

Received: September 27, 1971 [Z 532 IE]
German version: Angew. Chem. *84*, 67 (1972)

CONFERENCE REPORTS

Radiochemical Investigations on Noble Gas Compounds

By *J. P. Adloff*[*]

The noble gases occupy an important place in radiochemistry. Noble gas nuclides are formed in various nuclear reactions, and, in particular, in nuclear fission; xenon and krypton nuclides are being produced in ever-increasing amounts in nuclear fuel reprocessing plants.

Although the chemical reactivity of the noble gases increases with increasing atomic number of the element, most of the data published so far for the elements of Group 0 concern xenon and its compounds. Investigations on radon compounds can be carried out only with tracer amounts of the element since the longest-lived isotope, ^{222}Rn, decays with a half-life of 3.8 d. Radon difluoride, formed by reaction of radon with fluorine, is soluble in halogen fluorides and liquid hydrogen fluoride. Radon difluoride solutions are also obtained by spontaneous reaction of radon with FCl, F_3Cl, F_5Br *etc.*, the radon functioning either as anion or as cation depending on the nature of the solvent. Radon compounds are much more ionic in character than the corresponding xenon compounds.

Noble gas compounds are also formed in nuclear transformations. Thus, several xenon compounds are obtainable *via* β-decay of iodine isotopes in iodine compounds, *e.g.* periodate and iodobenzene. Such compounds have also been detected by Mössbauer spectroscopy. It is possible that noble gas compounds are also formed in naturally occurring nuclear reactions; thus, xenon oxides could be formed by spontaneous fission in uranium ores.

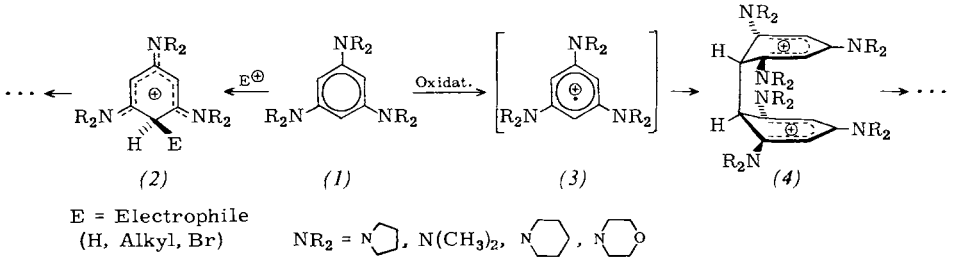
Lecture at Freiburg, June 28, 1971 [VB 320 IE]
German version: Angew. Chem. *83*, 986 (1971)

[*] Prof. Dr. J. P. Adloff
Laboratoire de Chimie Nucléaire
Université de Strasbourg
F-67 Strasbourg 3, B. P. 20 CR (France)

Model Reactions for Electrophilic Substitution of Aromatic Compounds

By *Franz Effenberger*[*]

Symmetrical triaminobenzenes are particularly suitable as model compounds for studying electrophilic aromatic reactions; due to the additive electron releasing influence of three mutually *meta* dialkylamino groups in *(1)*, cationic intermediates are stabilized to such a degree that individual steps of electrophilic substitution can be separately studied. The stabilizing effect increases in the order morpholino < piperidino < dimethylamino < pyrrolidino. By HMO calculations, the mesomeric interaction of the individual amino groups with the aromatic π system may be assessed quantitatively from the position of the ^1H-NMR ring proton signals if anisotropic effects are carefully eliminated.



The σ complexes *(2)* formed on protonation, alkylation, and bromination of tripyrrolidinobenzene prove to be isolable; in some cases, primary reaction at a dialkylamino nitrogen of *(1)* and subsequent rearrangement to *(2)* can be established. In contrast to the intermediates described by *Olah*, compounds *(2)* are true "Wheland intermediates", *i.e.* cationic analogs of the Meisenheimer complexes formed in the course of nucleophilic aromatic substitution.

Tris(dialkylamino)benzenes *(1)* may be oxidized readily; the isolable intermediates *(4)* are presumably formed by dimerization of *(3)*. Spectra and model calculations offer unequivocal evidence for the "*endo*" conformation of *(4)*; the preorientation thus indicated for dimerization of *(3)* is significant also with regard to the benzidine rearrangement.

[*] Prof. Dr. F. Effenberger
Institut für Organische Chemie der Universität
7 Stuttgart, Azenbergstrasse 14 (Germany)

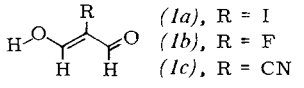
In many cases the information gained from reactions of *(1)* can be successfully applied to the reactions of *N,N*-dialkylanilines. Although isolation of cationic intermediates is not feasible here under normal conditions, the product-determining steps may be influenced in a clearly defined way, based on the model concepts developed for *(1)*. This principle is exemplified by the action of bromine on *N,N*-dialkylanilines and the reversibility of bromination of dialkylanilines.

Lecture at Tübingen on June 25, 1971 [VB 322 IE]
German version: Angew. Chem. *84*, 37 (1972)

Preparation and Reactions of Halomalonaldehydes

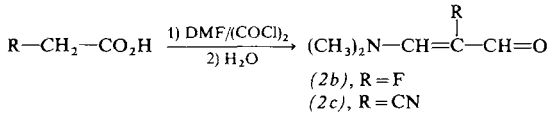
By *Klaus Halbritter, Wolf-Dieter Kermer,* and *Christian Reichardt*[*]

The series of existing halomalonaldehydes was supplemented by the synthesis of the previously missing members iodo- and fluoromalonaldehyde[1]. Iodomalonaldehyde *(1a)* was synthesized in 85% yield by substitution reaction of malonaldehyde with iodine(I) chloride.



(1a), R = I
(1b), R = F
(1c), R = CN

Fluoromalonaldehyde is formed on alkaline hydrolysis of 2-fluoro-3-dimethylaminoacrolein *(2b)*, which can be obtained by Vilsmeier formylation of sodium fluoroacetate in the presence of triethylamine in 40 to 50% yield according to a method described in principle by *Arnold*[2].

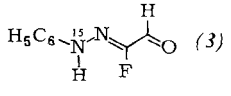


(2b), R = F
(2c), R = CN

Vilsmeier formylation of cyanoacetyl chloride in the presence of triethylamine gives initially 3-dimethylaminoacrylonitrile which affords 2-cyano-3-dimethylaminoacrolein *(2c)* on renewed formylation, and cyanomalonaldehyde *(1c)* on hydrolysis. Acetonitrile can be converted directly into *(2c)* in 32% yield by reaction with DMF/$POCl_3$.

IR and NMR spectroscopy show that in solution all three dialdehydes exist as the enol forms *(1a)*–*(1c)* (Z configuration) which are stabilized by intermolecular hydrogen bonds.

Condensation of fluoromalonaldehyde with heterocyclic *N*-alkylimmonium salts gives novel γ-fluoropentamethinecyanine dyes; coupling with aryldiazonium salts proceeds *via Japp-Klingemann* cleavage to give 2-fluoroglyoxal 2-phenylhydrazone *(3)* whose structure and configuration



(3)

were established by ^1H- and ^{19}F-NMR spectra of a [α-^{15}N]-labeled compound.

A ^{19}F-^{15}N coupling constant of 11 Hz extending over three bonds was observed for the first time in the ^{19}F-NMR spectrum of labeled *(3)*.

Halomalonaldehydes are important starting materials for the production of halogen-substituted heterocyclic compounds. Condensation of *(1b)* and *(2b)* with suitable bifunctional reactants leads to a large number of fluorine heterocycles that were previously not easily or not at all accessible: 4-fluoropyrazoles; 2-substituted 5-fluoropyrimidines (R^2 = H, CH_3, C_6H_5, OH, SH, NH_2); 3-fluoro-2*H*-indazolo[2,3-*a*]pyrimidine from *(1b)* and 3-aminoindazole; and 1,4-diphenyl-6-fluoro-2,3-dihydro-1,4-diazepinium salts from *1b)* and 1,2-dianilinoethane.

Lecture at Stuttgart on October 21, 1971 [VB 323 IE]
German version: Angew. Chem. *84*, 68 (1972)

[1] *C. Reichardt* and *K. Halbritter*, Liebigs Ann. Chem. *737*, 99 (1970).
[2] *Z. Arnold*, Collect. Czechoslov. Chem. Commun. *26*, 3051 (1961).

[*] Dr. K. Halbritter, Dipl.-Chem. W.-D. Kermer, and Prof. Dr. C. Reichardt
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

Reactivity of the Double Bond in Higher Olefins Depending upon Position and Geometrical Configuration

By *Friedrich Asinger*[*]

The nine isomers of *n*-undecene were first prepared and their purity investigated. The reactivity of these different olefins was then examined by studying their reaction with hydrogen bromide and with bromine, as well as their hydrogenation in a homogeneous system, epoxidation, addition of thioacetic acid, methoxymercuration, production of lubricants by the action of anhydrous aluminum chloride, and finally hydroalumination with diisobutylaluminum hydride.

It was observed that in some cases α-olefins react faster, in other cases those with nonterminal double bonds. *trans*-Olefins generally react more slowly than *cis*-olefins. A decline in the quality and yield of the lubricating oils obtained by polymerization of the olefins with aluminum chloride is observed practically only with *trans*-olefins the nearer the double bond is to the center of the molecule.

The α-olefins react about 240 times faster than those having nonterminal double bonds on addition of diisobutylaluminum hydride. Catalytic amounts of titanium tetrabutoxide, however, accelerate the addition of diisobutylaluminum hydride to olefins having nonterminal double bonds to such an extent that they react just as fast as α-olefins in the absence of a catalyst. The titanium alkoxide promotes isomerization of the organoaluminum compound at elevated temperatures (100—120 °C). The aluminum-containing group migrates to the end of the molecule where it is irreversibly bonded. Olefins with nonterminal double bonds thus yield primary straight-chain alcohols in good final yields after air-oxidation of these aluminum compounds to aluminum alkoxides and subsequent hydrolysis.

Since mixtures of higher olefins having statistically distributed or symmetrically positioned double bonds are nowadays readily available on an industrial scale

[*] Prof. Dr. F. Asinger
Institut für Technische Chemie und Petrolchemie der Technischen Hochschule
51 Aachen, Alte Maastrichter Strasse 2 (Germany)

through the UOP Olex-Pacol process or the Phillips' metathetic process, the above route to alcohols is worthy of interest.

Lecture at Frankfurt on June 3, 1971 [VB 321 IE]
German version: Angew. Chem. *84*, 37 (1972)

Development of a New Type of Polyamide

By *Gerhard Bier*[*]

Until recently only purely aliphatic polyamides, such as perlon, nylon 6,6, nylon 11, *etc.*, have been produced for thermoplastic processing techniques. Completely aromatic polyamides like polymetaphenyleneisophthalamide (raw material of NOMEX fibers) or aliphatic-aromatic polyamides like that formed from hexamethylenediamine and terephthalic acid (m.p. 370 °C) cannot be processed thermoplastically in practice.

Preliminary work by *R. Gabler* was taken up at Dynamit Nobel and a polyamide was subsequently synthesized from a branched-chain aliphatic hexamethylenediamine and terephthalic acid and tested for possible applications. The polyamide (which has been given the trade name TROGAMID T®) is amorphous and has a glass transition temperature of about 150°C. It can readily be processed by thermoplastic techniques. The influence of the aromatic component, of the methyl side chain, and of the carboxamide group on crystallinity and glass transition temperature was studied in detail with the aid of model compounds. It was found, *inter alia*, that for a constant formula weight the positions of the carboxamide groups have a considerable effect on the glass transition temperature. In spite of the amorphous nature of the polymer a high degree of structural order must exist for almost all the carboxamide groups are linked by hydrogen bonds. Above the glass transition temperature the number of NH groups not participating in hydrogen bonding rapidly increases.

TROGAMID T® is characterized by a high tensile strength and dimensional stability as well as resistance to tracking currents, resistance to attack by chemical reagents, resistance to cracking when subjected to a pulsating compression and by transparency. These properties, in conjunction with the low shrinkage in processing, make TROGAMID T® suitable for uses in the automobile industry and for electronics and electrical engineering, filter manufacture, the dairy industry, watch- and clockmaking, production of umbrellas, and measurement and control engineering. Examples include shock absorber pistons, switch knobs, casings for high performance switchgear, caps for ends of cables, transparent filter units, parts for milking machines, filter cups, watch glasses, umbrella frames, and flowmeters for gases and liquids.

Lecture at Stuttgart on November 11, 1971 [VB 325 IE]
German version: Angew. Chem. *84*, 69 (1972)

[*] Dr. G. Bier
Dynamit Nobel AG
521 Troisdorf (Germany)

New Aspects of the Structure of Randomly Branched Macromolecules

By *Walther Burchard*[*]

In contrast to unbranched chain molecules little is known about the structure of randomly branched macromolecules. The reason may be seen in the difficulties resulting from the large width of the molecular weight distributions (M_w/M_n *ca.* 100–150) and the extreme variety of isomeric structures. The current practice of approximating the physical properties by results obtained for fixed structures (star and comb polymers) holds out of relatively little promise because these structures are probably not representative of the randomly branched chain molecules.

The difficulties can be largely overcome by two techniques novel to polymer science:

1) Branched molecules can be regarded as "trees". After choice of an arbitrary chain element as root, the resulting tree exhibits practically all the characteristics of a family tree which can be unequivocally divided up into different generations. From this results a clear system of ordering and numbering.

2) Methods common in the statistical treatment of population growth processes (demographic methods) can be applied to these "trees". Particular mention should be made in this context of the generating functions which have properties similar to a Fourier transformation of a probability distribution. The advance in the treatment of randomly branched structures results essentially from two properties of generating functions:

a) Straightforward differentiation of the generating functions with respect to the auxiliary variable yields physically meaningful average values that are accessible to measurement and cover both molecular-weight and isomer distributions.

b) The generating functions can be boxed into one another in the form of a cascade (1st, 2nd, 3rd... generation); structures of trees are thereby reproduced which are characteristic of the branched molecules.

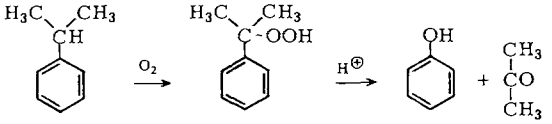
In this way it was possible to calculate for a number of branching types the weight- and number-average molecular weights as well as the z-averages of the mean square radius of gyration and of the particle scattering factor for light scattering. The linear chain is always included in the cascade process as a limiting case. Details were given of measurements on alternating copolymers of decamethylene glycol and benzene-1,3,5-triacetic acid as well as of measurements on star molecules having glycogen as nucleus.

Lecture at Marl on November 3, 1971 [VB 324 IE]
German version: Angew. Chem. *84*, 69 (1972)

[*] Doz. Dr. W. Burchard
Institut für makromolekulare Chemie der Universität
78 Freiburg, Stefan-Meier-Strasse 31 (Germany)

"Selected Abstracts", a part of the journal previously containing summarized versions of primary publications of topical interest, will in future be devoted exclusively to abstracts of publications of a more comprehensive nature (reviews, progress reports, *etc.*). The editorial staff will make every effort to ensure that this modification of the "Selected Abstracts" section will provide readers of "Angewandte Chemie — International Edition" with an even more representative and up-to-date survey of current developments in each of the branches of chemistry than heretofore.

Kinetics of autoxidation of hydrocarbons in the liquid phase is the theme of an article by *J. Betts*. In contrast to combustion, autoxidation is taken to mean oxidation by molecular oxygen under mild conditions; practical applications include the atmospheric drying of linseed oil paints and the manufacture of phenol and acetone from cumene *(1) via* the hydroperoxide and its decomposition with strong acids:



(1)

The reaction involves free radicals. The author discusses, *inter alia*, autoxidation chains and the determination of rate constants, relationships between structure and reactivity, autoxidation of polymers and carbanions, reactions with singlet oxygen, and the action of antioxidants. [The Kinetics of Hydrocarbon Autoxidation in the Liquid Phase. Quart. Rev. Chem. Soc. *25*, 265—288 (1971); 94 references, 4 tables]

[Rd 420 IE –K]

Properties of clean metal surfaces and reactions thereon are surveyed by *R. P. H. Gasser*. Such work must be conducted in ultrahigh vacuum at pressures no higher than 10^{-9}, or better at 10^{-10} torr. The following steps of the reaction are of interest: a) adsorption; b) reactions on the surface; c) desorption. During the reaction either the composition of the gas or changes in a property of the metal are monitored. Apart from the theory of adsorption, the article considers, *inter alia*, application of the flash filament method, field-emission and field-ion microscopy, diffraction studies with slow electrons (LEED), and mass spectroscopy. [Properties and Reactions of Clean Metal Surfaces. Quart. Rev. Chem. Soc. *25*, 223—238 (1971); 12 references, 6 figures]

[Rd 418 IE –K]

How are metal atoms formed in flames? This question of analytical importance is posed in a paper by *D. T. Coker, J. M. Ottaway*, and *N. K. Pradhan*. Among other effects, the concentration dependence of ground-state atoms (determining generally the signal strength in atomic absorption spectrophotometry) on the oxygen content of fuel lean flames points to the fact that the dissociation energy of the metal monoxide plays an important role. The influence of anions in the sample solution (halides or oxy-anions) and of the nature of the flame constituents (hydrogen-air, acetylene-air, acetylene-nitrous oxide) lead to the same conclusion. [Metal Atom Formation Processes in Flames. Nature Phys. Sci. *233*, 69–71 (1971). 13 references, 6 figures.]

[Rd 430 IE –H]

The absorption spectra of tetragonal fluorides from the first transition metal series are discussed by *D. Oelkrug*. Complex ions that would have an orbitally degenerate ground state in a ligand field of regular octahedral symmetry are known to be distorted from this symmetry in a way removing that degeneracy (Jahn-Teller effect). The structures of fluorides with Jahn-Teller sensitive ground states are considered using "ionic" and "covalent" bonding models, and their absorption spectra are interpreted under these aspects. [Absorption Spectra and Ligand Field Parameters of Tetragonal 3d Transition Metal Fluorides. Structure and Bonding *9*, 1–26 (1971); 91 references, 8 figures, 4 tables.]

[Rd 431 IE –H]

Structures and bonding properties of β-diketone chelates are reported by *D. W. Thompson*. The different geometries of such compounds, *e.g.* of metal pentanedionates (acetylacetonates) are discussed, and a detailed account is given of the electronic structure of such complexes. Special attention is paid to the question of the "aromatic" character of the chelate rings. [Structure and Bonding in Inorganic Derivatives of β-Diketones. Structure and Bonding *9*, 27–47 (1971); 69 references, 3 figures.]

[Rd 432 IE –H]

The coordination chemistry of metalloporphyrins is reviewed by *P. Hambright*. Introductory sections about structures and acid-base equilibria of metal-free porphyrins are followed by a list of metal ions forming porphyrin compounds, together with selected structures, magnetic properties, and stability constants. The review concludes with discussions of mechanisms of metal ion incorporation, the stability of the complexes against demetalation, and substitution and electron transfer reactions on metalloporphyrins. [The Coordination Chemistry of Metalloporphyrins. Coord. Chem. Rev. *6*, 247–268 (1971); 145 references, 3 figures, 1 table.]

[Rd 433 IE –H]

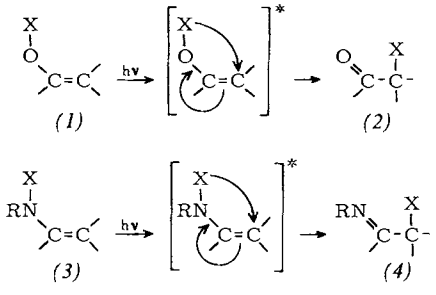
The stereochemistry of the halocarbonylphosphanes and arsanes of molybdenum and tungsten is summarized by *R. Colton*. The main emphasis is on complexes with bidentate phosphanes and arsanes. Preparative methods are outlined briefly; in the main part, the influence of different ligands on the coordination numbers and the geometries of the complexes is depicted, with special reference to the results of NMR and IR measurements. [Steric Effects in Substituted Halocarbonyls of Molybdenum and Tungsten. Coord. Chem. Rev. *6*, 269–284 (1971); 29 references, 1 figure, 1 table.]

[Rd 434 IE –H]

How many solvent molecules are nearest neighbors to a metal ion in solution? This question is discussed in a review by *S. F. Lincoln*. The problems of a sound definition of the "first coordination sphere" and the methods to measure coordination numbers, *e. g.*, X-ray diffraction, ion exchange, and NMR methods are considered. "Indirect" methods, *i. e.*, methods evaluating coordination numbers from measurements of bulk solution properties, are also mentioned. The results of investigations on solutions in single and mixed solvents are discussed; a chapter about contact ion pairs concludes the review. [Solvent Coordination Numbers of Metal Ions in Solution. Coord. Chem. Rev. *6*, 309–329 (1971); 133 references, 5 figures, 1 table.]

[Rd 435 IE –H]

The photo-Fries rearrangement and related photochemical [1,j]-shifts (j = 3, 5, 7) of carbonyl and sulfonyl groups have been reviewed by *D. Belluš*. Characteristic of all these rearrangements is the 1,3 (or 1,5- or 1,7-) migration of a group X in compounds of the type *(1)* or *(3)* in which the double bond can be isolated, conjugated or aromatic.



Examples of type *(1)* are aryl esters of carboxylic acids and sulfonic acids, and enol esters of carboxylic acids; examples of type *(3)* are *N*-arylamides of carboxylic acids and sulfonic acids, and *N*-aryl lactams. [Photo-Fries Rearrangement and Related Photochemical [1,j]-shifts (j = 3, 5, 7) of Carbonyl and Sulfonyl Groups. Advan. Photochem. *8*, 109–159 (1971); 118 references, 8 tables]

[Rd 437 IE –M]

The use of radioisotopically labeled analytical reagents in organic chemistry is comprehensively reviewed up to the end of 1969 in a paper by *G. Ayrey, D. Barnard*, and *T. H. Houseman*. The examples described cover the quantitative and near-quantitative reaction of a labeled reagent with a special group of the molecule to be determined. An introduction to analytical methods, including, *inter alia*, isotope dilution analysis and isotope derivative analysis, is followed by a discussion of the labeled reagents themselves. The analyses of hydroxy, carbonyl, carboxy, thio, and amino compounds, and of radicals and compounds having metal-polymer bonds serve as examples. [Use of Radioisotopically Labeled Analytical Reagents in Organic Chemistry. Chem. Rev. *71*, 371—393 (1971); 230 references]

[Rd 449 IE –M]

Isomerizations of metal β-diketone chelates are reviewed by *J. J. Fortman* and *R. E. Sievers*. Conceivable reaction mechanisms are first discussed: intramolecular processes with or without bond rupture and intermolecular processes with primary dissociation or bimolecular substitution processes. An account is then given of investigations on individual compounds; the bulk of the data concerns 6-coordinate compounds. Since all these reactions proceed rather rapidly, NMR spectroscopy is almost exclusively used for following the kinetics of such processes. [Optical and Geometrical Isomerization of β-Diketonate Complexes. Coord. Chem. Rev. *6*, 331—375 (1971); 133 references]

[Rd 441 IE –H]

Methods for calculation of stability constants of metal complexes in solution are critically evaluated by *A. M. Bond*. Examples are presented of the way in which different calculation methods using the same experimental data can give substantially different stability constants. There is no "best" method of calculation; on the contrary, it is always a necessity to chose critically between several methods. A preliminary graphic analysis of the experimental data is always helpful for this purpose. [Some Suggested Calculation Procedures and the Variation in Results Obtained from Different Calculation Methods for Evaluation of Concentration Stability Constants of Metal Ion Complexes in Aqueous Solution. Coord. Chem. Rev. *6*, 337—405 (1971); 43 references]

[Rd 442 IE –H]

Infrared spectra of pseudo-halide complexes (thio- and isothiocyanate, seleno- and isoselenocyanate, cyanate, and fulminate) are reported on by *R. A. Bailey, S. L. Kozak, T. W. Michelsen*, and *W. N. Mills*. The spectra in the region of internal ligand frequencies are discussed extensively; the review concludes with chapters about metal-ligand vibrations, which have been investigated to a lesser extent, and about the spectra of mixed complexes. Among other topics, all vibrational frequencies are evaluated with respect to the possibilities they offer to discern coordination of the different ends of the ligand ions. [Infrared Spectra of Complexes of the Thiocyanate and Related Ions. Coord. Chem. Rev. *6*, 407—445 (1971); 90 references]

[Rd 443 IE –H]

The electronic spectra of the hexafluoro complexes of the first transition series are discussed by *G. C. Allen* and *K. D. Warren*. An introductory chapter about the basic theory of interpretation of spectra including a fairly extensive account of LCAO-MO theory of complexes is followed by an appraisal of diffuse reflectance spectroscopy as the most important measuring tool. After discussion of the individual spectra, comparisons are made with those of hexachloro compounds and of complexes from the higher transition series. In the concluding chapters, optical electronegativities, vibrational structures, and the influence of the Jahn-Teller effect are reviewed. [The Electronic Spectra of the Hexafluoro Complexes of the First Transition Series. Structure and Bonding *9*, 49—138 (1971); 137 references]

[Rd 444 IE –H]

Unusual electrophilic aromatic substitutions of preparative interest are reviewed by *D. E. Pearson* and *C. A. Buehler*. Examples are enhancement of *p*-substitution in the formation of aromatic ketones, sulfonic acids, alkylbenzenes, nitroanilines, and nitroarenes as a result of bulkiness of substituent and reagent, and of thermodynamic control in compounds containing *meta*-directing substituents; a further example is *ortho* enhancement in the case of

phenols, aromatic ethers, arylamines and anilides, alkylbenzenes, and benzoic acid by coupling of reagent and substituent before entering the *o*-position. Increased *m*-substitution in aniline and its derivatives, alkylbenzenes, aromatic ketones, substituted phenols, aromatic halides, naphthalenesulfonic acids, and [2.2]metacyclophanes is usually achieved by protonation. [Unusual Electrophilic Aromatic Substitution in Synthesis. Synthesis *1971*, 455 to 477; 73 references].

[Rd 440 IE –M]

Influence of non-bonded H atom repulsions in bis-chelates of 2,2'-bipyridyl and 1,10-phenanthroline on the configuration of the complexes formed is treated by *E. D. McKenzie*. The possibilities of minimizing the van der Waals repulsions in different coordination polyhedra are discussed, and the use of physical methods (X-ray diffraction; electronic, vibrational, and magnetic resonance spectra; Mössbauer effect) for configuration assignments is evaluated very critically. Finally, configurations of known compounds are discussed. [The steric effect in bis(2,2'-bipyridyl) and bis(1,10-phenanthroline) metal compounds. Coord. Chem. Rev. *6*, 187—216 (1971); 145 references, 7 figures, 4 tables]

[Rd 424 IE –H]

The melting of d(T-A) oligomers as a model reaction for the melting of DNA forms the subject matter of a report by *R. L. Baldwin*. $d(T\text{-}A)_n$, $5 \leq n \leq 25$, consists of deoxythymine and deoxyadenine; "melting" is defined as the transition of the helix form to a form devoid of base pairing. Particular interest was commanded by the behavior of hairpin loops formed on base pairing within a strand. The smallest possible loop contains four bases. Methods are described for determining the parameters required for calculation of melting curves. In the presence of high counter-ion concentrations the melting curves of linear oligomers are as predicted by theory, while at lower concentrations the length of the oligomer must be taken into account. The article closes with remarks concerning the kinetic behavior of hairpin helices. [Experimental Tests of the Theory of Deoxynucleic Acid Melting with d(T-A) Oligomers. Accounts Chem. Res. *4*, 265—272 (1971); 38 references, 4 figures]

[Rd 417 IE –L]

The calculation of vibrational frequencies and force constants without the aid of empirical data *(ab initio)* is treated in a review by *C. J. H. Schutte*. Firstly, the basic assumptions underlying this kind of calculation are discussed; among them, the Born-Oppenheimer approximation (independence of electronic and nuclear movements) is common to all present computational procedures. Various approaches to the determination of vibrational frequencies of diatomic molecules, characterized by the introduction of further approximations in different stages of the calculation, are outlined in the major part of the review. Finally, reference is made to calculations of polyatomic molecules, where, in some cases, symmetry considerations can lead to a simplification of the huge problems encountered generally. [The Ab-Initio Calculation of Molecular Vibrational Frequencies and Force Constants. Structure and Bonding *9*, 213—263 (1971); 160 references]

[Rd 447 IE –H]

The assessment of the interelectronic repulsion parameter of ligand field theory is commented on by *E. König*. The report is confined to the evaluation of spin-allowed bands in electronic configurations d^2, d^3, d^7, and d^8, these being easier accessible to theoretical treatment. Different procedures of fitting ligand field parameters to the band maxima measured are compared and reasons are discussed for the differences in the results obtained. The most important reason is that band maxima do not correspond to transitions between minima of potential hypersurfaces of the electronic states involved, as the transitions take place between states of different ligand field configurations. [The Nephelauxetic Effect. Calculation and Accuracy of the Interelectronic Repulsion Parameters. I. Cubic High-Spin d^2, d^3, d^7, and d^8 Systems. Structure and Bonding *9*, 175—212 (1971); 64 references, 9 tables]

[Rd 446 IE –H]

The interaction of protons and metal ions with ribonucleic acid, deoxyribonucleic acid, and their constituent bases, nucleosides, and nucleotides are examined in a review by *R. M. Izatt, J. J. Christensen*, and *J. H. Rytting*. The literature is covered up to August 1970. Special consideration is given to the coordination sites of the ions, alkali and alkaline earth metal ions, and ions of Cr, Mn, Fe, Co, Ni, Cu, Zn, Ag, Cd, Pb, Hg, U, and the lanthanoids. Tables of thermodynamic data for the interactions are also given. [Sites and Thermodynamic Quantities Associated with Proton and Metal Ion Interactions with Ribonucleic Acid, Deoxyribonucleic Acid, and Their Constituent Bases, Nucleosides, and Nucleotides. Chem. Rev. *71*, 439—481 (1971); 229 references]

[Rd 451 IE –M]

The physical chemistry of iron(II) complexes with ligands containing the structural element N=C—C=N is reviewed by *P. Krumholz*. Accounts are given of the magnetochemistry, electronic and vibrational spectra, and of the thermodynamics and kinetics of formation and dissociation of such complexes. A special chapter is devoted to the importance of "back coordination" for understanding the properties of this class of compounds. [Iron(II) Diimine and Related Complexes. Structure and Bonding *9*, 139 to 174 (1971); 233 references]

[Rd 445 IE –H]

Preparation, properties, and applications of vitreous carbon are surveyed by *V. D. Chekanova* and *A. S. Fialkov*. Vitreous carbon possesses a number of specific properties not exhibited by the better known modifications. Its high mechanical strength, its resistance to corrosive agents, and its impermeability to gases are being increasingly exploited. The article deals not only with the preparation of vitreous carbon but also with its physical and chemical properties. [Vitreous Carbon (Preparation, Properties, and Applications). Russ. Chem. Rev. *40*, 413—428 (1971); 97 references, 10 tables, 18 figures]

[Rd 427 IE –M]

Modern Electrochemistry. An Introduction to an Interdisciplinary Area. Vol. 1. By *J. O'M. Bockris* and *A. K. N. Reddy*. Macdonald Technical and Scientific, London and Plenum Press, New York 1970. 1st edit., lx, 622 pp., 245 figures, 119 tables, $ 19.50.

It is the authors' declared intention that this book should provide readers from many different disciplines with as complete as possible an introduction to present-day electrochemistry. In order to achieve these ambitious aims, they have based their approach upon a series of key ideas: clarity is striven for even at the cost of brevity; frequent repetitions thus have to be accepted. Each individual section begins at a simple level and works its way up to the current viewpoint. The background knowledge required for comprehension is given in full. The presentation should be modern in form and content; out-of-date concepts are therefore eliminated. Each phenomenon is discussed on the basis of only one theory, and that is the one which appears to reproduce the facts most consistently. For the sake of clarity the book is kept to the style of a lecture, which in the last analysis is what it is (rather in the sense of "The Feynman Lectures on Physics").

The literature references are limited to fundamental original work (about 300) and more advanced monographs and review articles (about 150) from recent years, generally up to 1968. Each block of references, arranged in chronological order, comes at the end of the appropriate subsection, which is usually about 25 pages long. Unfortunately, there is no explicit reference to them in the text. The search for papers on a given topic would have been considerably simplified if their titles had also been given, or if specific reference had been made to them at the appropriate points. The mathematical derivations, which can break up the flow of a text, are also separated off as appendices to the corresponding chapters (11 in all in the two volumes). Each volume contains a detailed contents list and there is a subject index (with about 2500 entries) for the two volumes. There is no author index, nor is there a list of symbols used. The work contains some 800 illustrations, in the form of line diagrams, figures, and schematic representations. Numerical material is summarized in about 200 tables.

Apart from a brief introduction to the subject as a whole, the shorter volume 1 is concerned with ions in liquids. This topic is called "ionics", in contrast to "electrodics" which is the subject of volume 2. First of all the ion-solvent interaction is dealt with, initially without and then with reference to structure. Here the central position is occupied by the ion-dipole and the ion-quadrupole interaction. Further subsections are concerned with the solvation number, the dielectric constant, and the effect of dissolved non-electrolytes. The next chapter is on ion-ion interactions. The Debye-Hückel theory is critically examined, and the influence of the solvent on the activity coefficients is studied; ion associations, the quasilattice treatment of concentrated electrolyte solutions, and experimental methods are also discussed. The subsequent chapter on ion transport relates principally to aqueous solutions. Separate chapters are concerned with protons in solution and with melts, in which simple models oriented toward the lattice or the gas are discussed and transport phenomena and mixed phases are dealt with.

There is no difficulty in using this volume independently of volume 2, which, considering the high price, is an advantage. It provides a detailed introduction into the present state of knowledge on ions in liquids.

Hermann Göhr [NB 998a IE]

Modern Electrochemistry. An Introduction to an Interdisciplinary Area. Vol. 2. By *J. O'M. Bockris* and *A. K. N. Reddy*. Macdonald Technical and Scientific, London and Plenum Press, New York 1970. 1st edit., lxi, 810 pp., 446 figures, 83 tables, $ 22.50.

Volume 2 of this large-scale textbook on electrochemistry is devoted to "electrodics", *i. e.* the phenomena in the boundary layer between electronic and ionic conductors. Since the character of the overall work was described in the review of the first volume, the present review will be concerned mainly with volume 2.

The first of the five chapters is concerned with electrified interfaces. The fundamental concepts of electrodics are critically discussed. In reading this it becomes very clear how little we still know about double layers on solid metals (in contrast with mercury). Here there are also sections on double layers on semiconductors, electrokinetics, and colloid chemical phenomena. The next two chapters deal with electrode reactions; the first with charge-transfer kinetics, the second with mechanisms. Next a selection of specific types of electrode reactions are described: electrocatalysis, metal electrocrystallization, hydrogen and oxygen evolution. In the final chapter on systems of technological interest, corrosion and related phenomena, electrochemical energy conversion (fuel cells), and storage devices (accumulators and cells) are discussed in detail.

This volume, too, can be used by itself. The arrangement of the field of electrodics is mainly governed by teaching considerations. However, despite the pleasing overall impression, I cannot overlook one or two defects. Experimental methods of investigation are certainly mentioned, but any critical discussion—which one might well expect in a book of this scope—is missing. In the tables and diagrams there are no indications of the experimental or theoretical routes by which the data are obtained. In many of these cases even a literature reference would have helped. There are also several minor errors, such as incorrect signs in equations (*e. g.* in (7.40) to (7.46)) or a reference to a non-existent appendix (A 7.2); however, these shortcomings are no worse than one might expect to find in a first edition.

The two-volume work taken as a whole is a modern, comprehensive textbook on electrochemistry. Since it is written clearly, in detail, and at an elementary level, it is fairly easy to read. To this extent it may be described as an "Introduction". But who, other than an enthusiast, could be expected to read a work of some fifteen hundred pages? The very size of the work prevents it from fulfilling its function of really acting as an introduction.

Hermann Göhr [NB 998b IE]

Standard Methods of Clinical Chemistry, Vol. 6. By *R. P. MacDonald*. Academic Press, New York–London 1970, 1st ed., xiv, 281 pp., bound, $ 14.50.

Six volumes of Standard Methods of Clinical Chemistry have now appeared since 1953 under the auspices of the

American Association of Clinical Chemists. The aim has been the same throughout the series, namely to provide a critical collection of the scattered methods used in clinical chemistry, and this aim has been achieved. In appearance, these volumes remind one of two other series: Organic Synthesis and Methods of Enzymology. The sixth volume, which has just been published, is just as much of a standard work as the previous ones, and belongs on the shelves of any library where this subject is covered at all.

The sixth volume gives a wide variety of methods, determinations, and general topics of interest to clinical chemists, examples being the handling of toxicological problems in the laboratory, the subject of standardizing enzyme activity determinations, and proposals for the nomenclature of quantities and units used in clinical chemistry. The discussion of these very topical questions with such clarity is of great value. It is sufficient to think how much diagnostic information may be lost if we do not soon accept rules for the standardization of enzyme activity determinations. Of course, the difficulties of reaching international agreements are well known.

One hesitates to accept as standard laboratory methods some of the determinations proposed here, for example *Babson*'s color reaction for the GOT activity (p. 149). It is true that this method needs only simple equipment, and for this reason it may be discussed here, but it uses an unstable reference substance, oxalacetate. Another example is the triglyceride determination (p. 215), which comprises no fewer than twelve steps and is therefore certainly unsuitable as a standard method for routine use. A better method was devised for this purpose by *Eggstein* in 1966.

The interference by dextran-type plasma extenders is not taken into account in the description of the *o*-toluidine-glacial acetic acid method for the determination of blood sugar (p. 159), although it can give erroneously positive results with all its consequences, as is well known.

All this, however, does not detract from the fact that this volume too offers very useful analytical methods (*e.g.* for the determination of hemoglobin in the plasma; cf. p. 107) that can be used in large routine laboratories and in research laboratories. Even the "Notes" in small print offer much technical help in laboratory work. The subject index on eight pages is sufficiently extensive to permit anything to be found quickly and easily.

W. Wahlefeld [NB 1 IE]

Autoradiographie (Autoradiography). By *H. A. Fischer* and *G. Werner*. Walter de Gruyter & Co., Berlin 1970. 1st edit., ix, 214 pp., 93 figures, 14 tables, bound, DM 42.—.

Autoradiographic methods have been successfully used in almost every field of science. The collection of people concerned with this technique is therefore a heterogeneous one, and up to now there has been no comprehensive and complete presentation in German of the theoretical and practical fundamentals of this wide-ranging topic. The present book should fill this gap. The authors intend it primarily as a guideline for those interested in the method and as an introduction for those who are unfamiliar with autoradiographic techniques.

After a short explanation of the physical foundations and the method of labeling with radioactive isotopes, there is a survey of the autoradiography of macroscopic, microscopic, and electron-microscopic objects; this section contains a wealth of practical examples from a wide range of applications. To name but a few: studies of metals, applications to chemical and biochemical analysis, biology (autoradiography of whole animals, *etc.*), criminological investigations, mass transport in earth samples, and many others. The techniques of operating with stripping film and "liquid" emulsions are discussed, together with their advantages and limitations. One section is specially devoted to the very important and difficult topic of the autoradiography of dislocatable substances. The possibilities for the autoradiography of electron-microscopic objects are critically discussed on the basis of numerous examples. In each individual section there are separate notes on the selection of the suitable film material and the photographic technique. The objectivity of the presentation can be seen from the numerous notes on artefacts, which all too often lead to misinterpretations of autoradiograms. The book closes with a chapter on the use of autoradiography as a quantitative method; there is a comprehensive bibliography including recent publications.

The fact that some of the captions have been applied to the wrong picture does not detract much from the quality of the book. A further point to be noted in a new edition would be a standardization of the units of measurement, taking the SI units into consideration.

Over and above its value as a guide for the beginner, this book will also offer to the worker familiar with this topic many useful suggestions and a highly informative insight into other specialist fields, which in turn will contribute to an enrichment of his own field. In closing, it may be mentioned that the book is very attractive in outward appearance, but the reproduction of some of the original autoradiograms could have been better.

Hans-Martin Kellner [NB 2 IE]

Chemie der Metall-Olefin-Komplexe (Chemistry of Metal-Olefin Complexes). By *P. Heimbach* and *R. Traunmüller*. Chemische Taschenbücher Vol. 10. Verlag Chemie GmbH, Weinheim/Bergstr. 1970. ix, 180 pp., 85 figures, 30 tables, paperback DM 20.—.

The present monograph is devoted to one of the most interesting fields, and probably also the most topical, of organometallic chemistry. The authors, who are themselves active in this field, have tried to select the results that seem most important to them from the wealth of available material, and to throw light on the chemistry of metal-olefin complexes from various angles.

After an introductory chapter with a very brief discussion of bonding models known at present, the first part of the book describes a number of important preparation methods, mainly those giving isolable, kinetically stable metal-olefin complexes. Syntheses of alkylmetals and metal hydrides are also mentioned, though these do not strictly fall within the realm of the subject proper. Chapters 5 and 6 ("Effects of complex formation on olefin and allyl ligands" and "Olefins and allyl groups as complex ligands") survey the methods and results of structural investigations and also take bonding problems into account. The second part of the monograph presents a very detailed discussion of catalytic processes in which metal-olefin and metal-allyl complexes play a part, usually as kinetically labile intermediates. This discussion is centered on the work of *G. Wilke* and the Mülheim school. It is in these chapters that it becomes very plain

that the authors are approaching the chemistry of metal-olefin complexes primarily from the standpoint of the organic chemist, which will undoubtedly please a wide readership.

As to criticisms, the reviewer was surprised to find almost more on metal-allyl complexes than on metal-olefin complexes in a book with the above title. A longer and more detailed title would have been better. Another notable shortcoming is that though the relationships between olefin and allyl complexes are rightly emphasized, there is no reference to similar relationships between olefin and aromatic complexes (*e.g.* between $C_5H_6ML_n$ and $[C_5H_5ML_n]^+$, $C_7H_8ML_n$ and $[C_7H_7ML_n]^+$). The discussion of the extremely interesting olefin-metal compounds with "fluctuating structures" is also much too short.

Despite these objections, the monograph, which is a true pocket book, fulfills its purpose. It is recommended in particular to those who wish a general picture rather than special information and who are interested in particular in the use of organometallic complexes for synthetic problems.

Helmut Werner [NB 11 IE]

An Introduction to the Chiroptical Methods in Chemistry. By *P. Crabbé*. P. de Aguinaco, Mexico 1971. 1st edit., 121 pp., 54 figures, $ 4.00.

P. Crabbé, who has also written an extensive monograph on the same topic, here presents a brief introduction to chiroptical methods (circular dichroism (CD) and optical rotatory dispersion (ORD)). Of course, it cannot be regarded as a substitute for a detailed textbook, but is a means of bringing oneself up to date with the recent literature, using the index which is arranged by chromophores. After a brief description of the fundamental concepts, the individual groups capable of bringing about a Cotton effect are enumerated, together with the more important rules applying to them; a critical comparison is lacking here. The topic of biopolymers is not dealt with in quite so much detail, but the book does include details on both inorganic complexes and the Faraday effect. This small book, which is printed on extremely hard-wearing paper, contains an extraordinary wealth of literature references, which actually extend into the early part of 1971 and is thus a valuable addition to this branch of spectroscopy which up to now has received only sporadic attention.

Günther Snatzke [NB 3 IE]

Messung radioaktiver Nuklide (Measurement of Radioactive Nuclides). By *K. Bächmann*. Verlag Chemie GmbH, Weinheim/Bergstr. 1970. 1st Edit., xii, 187 pp., 194 figures, 30 tables, bound DM 58.—.

This book is a comprehensive account of methods for the detection of nuclear radiation. It provides the scientist, the engineer, or the student with a detailed guide to the execution and evaluation of radioactivity measurements. Numerous measuring arrangements and methods for this purpose are described, and their usefulness for the solution of particular measurement problems is assessed.

The layout and arrangement are very clear. The first few chapters describe the construction of radiation detectors and the interactions of nuclear radiation with matter that are necessary for an understanding of the detectors. A chapter on electronic aids unfortunately deals mainly with tube circuits (cathode follower, coincidence stage, Schmitt trigger) and omits the transistor circuits that are now in common use. This is followed by detailed chapters on the detection of the various types of radiation and the determination of their energy. A useful section is included for practical workers on the evaluation of γ spectra. A chapter on the relationship between count rate and activity is important to the evaluation of results. The book ends with practical advice on measuring arrangements, standard preparations, and the dosimetry of nuclear radiation.

The practical value of the (relatively expensive) book is enhanced by bibliographies to the various chapters and a reliable subject index.

Helmut Müh [NB 12 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 8th, fully revised edition. Issued by the Gmelin-Institut für anorganische Chemie und Grenzgebiete of the Max-Planck-Gesellschaft zur Förderung der Wissenschaften under the direction of *Margot Becke-Goehring*. Verlag Chemie GmbH, Weinheim/Bergstr.

System No. 46. Zinn, Teil A (Tin, Part A).
Historical. Occurrence. Chief editor: *Wolfgang Müller*. 1971. vi, xiii, 451 pp., 32 figures, bound. DM 532.—.

Together with gold, silver, and copper, tin is one of the first few metals used by man. The first chapter of the present volume is a 172-page presentation of the history of tin, and at the same time is a form of cultural history of the last five millenia, woven around the use of this metal. Although this undoubtedly makes interesting reading, it would seem to the present reviewer that it is extending the scope of this chapter too far to devote several pages to the origin of the name of the element, and finally to consider the problem of whether the *Publius Crassus* mentioned in a report by the geographer *Strabo* (of Amasia in Pontus) was the younger son of the member of the 1st triumvirate, who subdued Aquitania under *Caesar* in 57 BC, or whether he was the Spanish proconsul in 97 BC, although it is not known whether the latter "undertook any exploratory travels". This is not to criticize the presentation of the history of tin, which among other things contains many detailed quotations from ancient sources that are not readily accessible, but only to ask whether this amount of detail in a handbook of inorganic chemistry, which in general will only be consulted by chemists and representatives of closely allied disciplines, is not paid for at too high a price. There is no doubt that the presentation would be of interest to a very wide circle of readers. The present reviewer would therefore suggest that such detailed historical presentations should in future be published as separate volumes, which could be offered to a much wider circle of readers, with a possible reduction in cost.

After the sections on names and symbols, tin in early cultures, tin in east Asia, India, Africa, America, and tin in the Arab civilization, there are sections concerned with tin ores and their extraction and processing. Detailed descriptions are given of tinning processes, particularly with regard to the manufacture of tinplate. Special attention is given to the various regions where the tinplate industry

has developed, in various parts of Germany as well as in other European countries and America. In the final section of the "Historical" chapter a number of tin compounds that have been known and used for many centuries are described.

The second part contains a chapter on the geochemistry of tin and also a chapter on minerals and workable deposits. The chapter on cosmochemistry gives information on the frequency of occurrence of tin in the universe and its occurrence in the solar spectrum, in star spectra, and in meteorites. The up-to-date nature of the material is particularly clear from a short section on the tin content of moon rocks (for the entire volume, the literature has been scanned up to 1970). The chapters on geochemistry and minerals occupy a large amount of space (160 pages), and describe the behavior of tin in rock and deposit formation, and also the paragenesis and the chemical and physical properties of the tin minerals. Information on the deposits, as far as they are used, is to be found in the final chapter. This also gives the major producers, the production figures for individual countries over the last few decades, tin reserves, and a survey of the price variations of the metal, both in general and in detail.

System No. 61. Silber, Teil B 1 (Silver, Part Bl). Compounds with the inert gases, hydrogen, oxygen, nitrogen, fluorine, and chlorine. Chief editor: *Rudolf Keim*, 1971, vi, xxiv, 542 pp., 154 figures, bound. DM 648.—.

It is only a short while since part A of System No. 61, dealing with the history and occurrence of silver and also with the element as such, was published[1], and now we have here the first section of Part B, which deals with the compounds of silver. As in some of the other recent volumes of this series, in many places the strictly systematic approach is allowed to break down in order to give a chemically clearer picture. Alkali metal and alkaline earth metal double compounds with the same silver-containing anions are handled at the same time as the corresponding silver compound. For example, the description of Ag(II) fluoride is followed by a description of all the fluoroargentates(II). In general, this will be welcomed by the chemist. However, anyone for whom the topic in question is completely unfamiliar will find literature searching more difficult, and this is even more true for the non-chemist. It is therefore hoped that the alphabetical subject index announced for the final volume of "Silver—B" will help to reduce this difficulty.

The present volume begins with a description of the sorption of the inert gases and hydrogen by silver, and also of their solubility and diffusion in silver. Although no well-defined compounds between silver and the inert gases are, as yet, known, silver does react with hydrogen to form a compound with the composition AgH, which exists at any rate in the gaseous state. Solid silver hydrides have certainly been described, but their existence is uncertain. In the silver-oxygen system, Ag_2O occupies the most space. In addition, oxides are known in which silver occurs in the oxidation states of +2 and +3. In the silver-nitrogen system, the description of silver nitrate occupies 37 pages. A further 66 pages are taken up with solutions of $AgNO_3$ and systems containing silver nitrate and alkali metal and alkaline earth metal nitrates. More interesting and stimulating for the chemist, however, are the sections on "Berthollet's silver fulminate", the main component of which is Ag_3N, and on silver azide, silver amide, silver imide, and the silver salts of the lower nitrogen oxy-acids. Most of the papers on the silver-fluorine system are of recent date, if one ignores those on the binary silver fluorides Ag_2F, AgF, and AgF_2. In particular, the fluorine compounds of Ag^{II} and Ag^{III} have become known due to the work of *R. Hoppe*, mainly over the past two decades.

In the silver-chlorine system, AgCl is the only binary silver-chlorine compound whose existence has been definitely proved at present. The AgF_2 analog $AgCl_2$ may exist in the gas phase. AgCl is one of the most thoroughly investigated of all chemical compounds, among other things because of its photochemical properties. The formation and the crystallographic, mechanical, magnetic, electrical, optical, and chemical properties of the pure compound occupy 147 pages, and the description of AgCl-containing systems takes another 30 pages. The rest of the volume is concerned with the silver salts of chlorine oxy-acids.

The literature is covered up to the end of 1969, and in some cases (*e.g.* $KAgF_3$, $RbAgF_3$, and $CsAgF_3$) as far as 1970.

Although recent Gmelin volumes have contained more tables than previously, the present reviewer feels that still more information should be presented in tabular form, thus making the rest of the text easier to read. This would be of particular assistance to users who cannot read German.

Ekkehard Fluck [NB 14 IE]

Survey of Organic Syntheses. By *C. A. Buehler* and *D. E. Pearson*. John Wiley & Sons Ltd., Chichester 1970. 1st Edit., ix, 1166 pp., bound £ 13.00.

The book presents a survey of the principal methods for the preparation of organic compounds. The discussion of each reaction is headed by a general reaction scheme which is followed by a description of the possible uses and the limitations of the method in question. Corresponding to the entirely practical orientation of the book, reaction mechanisms are considered in only a few instances. Finally, the uses of the method are illustrated by well-chosen examples with the relevant literature references. The arrangement of the book is based consistently on the type of compound being prepared. The 20-chapter book begins with the methods for the synthesis of alkanes and ends with those for nitro compounds.

I must confess that the incongruity of the book's claim that it presents a substantially complete account of the methods of practical importance and its relatively small size made me skeptical at first, particularly since the book is aimed both at students and at research chemists. However, a close examination provided a pleasant surprise.

The authors have been very successful in their presentation of the subject matter with special concentration on what is essential. All the methods that have proved useful in laboratory practice are presented briefly but without omission of any essential points. Important experimental data are given in every case. The selection of the methods, the examples, and the references reflect critical judgment of a high order. The use of the book is greatly facilitated by a comprehensive author and subject index.

[1] Cf. Angew. Chem. internat. Edit. *10*, 526 (1971).

In conclusion, it can be said that the book succeeds in providing a really useful survey of methods for the preparation of organic compounds. It is of great practical value, and should soon become a standard work for the organic laboratory.

H. Stetter [NB 16 IE]

Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel (Chemistry of Plant Protection Agents). Edited by *R. Wegler*, Springer Verlag, Berlin–Heidelberg–New York, 1970, 1st ed., vol. 1: Einführung, Insektizide, Chemosterilantien, Repellents, Lockstoffe, Akarazide, Nematizide, Vogel- bzw. Säugetierabschreckmittel, Rodentizide (Introduction, Insecticides, Chemosterilizers, Repellents, Attractants, Acaricides, Nematicides, Chemicals Repelling Birds and Mammals, Rodenticides). xxiv, 671 pp., 23 figures, bound, DM 180.—. Vol. 2: Fungizide, natürliche Pflanzenwuchsstoffe, Rückstandsprobleme. (Fungicides, Natural Plant Growth Substances, Residue Problems). xxix, 550 pp., 24 figures, bound, DM 148.—.

This work will "enable students and young industrial chemists to become thoroughly familiar with the field of plant protection, while offering advice and help to specialists". In addition, it helps to fill a gap as a textbook and a survey of this field. The authors are chemists and biologists working mainly in industry (23 for Farbenfabriken Bayer AG, one for Shell Research Ltd., one for Farbwerke Hoechst AG, and two for the Department of Ecological Chemistry, Gesellschaft für Strahlenforschung mbH). The authors "tried to mold the large mass of data into a coherent whole. They also aimed to present the material in homogeneous sections, but primarily in a form dictated by the subject". The biological background is given "whenever it is needed for understanding the subject".

After the Introduction, devoted to the scientific significance of plant protection (17 pp., 22 refs.), volume 1 deals with the development of new plant protection agents (25 pp., 22 refs.), commercial formulations (14 pp., no refs.), and in the chapter on Insecticides—with the general aspects of the biology and testing of insecticides and acaricides (19 pp., 23 refs.), the combatting of the emergence of resistance (19 pp., 14 refs.), naturally occurring insecticides (33 pp., 353 refs.), chlorinated hydrocarbons (98 pp., 553 refs.), carbamates (27 pp., 160 refs.), insecticidal phosphoric esters (205 pp., 810 refs.), insecticides belonging to other groups (10 pp., 30 refs.), and contact insecticides (9 pp., 25 refs.). It also covers chemosterilizing agents (11 pp., 65 refs., alkylating agents, antimetabolites, *etc.*), insect repellents (9 pp., 33 refs.), insect sex attractants (25 pp., 73 refs.), acaricides (44 pp., 248 refs.; biology, historical, active substances), nematicides (10 pp., 27 refs.), bird and mammal deterrents (13 pp., 152 refs.), and rodenticides (43 pp., 1000—1200 refs.).

This comprehensive book gives an excellent survey of the fields mentioned above, and the extensive references permit these fields to be studied in depth. Stock protecting agents and the chemical analysis of active substances receive a somewhat cursory treatment. Questions of nomenclature, which are so important, are dealt with in the chapter on phosphoric esters.

The second volume is particularly valuable because it surveys the important fungicides (166 pp., 440 refs.) and herbicides, and comprises an excellent chapter on the residues of plant protection agents which can be detected in food and in the environment. The textbook nature of this work is enhanced by the color pictures of the main fungal plant diseases in the general part of the chapter on fungicides (40 pp., 43 refs.), and by color pictures of the main weeds in the section on herbicides. There is a very interesting section on phytohormones or natural plant growth substances (30 pp., 300 refs.). These two volumes can altogether be warmly recommended, and should not be missing from the bookshelves of any laboratory dealing with residue problems.

Konrad Pfeilsticker [NB 4 IE]

Experimentelle Einführung in die Anorganische Chemie (Introduction to Experimental Inorganic Chemistry). By *H. Biltz, W. Klemm*, and *W. Fischer*. Walter de Gruyter u. Co., Berlin 1971, 63.—70. Revised edition, 228 pp., 28 figs., 1 table, bound, DM 21.—.

The revised edition of Biltz, Klemm, and Fischer differs from the previous one principally in that the theoretical chapters have been considerably enlarged. The section on chemical bonding gives a concise and up-to-date treatment of the atomic structure of elements, and then describes the three types of bonding (ionic, covalent, and metallic). Although this only takes 7 pages, nothing essential has been omitted, and the topic is presented in a clearly understandable fashion. Appropriately, the most recent definition of the acid-base concept is also given, and the concept of pK is introduced.

The text is amplified with tables of data on the most important indicators (with end-point range and color of the indicator acid or base), solubilities, pK_A and pK_B values for the more important acids and bases, and oxidation and reduction potentials. Such data are very important for the quantitative description of chemical processes.

Despite these improvements, the size of the book has increased only slightly, if at all, due to the deletion of some data from the analytical section and certain sections, *e.g.* "Electronegativity".

The book, which is very attractive typographically and in its general appearance, is a considerable improvement over the previous edition, and will certainly please those who are already Biltz, Klemm, and Fischer enthusiasts. It can be recommended without reservations to all first-year chemistry students and to any student who is taking inorganic chemistry as a subsidiary subject.

Alois Haas [NB 22 IE]

Isonitrile Chemistry. Organic Chemistry, a Series of Monographs, Vol. 20, By. *I. Ugi*. Academic Press, New York, 1971. 1st Edit., xii, 278 pp., numerous illustrations, 8 tables, bound $ 14.50.

Despite the fact that review articles have appeared recently on individual aspects of isonitrile chemistry *(B. Zeeh; L. Malatesta)*, the present book deserves a warm welcome for the way in which it summarizes the information on the structure, syntheses, and reactions of isonitriles (isocyanides) in a single monograph of 256 pages. Not only does this book provide an introduction to the chemistry of isonitriles, but it also takes the trouble to present the position as it exists today.

The material is divided into the following chapters: 1, The Structure of Isonitriles; 2, Isonitrile Syntheses; 3, Kinetics

of the Isonitrile-Nitrile Rearrangement; 4, Simple α-Additions; 5, Cyclization Reactions; 6, The Reaction of Isonitriles with Boranes; 7, The Passerini Reaction and Related Reactions; 8, Four-Component Condensations and Related Reactions; 9, Peptide Syntheses; and 10, Coordinated Isonitriles. This arrangement leads, of necessity, to a certain amount of overlap. For example, many reactions are found both in Chapter 4 and in Chapter 5.

In some of the chapters the material is subjected to a critical review, but in others this review is rather too short. Nevertheless, this monograph can be highly recommended, since it enables the chemist to obtain a quick and comprehensive insight into the chemistry of isonitriles.

Kurt Lev [NB 15 IE]

Komplexchemie (The Chemistry of Complexes). By *M. Becke-Goehring* and *U. Hofman*. Springer Verlag, Berlin–Heidelberg–New York 1970. 1st edit., viii, 245 pp., 104 figures, bound, DM 18.80.

This book is an up-to-date introduction to the chemistry of complexes from the chemist's viewpoint. After an explanation of the meaning of the "chemistry of complexes" and a short historical introduction, the first part of the book deals systematically with the phenomenology of complex compounds. The types of isomerism are described, with particular reference to stereoisomerism, which is of great importance when establishing structural formulas. One chapter is devoted to chelate complexes. All the important classes of complexes (metal carbonyls, hydrido complexes, *etc.*) are considered in relation to their importance, as also are the very recent developments in the field of complex chemistry (*e.g.* complexes with N_2 as the ligand and the electron donor-acceptor complexes). A consideration of the stability of complexes, particularly in aqueous solutions, closes the second part of the book. In the third part are described the structures of complex compounds with the central atoms having coordination numbers of 2 to 9.

In Part 4 the authors go into the theories of bonding between the central atom and the ligands. First of all the valence bond theory is described and its achievements are demonstrated. Any discussion of the chemistry of complex compounds which did not involve ligand field theory would now be unthinkable. The authors have successfully accomplished this far from easy task without recourse to the development of mathematical foundations. The use of the ligand field theory is clearly explained.

Finally, the authors deal with the substitution reactions of complexes of octahedral and quadratic structure, and also with the *trans* effect and the chelate effect. The concepts of "hard and soft acids or bases" which have been much used recently, bring the book to a close.

The book gives an extremely good overall picture of the chemistry of complexes. It is distinguished by a strictly systematic approach and by a clear and precise style of writing. Practically all the viewpoints and principles which are in any way of importance in complex chemistry have been taken into consideration. However, the present reviewer would welcome it if when a new edition appears there could be some mention of the approach of *Magnus*, with its electrostatic basis. Whether or not a complex exists and and is stable in the solid crystalline state depends on the energy of complex formation and, under certain circumstances, also on the lattice energies of the substances involved. It is striking that in recent books on the chemistry of complexes the ligand field theory gets its due mention, but Magnus' electrostatic approach, which permits a simple energetic interpretation of the coordination number, is left out in the cold.

Finally, I should like to emphasize that this excellent introduction to the chemistry of complexes can be warmly recommended to students of chemistry. The expert will read the book with pleasure and be stimulated by the way in which the information is conveyed. The use of extensive literature references is particularly valuable.

Otto Schmitz-Du Mont [NB 8 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of thus issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 4036/4037, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (06201) 4031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition
VOLUME 11 · NUMBER 2
FEBRUARY 1972
PAGES 73 - 158

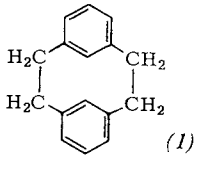
Stereochemistry of [2.2]Metacyclophanes

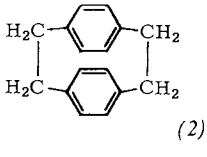
By Fritz Vögtle and Peter Neumann[*]

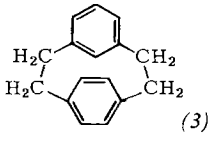
Increasing numbers of investigations have been carried out on bridged aromatic compounds, the independence of which was very recently acknowledged in the class name "phanes". Special attention is being attracted by the [2.2]metacyclophanes, whose molecular architecture raises many interesting theoretical questions, mainly with regard to intramolecular steric and electronic interactions. In the present progress report, a short description of the classification and nomenclature of the phanes is followed by a discussion of new physical and chemical aspects of the stereochemistry of [2.2]metacyclophanes and a number of related [2.2]phanes with other aromatic nuclei.

1. Introduction

In addition to demanding synthetic problems, the [2.2]phanes, the best-known of which are [2.2]metacyclophane *(1)*, [2.2]paracyclophane *(2)*, and [2.2]metaparacyclophane *(3)*, present interesting and varied theoretical aspects. This is true in particular of the stereochemistry and the resulting intramolecular steric and electronic interactions, as well as the transannular reactions. The [2.2]metacyclophane system, which will be considered more fully here, is particularly suitable for use as a model system for the investigation of such questions, owing to


(1)


(2)


(3)

the possibility of introducing a wide range of substituents into the interior of the ring. For example, it is possible to investigate interactions of fixed atomic groups with one another or with aromatic systems, the influence of extraannular substituents on such processes, and transannular ring closure reactions in compounds with comparatively simple structures. In view of the abundance of data available, a critically selective survey of the developments of recent years seems appropriate[1]. Since the situation is not very clear at present, the nomenclature and classification of bridged aromatic compounds will first be briefly described[2].

1.1. Classification of the Phanes

The class designation "phanes"[3] embraces all bridged aromatic compounds, provided that the following conditions are satisfied:

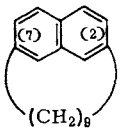
1. The *bridge* satisfies the IUPAC definition[4] in Rule A-31.1, Footnote: "A bridge is a valence bond or an atom or an unbranched chain of atoms connecting two different parts of a molecule."

2. The aromatic nuclei (or heteroaromatic nuclei) must be capable of being named in accordance with IUPAC Rule A-21.1 to A-22.5 (or B-1 to B-4).

The definition of phanes is as follows. *Phanes are any compounds containing at least one aromatic nucleus and at least one bridge.* The compound *(4)* is a simple example of a "phane".

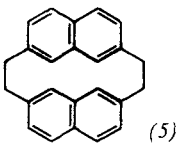
An important advantage of this group designation is that *e.g.* compounds such as *(5)* to *(8)* can be designated briefly and as a class by the name "[2.2]phanes", since this

[*] Prof. Dr. F. Vögtle and Dipl.-Chem. P. Neumann
Institut für Organische Chemie der Universität
87 Würzburg, Landwehr (Germany)

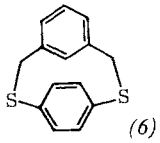


(4)

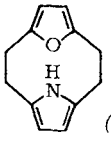
name unambiguously defines the common structural characteristic, *i.e.* the presence of two aromatic nuclei and two bridges of two atoms each[*].



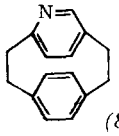
(5)



(6)



(7)



(8)

Moreover, the phanes can be divided into groups and subgroups according to the nature of their structural elements. Thus phanes such as *(5)* and *(6)* with carbocyclic aromatic nuclei (benzene, naphthalene, *etc.*) are called carbophanes, and those with heteroaromatic nuclei such as *(7)* are called heterophanes. If the character of the bridge is taken into account in the name, the prefixes carba- and hetera- show whether the bridge contains only carbon atoms or also contains hetero atoms. A phane such as *(6)* with carbocyclic nuclei and bridges containing hetero atoms thus belongs to the subgroup of hetera-carbophanes.

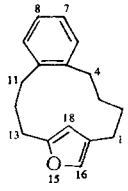
1.2. Phane Nomenclature

According to the basic rules of phane nomenclature[2b], the number of bridge atoms [*e.g.* 9 in *(4)*] between the bridgehead atoms in the aromatic ring [2 and 7 in *(4)*] is first given in square brackets. The bridgehead positions are then given in round brackets according to the IUPAC numbering of the aromatic nucleus. This is followed by the IUPAC name of the aromatic nucleus, to which the suffix -phane is attached with insertion of the letter o. *(4)* is thus [9](2,7)naphthalenophane. On historical grounds, however, an exception is made in the case of bridged benzene rings; these are called ortho-, meta-, or paracyclophanes.

If there are several aromatic nuclei and hence several bridges in the molecule, the start of naming and numbering is determined by the longest bridge [cf. *(9)*]. For bridges of equal length, as in the case of the [2.2]phanes, the aromatic nuclei are arranged alphabetically; in the case of the cyclophanes, the order is ortho, meta, para.

[*] The name "[*n.m*]phanes" unambiguously indicates compounds with two bridges and two nuclei even when *n* and *m* are large. It does not include compounds having two bridges and only one nucleus; these are called "[*n*][*m*]phanes" [2b]. In the latter designation the square brackets are not separated by the name of any aromatic nucleus. This is in marked contrast to the designations of the compounds *(6)*—*(8)*.

The phane designations for the compounds *(5)* to *(9)* are thus [2.2](2,7)naphthalenophane, 1,10-dithia[2.2]metaparacyclophane, [2](2,5)furano[2](2,5)pyrrolophane, [2]paracyclo[2](2,5)pyridinophane, and [4]orthocyclo[3](2,4)furanophane respectively. If the aromatic nuclei differ



(9)

only in the linkage positions, the two expressions in square brackets may be combined for simplicity [cf. *(6)*]. The same is true for identical linkage positions as in *(7)*: [2.2](2,5)furanopyrrolophane[**].

The phane concept will be further illustrated by the examples in the text.

2. Molecular Geometry and Physical Properties

2.1. [2.2]Metacyclophanes

The geometry of the [2.2]metacyclophane skeleton is known in detail from an X-ray structural analysis[5]. The crystal consists of discrete molecules, each of which has a center of symmetry. The two halves of the molecule form a stepped system (see Fig. 1). It is interesting to note that the benzene rings are not planar, but have a boat conformation (cf. Fig. 2), with the result that the molecule evidently avoids the steric interaction of the central carbon atoms C-8 and C-16 and of the attached hydrogen atoms. The C(8)—C(16) distance (a in Fig. 1) is 2.689 Å. The average length of the aromatic C—C bond was found to be 1.386 Å, and that of the aliphatic bond 1.543 Å. It is remarkable that the normally hexagonal, planar benzene ring suffers such a pronounced deformation with no appreciable change in the interatomic distances[6].

The X-ray structural analysis of 8,16-dimethyl[2.2]metacyclophane *(10)* confirms the results obtained for the

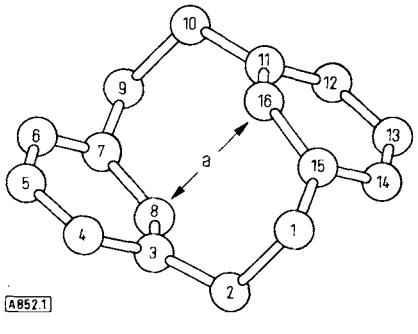


Fig. 1. Geometry of [2.2]metacyclophane *(1)*.

[**] It should be expressly mentioned that the numbers in square and in round brackets must not be omitted, since the number of similar aromatic nuclei (and naturally the number of bridges and atoms in them) can in many cases be deduced only from these figures [cf. *(4)* and *(5)*; see *(74)* and *(76)* in Section 4].

parent compound[7]. The increased strain in the molecule *(10)* as compared with that in the parent hydrocarbon *(1)* can be seen in particular in the distance between C-1 and C-2 (1.573 Å). It is also remarkable that the two methyl carbon atoms lie in one plane together with the carbon

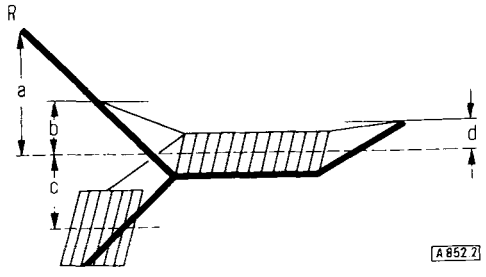
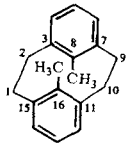


Fig. 2. Deviation of the benzene rings from planarity in *(1)*, *(10)*, and *(11)*. Only one half of the molecule is shown [5—8].

	R	a (Å)	b (Å)	c (Å)	d (Å)
(1)	H	—	0.143	0.368	0.042
(10)	CH_3	0.585	0.187	0.417 (0.453)	0.088
(11)	CH_2Br	0.494	0.178	0.367 (0.481)	0.080

atoms 8,7, and 3 and 16, 11, and 15 (cf. Figs. 1 and 2). The C(8)—C(16) distance is increased from 2.689 Å in *(1)* to 2.819 Å in *(10)*. The rotation of the methyl groups (which are fixed above the aromatic rings) about their axes appears to be hindered, if not blocked. However, proton resonance measurements down to −20 °C show no rotation barrier for the molecule in solution (see below).



(10)

The steric structure of 8,16-bis(bromomethyl)[2.2]metacyclophane *(11)* as found by X-ray structural analysis[8] largely corresponds to that of *(10)*; the benzene rings are deformed to a similar degree [C(8)—C(16) is 2.77 Å]. The C—Br bond length (1.981 ± 0.005 Å) is slightly greater than the usual values for aliphatic compounds (1.937 Å); this is attributed to steric factors. The CH_2—Br group is oriented in such a way that the bromine atom is on the side remote from the other benzene ring (Fig. 3).

The numerous ^{1}H-NMR investigations on dissolved [2.2]-metacyclophane *(1)*[9-17] agree excellently with the assumption of a "stepped" conformation such as is found in the crystal. Figure 4 shows the proton resonance spectrum of *(1)*[17]. The methylene protons of the two bridges are nonequivalent, since they have a fixed, staggered arrangement, and they therefore appear as an AA'BB' system[9]. A particularly striking feature is the absorption of the intra-annular protons H_i at unusually high field strengths ($\tau = 5.75$); this is explained by the fixation of their steric positions above the aromatic rings.

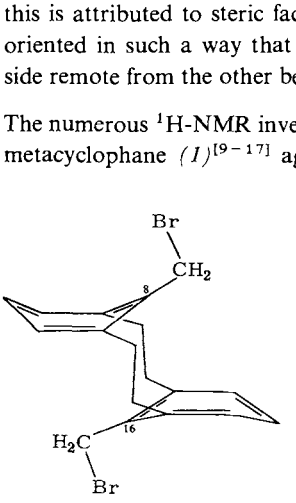


Fig. 3. Geometry of 8,16-bis(bromomethyl)[2.2]metacyclophane *(11)*.

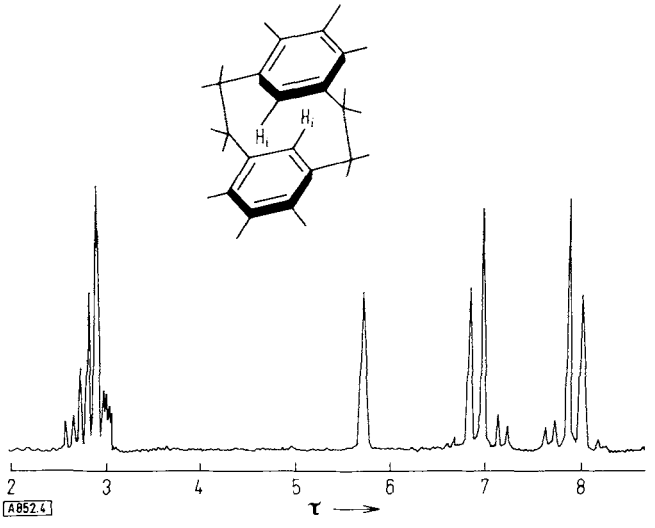
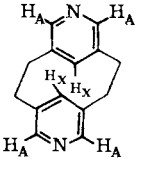


Fig. 4. ^{1}H-NMR spectrum of [2.2]metacyclophane *(1)* in $CDCl_3$ (60 MHz).

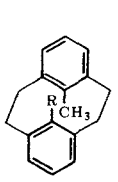
As is shown by the temperature-independence of the methylene resonance of *(1)* between −80 and +190 °C[12], the molecule is also perfectly rigid in solution; in agreement with molecular model considerations, ring inversion can be ruled out.

The molecular structure of [2.2](3,5)pyridinophane *(12)*, according to proton resonance results, agrees with that of *(1)*[18]. The protons of the pyridine nuclei absorb as an A_2X system, and the resonance of the intraannular protons H_X appears at a slightly lower field strength ($\tau = 5.49$) than in the case of *(1)* ($\tau = 5.75$); the same tendency is found for the protons of the methylene bridge, which form an AA'BB' system.

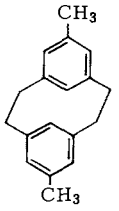


(12)

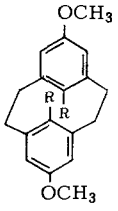
The anisotropy effect of the benzene nuclei is particularly evident in intra-annularly substituted [2.2]metacyclophanes. It is most pronounced in the case of 8-methyl[2.2]-metacyclophane *(13)*[19]. The absorptions of the intra-annular proton and also of the CH_3 group occur at the highest field strength so far found for such systems ($\tau = 6.28$ and 9.52 respectively; in $CDCl_3$). In 8,16-dimethyl[2.2]-metacyclophane *(10)*, on the other hand, the CH_3 resonance is displaced slightly less in relation to that of toluene [$\tau = 9.44$ for *(10)*, while $\tau = 7.68$ for toluene][9, 20].



(13), R = H
(10), R = CH_3



(14)



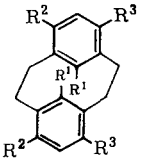
(15a), R = H[9]
(15b), R = CH_3
(15c), R = C_2H_5
(15d), R = C_3H_7

It is possible that each CH_3 group in *(10)* is more strongly removed from the sphere of influence of the opposite benzene ring than the methyl group in *(13)*, to compensate for the greater total strain. An X-ray structural analysis would be of value in clarifying this problem.

In 5,13-dimethyl[2.2]metacyclophane *(14)*, which also has a rigid conformation, the CH_3 groups absorb "normally" at $\tau = 7.64$, since they are not exposed to the shielding effect of the diamagnetic ring current of the benzene nuclei[9].

The rotation of intra-annular alkyl substituents about C—C single bonds does not appear to be hindered. For example, the CH_3 signal of *(10)* shows no broadening at $-20\,^{\circ}C$[9]. The ^{1}H-NMR spectra of *(15b)*[21], *(15c)*[22], and *(15d)*[23] also give no indication of hindered rotation.

The ^{1}H-NMR spectra of other [2.2]metacyclophanes of the type *(16)* with extra-annular substitution on the benzene rings were discussed by *Sato et al.*[24,25].

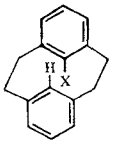


(16a), $R^1 = R^3 = H$, $R^2 = CH_3$
(16b), $R^1 = H$, $R^2 = R^3 = CH_3$
(16c), $R^1 = R^2 = R^3 = CH_3$
(16d), $R^1 = R^3 = H$, $R^2 = COOH$

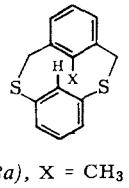
Further evidence of the rigid conformation of the [2.2]-metacyclophane system was provided by the resolution of *(16a)* and *(16d)* into optical antipodes as complexes with (−)-α-(2,4,5,7-tetranitro-9-fluorenylidenaminooxy)-propionic acid and as the quinine salts[12].

In the unsymmetrically substituted phanes *(17a)* and *(17b)*[26], which recently became available by the pyrolysis of suitable sulfones, both the protons of the methylene bridges (ABCD system) and the inner aromatic protons absorb at characteristically high field strengths [$\tau(H_i) = 5.63$ and 6.06 respectively].

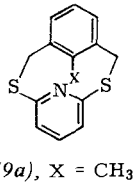
The chemical shifts of the methyl protons of *(18a)* and *(18b)* and of *(19a)* and *(19b)* show[27a] that the replacement of CH_2 groups in the bridges by sulfur atoms also leads to considerable upfield shifts; the $\tau(CH_3)$ value found for *(18a)* (9.41) is almost equal to that of *(10)* (9.44).



(17a), X = F
(17b), X = Cl



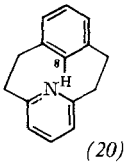
(18a), X = CH_3
(18b), X = OCH_3
(18c), X = CN[27b]



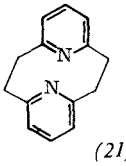
(19a), X = CH_3
(19b), X = OCH_3

The influence of the pyridine ring in *(19a)* leads to a rather smaller shift of the methyl signal to higher fields ($\tau = 8.41$). The signal of the intra-annular hydrogen atom H_i is shifted ($\tau = 5.05$) in the same way as the signal of the methyl group in *(18a)*. The effect is not so pronounced in *(18b)* and *(18c)* [$\tau(H_i) = 4.80$ and 4.93 respectively].

If the benzene nuclei in [2.2]metacyclophane are successively replaced by pyridine rings linked in positions 2 and 6, the products are [2]metacyclo[2](2,6)pyridinophane *(20)* and [2.2](2,6)pyridinophane *(21)*. In the ten-membered rings, one and both respectively of the intra-annular hydrogen atoms of [2.2]metacyclophane have been formally replaced by the lone pair of electrons of the pyridine N atom. The ^{1}H-NMR spectrum of *(20)*[28] shows an AX_2 system for the protons of the pyridine ring and an AB_2 system for the extra-annular protons of the benzene ring. The intra-annular proton in position 8 again appears at a specifically high field strength ($\tau = 5.60$). The methylene protons of the bridge absorb as an ABCD system, which is unchanged even at 200 °C. *(20)*, like [2.2]metacyclophane itself, thus exists as a rigid, *anti*-staggered ring system up to high temperatures. The free energy of activation for the ring inversion as calculated from the experimental data is >27 kcal/mole.



(20)



(21)

For *(21)* in solution[29] on the other hand, an inversion process of the type A⇌B (Fig. 5) must be assumed on the basis of the temperature-independence of the ^{1}H-NMR spectrum.

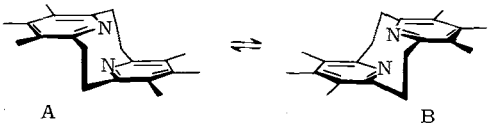
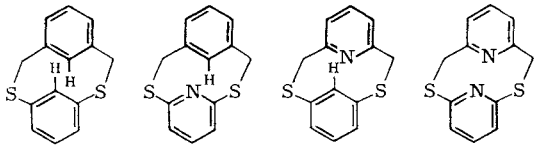


Fig. 5. Ring inversion process for *(21)*; schematic.

The free energy of activation ($\Delta G_C^{\ddagger}$) for this process was found to be 14.8, and the Arrhenius energy (E_A) is 15.3 kcal/mole. On the assumption of identical ring inversion mechanisms for *(1)*, *(20)*, and *(21)*, the steric hindrance in the transition state is evidently least in *(21)*, in which interaction occurs between two lone pairs of electrons on atoms that are not directly bonded to each other. It was therefore concluded that the space occupied by the lone pair of electrons on the nitrogen atom of pyridine is smaller than that occupied by a hydrogen atom attached to an aromatic nucleus.

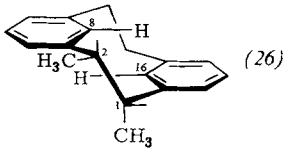
Detailed ^{1}H-NMR studies on a series of [2.2]phanes of the types *(22)*—*(25)*[30] have confirmed these results, and at the same time impressively demonstrated the value of the

study of the dynamic stereochemistry of the phanes for the qualitative and quantitative determination of steric and electronic effects ("non bonded interactions").



(22) (23) (24) (25)

The intra-annular hydrogen atoms of 1,2-dimethyl[2.2]-metacyclophane *(26)*[31] are magnetically nonequivalent. Whereas H-8 has the same chemical shift as the intra-annular protons of [2.2]metacyclophane ($\tau = 5.75$), the H-16 resonance is displaced to lower fields ($\tau = 5.50$). This displacement could be due to the influence of the methyl group on C-1 ($\tau = 9.15$), whereas a considerably weaker interaction is to be expected between H-8 and the equatorial CH_3 group ($\tau = 8.52$) on C-2. Double resonance experiments also confirm that the axial proton on C-2 couples with the protons of the equatorial CH_3 group.



(26)

The UV spectrum of [2.2]metacyclophane[14] has as its longest-wave absorption that at $\lambda_{max} = 272$ nm ($\log \varepsilon = 2.64$), with three inflections, which are displaced in relation to the reference substance 3,3'-dimethylbibenzyl. MO calculations taking the deformation of the benzene rings into account show satisfactory agreement with the spectroscopic findings[10].

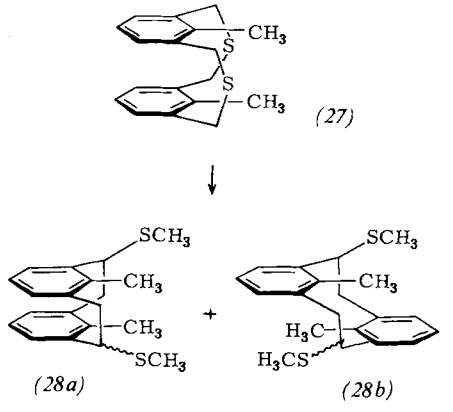
Transannular charge-transfer interactions between [2.2]-metacyclophane and tetracyanoethylene are regarded as the reason for the appearance of a band at 490 nm, which is characteristically displaced to longer wavelengths in relation to that of the corresponding complex with *m*-xylene[16]. Transannular charge-transfer interactions mean in this context that the benzene ring of [2.2]metacyclophane that is turned away from the tetracyanoethylene strengthens the donor action of the nucleus adjacent to the acceptor. However, the long-wave absorption of the [2.2]paracyclophane-tetracyanoethylene complex ($\lambda_{max} = 521$ nm)[32] is not attained.

Bands appearing between 1400 and 400 cm^{-1} in the IR spectrum of [2.2]metacyclophane, which are absent or are not present with comparable intensities in the spectra of the reference substances *m*-xylene, [2.2.2]metacyclophane, and [2.2.2.2]metacyclophane, are attributed to the deformation of the benzene nuclei[16].

The mass spectra of [2.2]metacyclophane and higher metacyclophanes have been discussed by *Jenny et al.*[14, 33] and by *Flammang et al.*[16].

Whereas the [2.2]metacyclophanes described so far, according to the spectroscopic findings, have the *anti* conformation with staggered benzene rings, the existence of a *syn* form for a [2.2]phane has recently also been detected[34].

Ring contraction (Stevens rearrangement) of the bis(sulfonium tetrafluoroborate) of *syn*-9,18-dimethyl-2,11-dithia[3.3]metacyclophane *(27)* led to a 3:1 mixture of *syn* and *anti* isomeric substituted [2.2]metacyclophanes *(28a)* and *(28b)*.



(27)

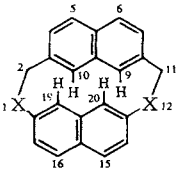
(28a) *(28b)*

The assignment of the isomers is based on the ^{1}H-NMR spectra. The *C*-methyl protons of the *syn* form *(28a)*, as expected, absorb at a very much lower field strength ($\tau = 8.0$) than those of the *anti* form *(28b)* ($\tau = 9.3$).

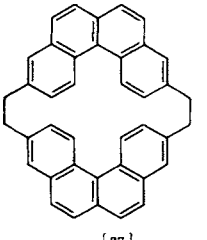
2.2. Compounds Analogous to [2.2]Metacyclophane

2.2.1. [2.2]Carbophanes

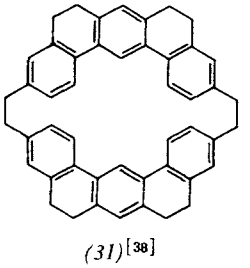
The molecular geometry of the [2.2]phanes *(5)* and *(29)* to *(31)* may be expected to be very similar to that of



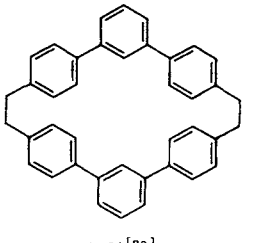
(5), X = CH_2[35]
(29), X = S[36]



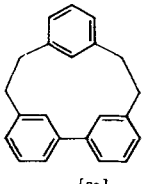
(30)[37]



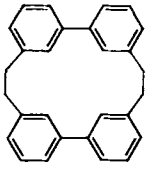
(31)[38]



(32)[38]



(33)[39]

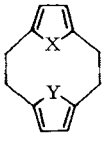


(34)[39]

[2.2]metacyclophane, since the two C_{Aryl}—CH_2 bonds from the aromatic nuclei enclose an angle of approximately 120° in each case. Rigid, stepped, *anti* conformations were in fact found in all cases, the unusually high field strength of the absorptions due to the intra-annular hydrogen atoms being taken as an important indication. The compounds *(32)*—*(34)* may also be regarded as metacyclophane analogs.

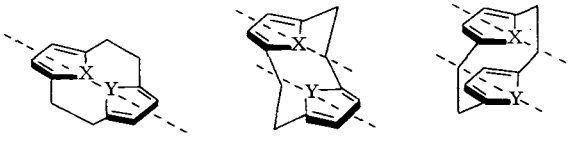
2.2.2. [2.2]Heterophanes with Five-Membered Aromatic Rings

In view of the entirely different geometry of "aromatic" five-membered rings, the [2.2](2,5)heterophanes *(35)* cannot be compared directly with [2.2](1,3)cyclophanes and [2.2](1,3)pyridinophanes[40]. On the basis of the Raman and IR spectra, *Winberg et al.*[41] proposed the *anti* conformation B with C_{2h} symmetry for [2.2](2,5)furanophane



(35a), X = Y = O
(35b), X = Y = S
(35c), X = O; Y = S .
(35d), X = Y = NCH_3

(35a) and [2.2](2,5)thiophenophane *(35b)*, and ruled out the *syn* form C and the coplanar conformation A. A staggered *(anti)* arrangement of the pyrrole nuclei can also be deduced for *(35d)* from ^{1}H-NMR observations[42].



A B C

In the course of a study on benzotrifuroxane *(36)*, *Kamenar* and *Prout*[43] carried out an X-ray structural analysis of a 1:1 π complex of this compound with *(35b)*. As in the case of [2.2]metacyclophane, the length of the C—C bonds of *(35b)* in this complex are practically the same as the normal values. However, the normally planar thiophene rings are appreciably deformed; they are in a sort of boat form. The bridgehead atoms C-2 and C-5 of each thiophene ring project 0.08 to 0.10 Å above the plane of the other ring atoms. However, the planes laid through each thiophene ring by the method of least squares are almost exactly parallel. The distance between two bridgehead atoms of the same CH_2—CH_2 bridge (2.80 and 2.82 Å) is exactly the same as in [2.2]paracyclophane *(2)*[44]. The S—S distance (3.19 Å) is about 1 Å greater than expected for an undistorted model molecule, but is still about 0.5 Å smaller than the van der Waals distance. The distances between the S atom of one thiophene ring and a bridgehead atom of the second thiophene ring (2.93—3.02 Å) are also considerably shorter than the sum of the van der Waals radii.

Even within this series of bridged heterocyclic five-membered rings, it is not entirely safe to draw conclusions regarding the space required by intra-annular atoms or electron pairs from the ring inversion barriers, since the bond lengths and

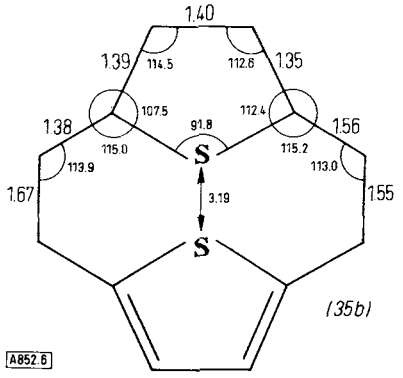
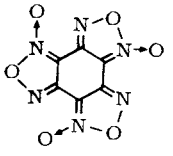


Fig. 6. Molecular geometry of [2.2](2,5)thiophenophane *(35b)* in the 1:1 adduct with benzotrifuroxane *(36)*.



(36)

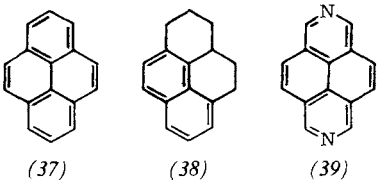
angles differ widely. The considerable difference between the conformational mobilities of the thiophenophane *(35b)*, the molecules of which are perfectly rigid, and of the furanophane *(35a)*, which is flexible, is certainly not due only to the difference in the bulks of the S and O atoms in the five-membered heterocycle. Unfortunately, there is no known X-ray structural analysis of *(35a)*, from which the influence of the bond angle might be estimated.

3. Molecular Geometry and Chemical Properties

3.1. Transannular Reactions

In the course of transannular (ring closure) reactions, one or more additional bridges, and hence new rings, are formed by linkage usually of atoms that lie opposite each other in the ring system, possibly with simultaneous or subsequent further changes in the carbon skeleton.

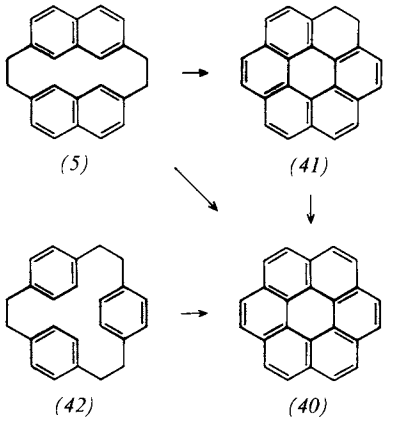
In the [2.2]metacyclophane system, such reactions normally lead to the pyrene skeleton *(37)*. Dehydrogenation of [2.2]metacyclophane *(1)* itself with palladium/charcoal at about 300°C leads to pyrene *(37)* in 60% yield; when *(1)* is heated with $AlCl_3$ in CS_2, however, only isomerization to the hexahydropyrene *(38)* takes place[45]. *Jenny* and *Holzrichter*[46] obtained 2,7-diazapyrene *(39)* in 30% yield from [2.2](3,5)pyridinophane *(12)* by heating with Pd/C (290°C) in triethylene glycol.



(37) *(38)* *(39)*

The coronene system *(40)* should be obtainable from the metacyclophane analog [2.2](2,7)naphthalenophane *(5)* by two transannular ring closures. However, the catalytic

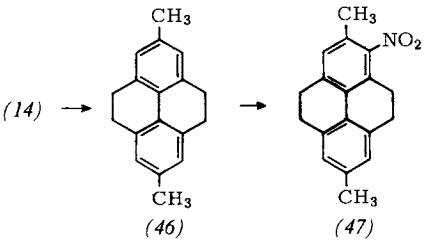
dehydrogenation of *(5)* leads only to traces of coronene, whereas treatment with $AlCl_3$ in boiling CS_2 in this case leads in good yields to a mixture of coronene *(40)* and 1,2-dihydrocoronene *(41)*. The compound *(41)* can be dehydrogenated to coronene with palladium in 87% yield[47]. [2.2.2]Paracyclophane *(42)* also gives coronene on oxidation[45b].



(5) *(41)* *(42)* *(40)*

It is interesting to note that the electrophilic substitutions investigated so far on [2.2]metacyclophanes[48] are associated with transannular ring closures.

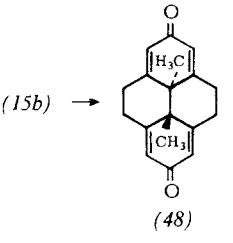
According to *Allinger et al.*[15], the nitration of [2.2]metacyclophane *(1)* probably proceeds *via* the tetrahydropyrene *(45)* (path A_1A_2), and not as a concerted transannular aromatic substitution (addition-elimination process B_1B_2), as had previously been assumed by the same group of workers[10]. *Sato et al.* also concluded that the 2-nitro-4,5,9,10-tetrahydropyrene *(43a)* that occurs as the nitration product of [2.2]metacyclophane even under mild conditions is formed not from *(44)*, $X=NO_2$, but from *(45)*[13]. The dimethyltetrahydropyrene *(46)* was in fact detected and isolated as an intermediate in the nitration of 5,13-dimethyl[2.2]metacyclophane *(14)*[15,24]. On the other hand, the intra-annularly substituted 4,6,8,12,14,16-hexamethyl[2.2]metacyclophane *(16c)* gave the 5-nitro derivative, which contains the metacyclophane structure, as is shown by its ^{1}H-NMR spectrum[24].



(14) → *(46)* → *(47)*

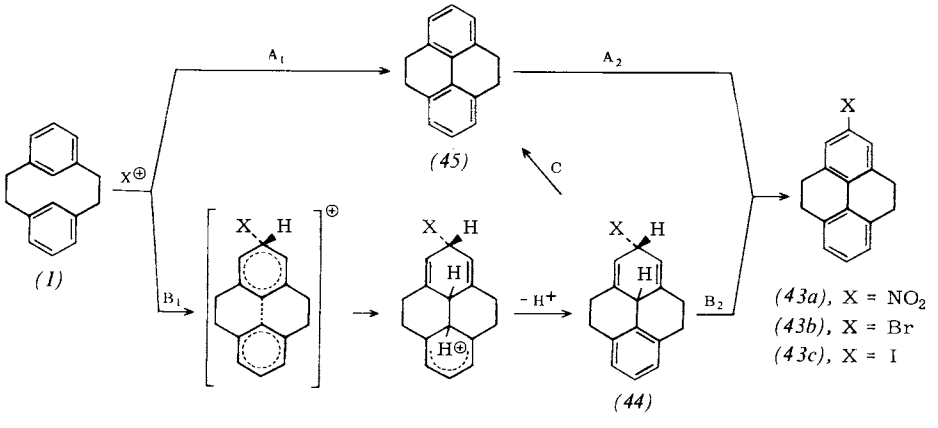
analogous to the nitration product[15], whereas *Sato et al.*, as in the iodination (with $I_2/AgClO_4$), obtained only 4,5,9,10-tetrahydropyrene *(45)*[49]. *Sato et al.*[49] therefore did not rule out the path B_1C for this reaction. On the other hand, the iodination of *(1)* with I_2/HNO_3, which leads to 2-iodo-4,5,9,10-tetrahydropyrene *(43c)*, is assumed to proceed by path B_1B_2.

The tendency of the [2.2]metacyclophanes to undergo transannular ring closure even under mild reaction conditions was used by *Boekelheide* for the preparation of 10b,10c-dialkylated dihydropyrene derivatives, which are of interest because of their aromaticity[21]. The transannular ring closure occurs surprisingly readily in the case of *(15b)*. The bis-dienone *(48)*, which is stable to acids, is obtained in practically quantitative yield on oxidation of *(15b)* with $FeCl_3$ in chloroform or with CrO_3/H_2SO_4 in acetone. The ethyl-substituted and *n*-propyl-substituted compounds *(15c)*[22] and *(15d)*[23] react in the same manner.



(15b) → *(48)*

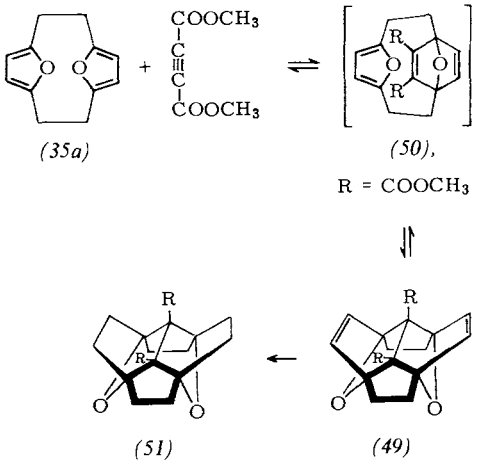
Interesting transannular reactions of some furanophanes have been described. Equimolar quantities of [2.2](2,5)-furanophane *(35a)* and dimethyl acetylenedicarboxylate, when heated at 105 °C, give a 1:1 adduct *(49)*, which decomposes back into the components at 165 °C[50]. The



(1) → *(45)* → *(44)* → *(43a)*, X = NO_2; *(43b)*, X = Br; *(43c)*, X = I

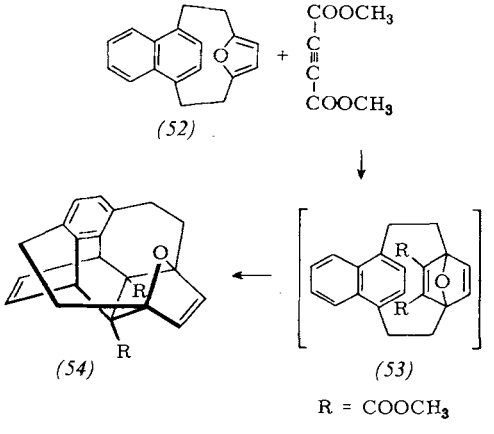
The situation is more complicated in the halogenation of [2.2]metacyclophane *(1)*. In the bromination, *Allinger et al.* obtained the 2-bromo-4,5,9,10-tetrahydropyrene *(43b)* formation of the symmetrical adduct can be explained by a plausible two-step mechanism. In the first step, an intermolecular Diels-Alder reaction leads to the intermediate

(50), which reacts further in a second Diels-Alder reaction, which is intramolecular in this case, to give *(49)*. The assignment of the structure *(49)* was based on spectroscopy (particularly ^{1}H-NMR spectroscopy) and on the formation of *(51)* on hydrogenation with H_2/Pd.



(35a) *(50)*, *(51)* *(49)*

In the case of the "mixed-nucleus" compound [2](2,5)-furano[2](1,4)naphthalenophane *(52)*, the furan ring, as the more active diene component, reacts first with dimethyl acetylenedicarboxylate, again in an intermolecular Diels-Alder reaction, to give *(53)*. The intramolecular 1,4-addition to form *(54)*, as can be deduced from mass-spectroscopic and ^{1}H-NMR-spectroscopic results, then takes place on the unsubstituted nucleus of the naphthalene grouping[51].



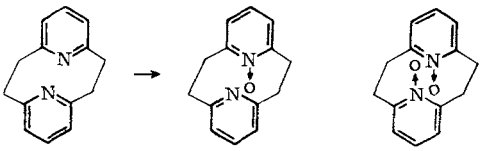
(52) *(54)* *(53)*

3.2. Intra-annular Reactions

Ideal intra-annular reactions occur exclusively in the interior of ring systems without subsequent reactions such as transannular linkage.

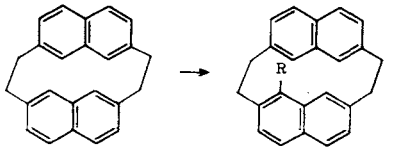
The mono-*N*-oxide and the di-*N*-oxide [*(55)* and *(56)*] of [2.2](2,6)pyridinophane *(21)* were obtained without difficulty[52].

Whereas electrophilic substitutions on [2.2]metacyclophane proceed with transannular ring closure (cf. Section 3.1), the nitro group is introduced into the interior of the ring in the nitration of [2.2](2,7)naphthalenophane *(5)* in



(21) *(55)* *(56)*

benzene/glacial acetic acid; 9-nitro[2.2](2,7)naphthalenophane *(57a)* is formed in 55% yield[35b]. The amine *(57b)* can be obtained by reduction of the nitro compound.



(5) *(57a)*, R = NO_2 *(57b)*, R = NH_2

3.3. Photochemical Reactions

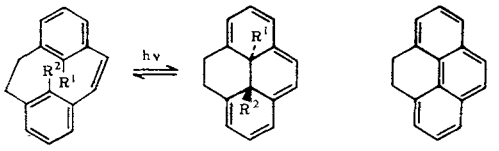
3.3.1. [2.2]Metacyclophanes

Transannular ring closure reactions of [2.2]metacyclophanes to form dihydropyrene derivatives can also proceed photochemically. After irradiation of a solution of [2.2]-metacyclophane *(1)* in cyclohexane in the presence of iodine and sodium hydrogen carbonate, *Sato et al.*[53] were able to isolate 4,5,9,10-tetrahydropyrene *(45)* in 86% yield. Since the starting material was simply recovered unchanged in the absence of iodine, the authors postulated free radicals containing iodine as intermediates in the reaction. Under comparable conditions, 5,13-dimethyl-[2.2]metacyclophane *(14)* similarly gave 2,7-dimethyl-4,5,9,10-tetrahydropyrene *(46)* in 26% yield; 4,6,8,12,14,16-hexamethyl[2.2]metacyclophane *(16c)*, on the other hand, exhibited no reaction[24].

3.3.2. [2.2]Metacyclophanes with Alkene Bridges

On irradiation with light of wavelength around 300 nm, the three metacyclophan-1-enes *(58a)*—*(58c)* undergo photoisomerization to form the colored 4,5,10b,10c-tetrahydropyrenes *(59a)*—*(59c)*[54, 55]. The equilibrium can be displaced back to the side of the [2.2]metacyclophan-1-enes both by irradiation with visible light (wavelength around 500 nm) and by thermal reaction (allowing the irradiated solution to stand in the dark). The equilibration and the kinetics of the dark reaction *(59)* $\rightleftharpoons$ *(58)* were investigated by UV spectroscopy. The reactions are first order. The reaction rate is greater for *(59c)* $\rightleftharpoons$ *(58c)* than for *(59b)* $\rightleftharpoons$ *(58b)* and *(59a)* $\rightleftharpoons$ *(58a)*. This surprising result is partly interpreted as a ring strain effect and partly attributed to a mass effect of the two methyl groups. *(59a)* and *(59b)* are extremely sensitive to oxygen, and are oxidized to 4,5-dihydropyrene *(60)*.

Because of the planarity of the valences at C=C double bonds, the stepped structure cannot be so pronounced in the [2.2]metacyclophane-monoenes and [2.2]metacyclophane-dienes as in the [2.2]metacyclophanes themselves. The absorptions of the intra-annular protons of [2.2]meta-

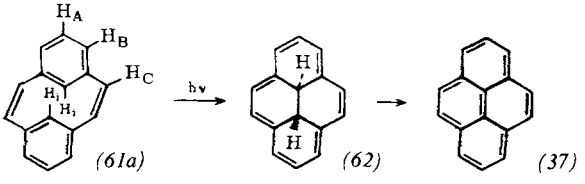


(58) (59) (60)

(a), $R^1 = R^2 = H$
(b), $R^1 = H$, $R^2 = CH_3$
(c), $R^1 = R^2 = CH_3$

cyclophan-1-ene *(58a)* and its 8-methyl derivative *(58b)*[19] occur at much lower field strengths ($\tau = 4.38$ and 5.10 respectively) than those of [2.2]metacyclophane *(1)* ($\tau = 5.75$) and of the monomethyl compound *(13)* ($\tau = 6.28$). Since the molecules *(58)* differ considerably in their overall geometry, it can hardly be assumed that this effect is entirely due to a deshielding action of the 1,2-double bond.

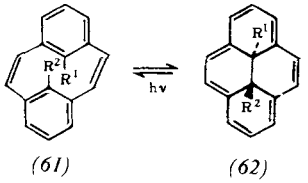
[2.2]Metacyclophane-1,9-diene *(61a)* has recently been prepared[56]. The structure of the compound was verified spectroscopically and by conversion into *anti*-[2.2]metacyclophane *(1)* and *trans*-10b,10c-dihydropyrene *(62)*.



(61a) (62) (37)

In the ^{1}H-NMR spectrum, the resonance of the intra-annular protons H_i ($\tau = 2.10$) appears at a much lower field strength than those of the other aromatic hydrogen atoms (AB_2 system). The olefinic protons (H_C) absorb as a singlet at $\tau = 3.78$.

The stability of *(61a)* is striking in comparison with that of the intra-annularly substituted [2.2]metacyclophane-1,9-dienes *(61b)*—*(61d)*. The 8,16-dialkyl[2.2]metacyclophane-1,9-dienes undergo spontaneous valence isomerization in the dark at room temperature to form the more stable aromatic *trans*-10b,10c-dialkyldihydropyrenes *(62b)*—*(62d)*[57,21-23]. The unsubstituted compound *(61a)*, on the other hand, gives a mixture of *trans*-10b,10c-dihydropyrene *(62)* and pyrene *(37)* only on irradiation.

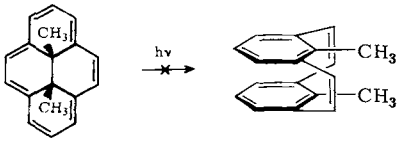


(61) (62)

(b), $R^1 = R^2 = CH_3$
(c), $R^1 = R^2 = C_2H_5$
(d), $R^1 = R^2 = n\text{-}C_3H_7$

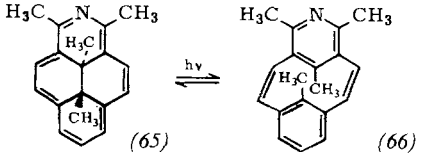
The dark reaction *(61)* $\rightleftharpoons$ *(62)* of the dienes follows first order kinetics. The rate is strongly dependent not only on peripheral substituents but also on the nature of the inner groups. For example, *(61c)* isomerizes six times as rapidly as *(61b)*, while the rate of rearrangement of *(61d)* lies between the values for *(61b)* and *(61c)*[23].

Whereas the reversible photoisomerization of *trans*-10b,10c-dimethyldihydropyrene *(62b)* to the valence-tautomeric *anti*-[2.2]metacyclophane-1,9-diene *(61b)* could be followed spectroscopically, attempts to achieve a photoequilibrium between *cis*-10b,10c-dimethyldihydropyrene *(63)* and *syn*-8,16-dimethyl[2.2]metacyclophane-1,9-diene *(64)* have so far been unsuccessful[34].



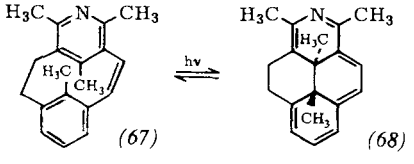
(63) (64)

On the basis of the ^{1}H-NMR spectrum, *Boekelheide* and *Pepperdine* assigned the structure of 8,12,14,16-tetramethyl-[2]metacyclo[2](3,5)pyridinophane-1,9-diene *(66)* to the product formed on UV irradiation of *trans*-1,3,10b,10c-tetramethyl-2-azadihydropyrene *(65)*[58]. The hydrochloride of *(66)* exhibits the fastest dark reaction known so far in the dihydropyrene series. The presence of a charge in one of the aromatic rings evidently promotes the formation of a bond to the other ring.



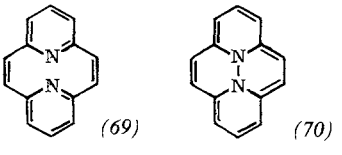
(65) (66)

Irradiation of the monoene *(67)*, as in the case of the compounds *(58)* described above, leads to a photoequilibrium with the dihydropyrene derivative *(68)*.



(67) (68)

The question which of the isomers, *i.e.* [2.2](2,6)pyridinophane-1,9-diene *(69)* or 10b,10c-diaza-10b,10c-dihydropyrene *(70)*, is present was decided spectroscopically (^{1}H-NMR, UV) in favor of the diene *(69)*[52]. No isomerization of *(69)* was observed.

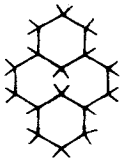


(69) (70)

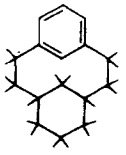
The conformational mobility in the molecule *(69)* would be difficult to investigate. Since the ^{1}H-NMR spectrum varies only slightly with the temperature, *Boekelheide* and *Lawson* assume that the molecule is not flexible[52].

3.4. Reduction of the [2.2]Phanes

The catalytic hydrogenation of [2.2]metacyclophane with platinum in glacial acetic acid leads in 91% yield to perhydro[2.2]metacyclophane *(71)*. If the hydrogenation is stopped after the uptake of 3 moles of hydrogen, the relatively strain-free 3,4,5,6,7,8-hexahydro[2.2]metacyclophane *(72)* can be isolated[10].

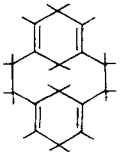


(71)

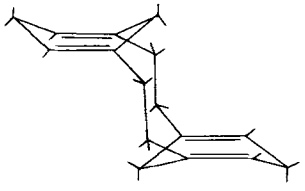


(72)

Birch reduction at −75 °C led to 5,8,13,16-tetrahydro[2.2]-metacyclophane *(73)*, for which *Reiner* and *Jenny*[59] postulated the mobile *anti* conformation *(73a)*.



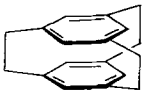
(73)



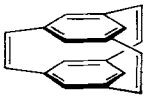
(73a)

4. Outlook

Though a large volume of experimental material on [2.2]-metacyclophanes already exists, as has been shown in this progress report, the investigations in this field, particularly with regard to the *syn*-[2.2]cyclophanes, the hetera[2.2]-cyclophanes, the [2.2]heterophanes, and the [2.2]cyclophanes with alkene bridges, can by no means be regarded as complete. However, the intensive stereochemical studies on [2.2]metacyclophanes have made a decisive contribution to our understanding of chemical and physical interactions in strained or sterically hindered ring systems of medium size. It was only on the basis of the experience and knowledge gained with the doubly bridged [*n.n*]cyclophanes that it also became possible to synthesize cyclophanes with larger numbers of bridges, among which [2.2.2](1,3,5)cyclophane *(74)* and the corresponding triene *(75)*, which have recently been prepared[60], merit attention.

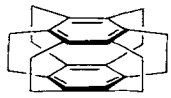


(74)

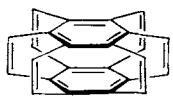


(75)

The ultimate achievement of work in the cyclophane field would be the synthesis, in the foreseeable future, of the fully bridged [2.2.2.2.2.2]-(1,2,3,4,5,6)cyclophane *(76)* and its hexaene *(77)*.



(76)



(77)

We are grateful to the Deutsche Forschungsgemeinschaft and to the Fonds der Chemischen Industrie for their support of our own work.

Received: April 26, 1971 [A 852 IE]
German version: Angew. Chem. *84*, 75 (1972)
Translated by Express Translation Service, London

[1] Earlier reviews in which bridged aromatic compounds were discussed from other points of view are: a) *D. J. Cram*, Rec. Chem. Progr. *20*, 71 (1959); b) *R. W. Griffin jr.*, Chem. Rev. *61*, 45 (1961); c) *B. H. Smith*; Bridged Aromatic Compounds. Academic Press, New York 1964.

[2] A detailed development of the phane concept can be found in *F. Vögtle* and *P. Neumann*, a) Tetrahedron Lett. *1969*, 5329; b) Tetrahedron *26*, 5847 (1970).

[3] The name "phanes" was first suggested in the following article: *F. Vögtle*, Tetrahedron Lett. *1969*, 3193.

[4] International Union of Pure and Applied Chemistry: Nomenclature of Organic Chemistry, Sections A and B. 2nd. Ed., Butterworths, London 1966.

[5] *C. J. Brown*, J. Chem. Soc. *1953*, 3278.

[6] A calculation of the energetically most favorable conformation from empirical potential functions gave satisfactory agreement with the experimental structural data: *R. H. Boyd*, J. Chem. Phys. *49*, 2574 (1968); for the determination of thermodynamic quantities and strain energies of [2.2]metacyclophane and other cyclophanes see: *C.-F. Shieh, D. McNally*, and *R. H. Boyd*, Tetrahedron *25*, 3653 (1969).

[7] *A. W. Hanson*, Acta Crystallogr. *15*, 956 (1962).

[8] *M. Mathew*, Acta Crystallogr. *B 24*, 530 (1968).

[9] *D. J. Wilson, V. Boekelheide*, and *R. W. Griffin jr.*, J. Amer. Chem. Soc. *82*, 6302 (1960).

[10] *N. L. Allinger, M. A. Da Rooge*, and *R. B. Hermann*, J. Amer. Chem. Soc. *83*, 1974 (1961).

[11] Analysis of the AA'BB' spectrum for the protons on the methylene bridges: *H. S. Gutowsky* and *C. Juan*, J. Chem. Phys. *37*, 120 (1962); Discuss. Faraday Soc. *1962*, 52.

[12] *T. Sato, S. Akabori, M. Kainosho*, and *K. Hata*, Bull. Chem. Soc. Japan *39*, 856 (1966); *41*, 218 (1968).

[13] *M. Fujimoto, T. Sato*, and *K. Hata*, Bull. Chem. Soc. Japan *40*, 600 (1967).

[14] *K. Burri* and *W. Jenny*, Helv. Chim. Acta *50*, 1978 (1967).

[15] *N. L. Allinger, B. J. Gordon, S.-E. Hu*, and *R. A. Ford*, J. Org. Chem. *32*, 2272 (1967).

[16] *R. Flammang, H. P. Figeys*, and *R. H. Martin*, Tetrahedron *24*, 1171 (1968).

[17] *F. Vögtle*, Habilitationsschrift, Universität Heidelberg 1969.

[18] *W. Jenny* and *H. Holzrichter*, Chimia *21*, 509 (1967).

[19] *H. Blaschke, C. E. Ramey, J. Calder*, and *V. Boekelheide*, J. Amer. Chem. Soc. *92*, 3675 (1970).

[20] *W. S. Lindsay, P. Stokes, L. G. Humber*, and *V. Boekelheide*, J. Amer. Chem. Soc. *83*, 943 (1961).

[21] *V. Boekelheide* and *J. B. Phillips*, J. Amer. Chem. Soc. *89*, 1695 (1967).

[22] *V. Boekelheide* and *T. Miyasaka*, J. Amer. Chem. Soc. *89*, 1709 (1967).

[23] *V. Boekelheide* and *T. A. Hylton*, J. Amer. Chem. Soc. *92*, 3669 (1970).

[24] *T. Sato, S. Akabori, S. Muto*, and *K. Hata*, Tetrahedron *24*, 5557 (1968).

[25] *S. Akabori, T. Sato*, and *K. Hata*, J. Org. Chem. *33*, 3277 (1968).

[26] *F. Vögtle*, Angew. Chem. *81*, 258 (1969); Angew. Chem. internat. Edit. *8*, 274 (1969).

[27] a) *F. Vögtle* and *P. Neumann*, Tetrahedron *26*, 5299 (1970); b) *F. Vögtle, M. Zuber*, and *P. Neumann*, Z. Naturforsch. *26b*, 707 (1971).

[28] *J. R. Fletcher* and *I. O. Sutherland*, Chem. Commun. *1969*, 1504.

[29] *I. Gault, B. J. Price*, and *I. O. Sutherland*, Chem. Commun. *1967*, 540.

[30] a) *F. Vögtle* and *A. H. Effler*, Chem. Ber. *102*, 3071 (1969); b) *F. Vögtle*, Tetrahedron Lett. *1968*, 3623.

[31] *R. W. Griffin jr.*, *R. W. Baughman*, and *C. E. Ramey*, Tetrahedron Lett. *1968*, 5419.

[32] *D. J. Cram* and *R. H. Bauer*, J. Amer. Chem. Soc. *81*, 5971 (1959).

[33] *R. Paioni* and *W. Jenny*, Helv. Chim. Acta *52*, 2041 (1969).

[34] *R. H. Mitchell* and *V. Boekelheide*, Tetrahedron Lett. *1970*, 1197; Chem. Commun. *1970*, 1555.

[35] a) *(5)* was first prepared by *W. Baker*, *F. Glockling*, and *J. F. W. McOmie*, J. Chem. Soc. *1951*, 1118; b) *R. W. Griffin jr.* and *N. Orr*, Tetrahedron Lett. *1969*, 4567.

[36] *F. Vögtle*, *R. Schäfer*, *L. Schunder*, and *P. Neumann*, Liebigs Ann. Chem. *734*, 102 (1970).

[37] *W. Jenny* and *R. Peter*, Angew. Chem. *77*, 1027 (1965); Angew. Chem. internat. Edit. *4*, 979 (1965); *R. Peter* and *W. Jenny*, Helv. Chim. Acta *49*, 2123 (1966).

[38] *F. Vögtle* and *H. A. Staab*, Chem. Ber. *101*, 2709 (1968).

[39] *F. Vögtle*, Liebigs Ann. Chem. *728*, 17 (1969).

[40] *F. Vögtle* and *R. Lichtenthaler*, Chemiker-Ztg. *94*, 727 (1970).

[41] *H. E. Winberg*, *F. S. Fawcett*, *W. E. Mochel*, and *C. W. Theobald*, J. Amer. Chem. Soc. *82*, 1428 (1960).

[42] *H. H. Wasserman* and *D. T. Bailey*, Chem. Commun. *1970*, 107.

[43] *B. Kamenar* and *C. K. Prout*, J. Chem. Soc. *1965*, 4838.

[44] *D. K. Lonsdale*, *H. J. Milledge*, and *K. V. Krishna Rao*, Proc. Roy. Soc. *A 255*, 82 (1960).

[45] a) *W. Baker*, *J. F. W. McOmie*, and *J. M. Norman*, Chem. Ind. (London) *1950*, 77; b) J. Chem. Soc. *1951*, 1114.

[46] *W. Jenny* and *H. Holzrichter*, Chimia *22*, 247 (1968).

[47] *W. Baker*, *F. Glockling*, and *J. F. W. McOmie*, J. Chem. Soc. *1951*, 1118.

[48] Far fewer articles have been published on electrophilic substitutions on [2.2]metacyclophanes than on similar reactions on [2.2]paracyclophanes.

[49] *T. Sato*, *M. Wakabayashi*, *Y. Okamura*, *T. Amada*, and *K. Hata*, Bull. Chem. Soc. Japan *40*, 2363 (1967).

[50] *D. J. Cram*, *C. S. Montgomery*, and *G. R. Knox*, J. Amer. Chem. Soc. *88*, 515 (1966).

[51] *H. H. Wasserman* and *R. Kitzing*, Tetrahedron Lett. *1969*, 3343.

[52] *V. Boekelheide* and *J. A. Lawson*, Chem. Commun. *1970*, 1558.

[53] *T. Sato*, *E. Yamada*, *Y. Okamura*, *T. Amada*, and *K. Hata*, Bull. Chem. Soc. Japan *38*, 1049, 1225 (1965).

[54] *H. Blaschke* and *V. Boekelheide*, J. Amer. Chem. Soc. *89*, 2747 (1967).

[55] *C. E. Ramey* and *V. Boekelheide*, J. Amer. Chem. Soc. *92*, 3681 (1970).

[56] *R. H. Mitchell* and *V. Boekelheide*, J. Amer. Chem. Soc. *92*, 3510 (1970).

[57] *H.-R. Blattmann*, *D. Meuche*, *E. Heilbronner*, *R. J. Molyneux*, and *V. Boekelheide*, J. Amer. Chem. Soc. *87*, 130 (1965).

[58] *V. Boekelheide* and *W. Pepperdine*, J. Amer. Chem. Soc. *92*, 3684 (1970).

[59] *J. Reiner* and *W. Jenny*, Helv. Chim. Acta *52*, 1624 (1969).

[60] *V. Boekelheide* and *R. A. Hollins*, J. Amer. Chem. Soc. *92*, 3512 (1970).

ESCA: Electron Spectroscopy for Chemical Analysis[**]

By Carl Nordling[*]

A substance on which X-rays fall emits photoelectrons and Auger electrons. The energy spectra of the electrons emitted provide information about the electronic structure in the specimen, ranging from the innermost atomic levels and their dependence on the chemical environment to the molecular orbitals of the valence electrons and the band structure in solids. Electron spectra of this nature can now be recorded with high-resolution instruments; their analysis offers new aspects for investigation of chemical composition. The method of electron spectroscopy developed for this purpose, which has now been developed to a high degree of perfection, will be referred to in the following discussion as ESCA (Electron Spectroscopy for Chemical Analysis).

1. Introduction

For spectroscopic investigations on the structure of atoms and molecules and on the dynamics of atomic processes, one can either analyze the electromagnetic radiation emitted or one can measure the kinetic energy of the electrons emitted as a result of various processes in the electron clouds of the atoms. In certain cases, *e.g.* in NMR and Mössbauer spectroscopy, the atomic nucleus is also used as a source of information about the electron cloud. Whereas the spectroscopy of electromagnetic radiation has been widely used since *Newton*'s time, the behavior of the electrons liberated from the electron clouds has only rarely been investigated. The development of precision instruments for the analysis of electron spectra has nevertheless led to very notable results during the past few years, which show that a spectroscopy based on the direct observation of electrons is a very valuable method for the study of atomic and molecular systems and of solids. Electron spectroscopy also yields information that is not obtainable by other methods, and so offers numerous interesting possibilities *e.g.* for applications in chemistry.

The following article is a report on the ESCA method (Electron Spectroscopy for Chemical Analysis) and on the results obtained with its aid by our research group at Uppsala. (A more detailed report covering the situation up to 1969 may be found in refs. [1, 2].)

[*] Prof. Dr. C. Nordling
Uppsala Universitet
Fysiska Institutionen
Box 530
S-751 21 Uppsala 1 (Sweden)

[**] Based on a lecture to the "Solid State Chemistry" Group of the GDCh on October 2, 1970, in Bonn.

2. Excitation of the Electron Spectra

Electron spectra can be induced in various ways. The main agent used for this purpose is characteristic X-rays, though UV light and electron bombardment are also employed. The energy analysis of the emitted electrons is carried out in double-focusing spectrometers of the electrostatic or

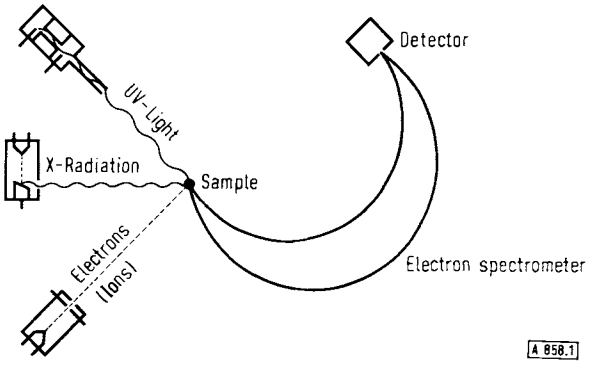


Fig. 1. Methods of exciting electron spectra for recording in high-resolution instruments.

magnetic types. The experimental arrangement is shown schematically in Figure 1, with an indication of the various modes of excitation. One of the magnetic instruments, with the ancillary electronic equipment, is shown in Figure 2.

as well as the molecular orbitals in free molecules and the energy bands in solids.

Excitation with *UV light* has the advantage of a small natural line width, but this process is restricted to the outermost parts of the electron clouds.

Electron bombardment can transfer the system under investigation into a highly excited state, which then decays with emission of an electron. This process, which is known as autoionization, thus produces a positively charged ion and an electron, whose kinetic energy is given by the formula

$$E_{\text{autoionization}} = E^* - E^+ = E^* - E_b \qquad (2)$$

In cases where the electron bombardment itself leads to an ionized initial state, the system becomes doubly ionized on decay. This transition from a singly ionized to a doubly ionized state with emission of an electron is known as the Auger effect, and the energy of the emitted Auger electron is given by

$$E_{\text{Auger}} = E^+ - E^{++} \approx E_b(1) - [E_b(2) + E_b(3)] \qquad (3)$$

Auger electrons can be liberated by high-energy light quanta. When X-rays act on a specimen, therefore, photoelectrons and Auger electrons are obtained together.



Fig. 2. View of an ESCA instrument.

In photoionization, the kinetic energy of the photoelectrons is equal to the difference between the energy $h\nu$ of the stimulating light quantum and the binding energy (ionization energy) E_b of the liberated electrons.

$$E_{\text{kin}} = h\nu - E_b \qquad (1)$$

X-rays of sufficiently high energy can liberate electrons from all levels, *i. e.* the inner atomic shells can be investigated

3. Chemical Shifts in the Spectra of the Inner Electrons

The binding energies E_b are not purely atomic quantities, but change slightly with the chemical environment. This property is manifested in the kinetic energies of the emitted electrons; it can be detected in the electron spectra by modern high-resolution instruments.

Figure 3 shows an ESCA spectrum of *N*-(2-pyridyl)-*p*-nitrobenzenesulfonamide. On excitation of the sample with $Mg_{K\alpha}$ radiation, photoelectrons were emitted, *inter alia*, from the K shells of the nitrogen atoms. Each of the three nitrogen atoms in the molecule has a different chemical environment; three different lines therefore appear in the electron spectrum.

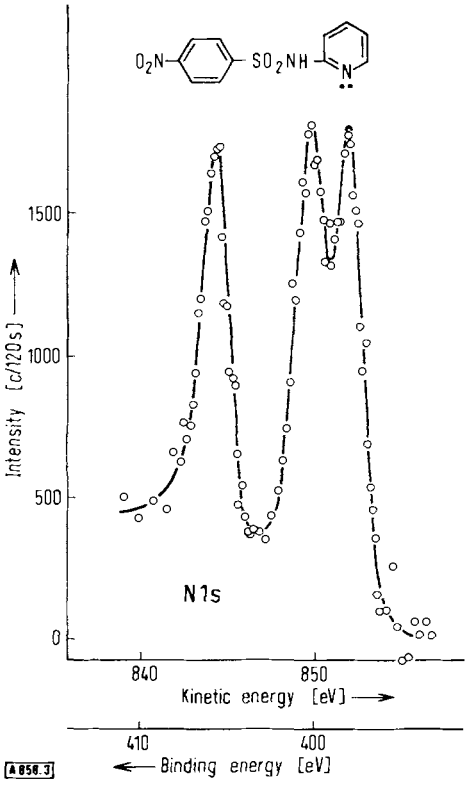


Fig. 3. ESCA spectrum for nitrogen (the 1s electrons) in *N*-(2-pyridyl)-*p*-nitrobenzenesulfonamide.

It is important to note that the electrons involved here are not the valence electrons, *i.e.* the electrons that are actually involved in the chemical bonding, but the electrons of the innermost parts of the electron cloud, which are usually "forgotten" by the chemist.

3.1. Calculation of Chemical Shifts

The binding energies E_b of the inner electrons in free molecules and their chemical shifts can be determined very accurately from quantum-mechanical calculations. In the best possible approximation method of the *ab initio* type for the solution of the Schrödinger equation, *i.e.* the Hartree-Fock (SCF) approximation, the binding energy is obtained as the difference between the total energies for the neutral molecule and the molecule-ion with a vacancy in the inner electrons. The shifts calculated so far by this method correspond to an accuracy of a few tenths of an electron volt, even though correlation effects and relativistic effects were disregarded. However, since the latter are independent of changes in the chemical environment in the case of the inner electrons, they do not affect the calculated chemical shifts.

Electron binding energies and chemical shifts can be obtained more easily from Hartree-Fock calculations with the aid of Koopmans' theorem. In this case the total energy of the neutral and the ionized systems is not calculated, but the binding energies are equated to the individual orbital energies for the neutral system; thus it is additionally assumed that the other electrons in the ion can be described by the same orbital wave functions as in the neutral molecule. The binding energies obtained in this way are systematically 10—20 eV higher than those found experimentally. They are also strongly dependent on the magnitude of the basis set used to describe the wave functions and on its optimization. However, they can be used for a comparison of theoretically calculated *shifts* in the binding energies and those found experimentally. Systematic calculations based on Koopmans' theorem are now available for the chemically induced shifts of the energies of the inner electrons; we have correlated them with the shifts observed experimentally[2].

Figure 4 shows a comparison of the measured chemical shifts for the 1s level of carbon in some small molecules with the orbital energy shifts from *ab initio* MO-LCAO-SCF calculations[3]. The method of least squares gave a straight line having a slope of 1.09. It was found in this case that the agreement of the calculated and the experimental shifts improves, *i.e.* the slope of the line becomes closer to 1, with increasing proximity to the Hartree-Fock limit.

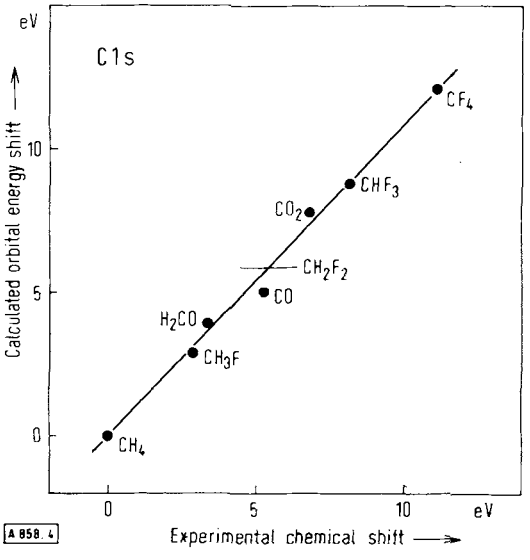


Fig. 4. Correlation between calculated orbital energy shifts for the 1s level of carbon in some small molecules and the experimentally determined shift.

3.2. The Potential Model

A simplification of the theoretical calculation of shifts in the binding energy can be achieved with an electrostatic potential model[1,2]. In this model, the shifts in the binding energy are correlated with the electron distribution in the neutral molecule. The model is entirely classical, but can also be described and applied in quantum-mechanical terms.

In the potential model, the chemical shift for the energy E_b of an inner electron is determined by a change in the potential of the inner electrons. This potential is obtained as the superposition of two potentials, one due to the electron distribution in the atom in question and one due to the charge distribution in the remainder of the molecule. The latter contribution, which we call the molecular potential, is easy to calculate if the charges of the other atoms in the molecule are imagined to be concentrated in point charges q_i (see Fig. 5). The contribution to the shift that is due to the charge distribution in the atom under consideration can be mainly attributed to the valence electrons. If we assume that these form an electron shell of radius r, and if the effective charge q of the atom is placed in this shell, the corresponding contribution to the potential is given by q/r. A theoretically better estimate of this contribution is given by the electrostatic interaction integral J between the inner electron orbital under examination and a valence electron orbital in the same atom. The expression for the chemical shift in the energy level of the inner electron then becomes:

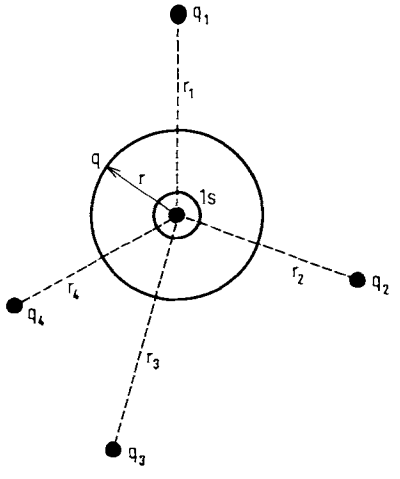
$$\Delta E = Jq + V + l$$

where the molecular potential is given by

$$V = \sum \frac{1}{r_i} \times q_i$$

and the constant l depends on the choice of the reference level. It is found that J is approximately equal to the expectation value $\langle 1/r \rangle$ for a valence electron.

Figures 6 and 7 illustrate the correlation between experimental chemical shifts for the 1s level of carbon and shifts calculated from the potential model with *ab initio* wave functions and with CNDO/2 wave functions respectively[3].



$$\Delta E\,(1s) = q/r + \Sigma q_i/r_i + l \qquad \boxed{A858.5}$$

Fig. 5. In the potential model, the chemical shift of E_b for an inner electron (*e.g.* 1s) is divided into a contribution from the interaction with the valence electrons of the atom in question and a contribution from the other atoms of the molecule. If the valence electrons of the atom in question are assumed to be concentrated in a spherical shell of radius r and having a net charge q, the first contribution is q/r. If the (net) charges of the other atoms are regarded as point charges q_i at distances r_i from the nucleus of the atom under investigation, the second contribution, *i.e.* the molecular potential, is $\Sigma q_i/r_i$.

The charges obtained from the *ab initio* wave functions are *Mulliken*'s "gross atomic charges". The constants J and l were determined in both cases by fitting the least square of $E - V$ to $Jq + l$; the values for J, 18.3 eV from the *ab initio* calculations and 23.5 eV from the CNDO/2 calculations, agree relatively well with the repulsion integrals J calculated for the 1s-2p electrons in a carbon atom.

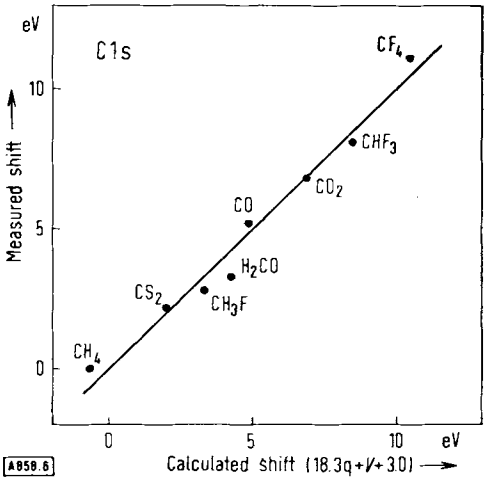


Fig. 6. Correlation between measured chemical shifts for the 1s level of carbon and the shifts calculated from the potential model, the charges being obtained from *ab initio* calculations.

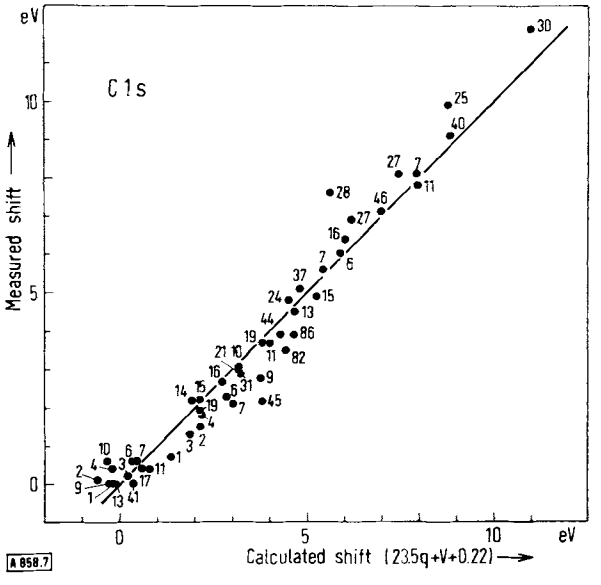


Fig. 7. Correlation between measured chemical shifts for the 1s level of carbon and shifts calculated from the potential model, the charges being obtained from CNDO/2 calculations. (For the assignment of the numbers, cf. [3].)

It can be seen with the aid of the simple potential model that the binding energy E_b of an inner electron increases (and the electron thus becomes increasingly difficult to remove from the electron cloud) with increasing positive charge on the atom. This can be demonstrated by the ESCA spectrum for carbon and oxygen in acetone (Fig. 8). The most strongly positive carbonyl C atom has the highest binding energy (left-hand line). The methyl C atoms (right-

hand line) are more nearly neutral. It can also be seen that the intensities of the lines reflect the relative abundances of the two different types of carbon atoms in the molecule. The intensities of the electron lines are proportional to the abundances of the elements, and can therefore be used for a quantitative elemental analysis, while information on the valences of the elements is obtained simultaneously.

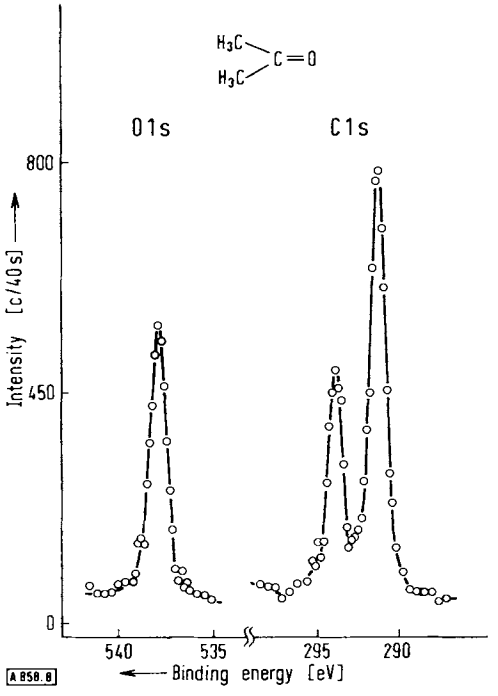


Fig. 8. ESCA spectrum for the 1s electrons of carbon and of oxygen in acetone.

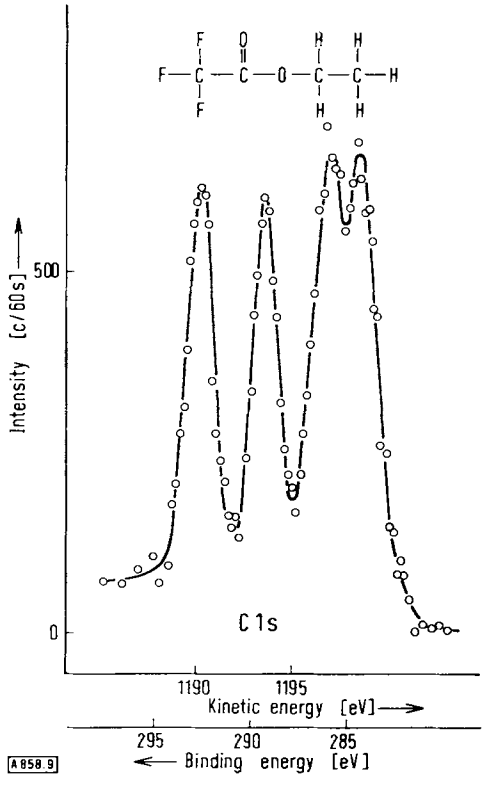


Fig. 9. ESCA spectrum for the 1s electrons of carbon in ethyl trifluoroacetate.

The carbon atoms in ethyl trifluoroacetate (Fig. 9) carry substituents having different electronegativities. The increasingly positive charge is clear from the positions of the lines in the ESCA spectrum of the compound. The lines, in order of excitation energy, are due to the four C atoms of the molecule in accordance with the notation used in Figure 9.

3.3. Charge Correlations

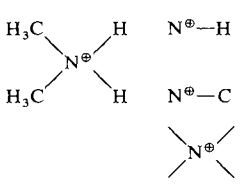
When ESCA is applied to chemical problems, it is often desirable to be able to interpret the chemical shifts in simple language that is understandable to any chemist. This has been found possible with the aid of the electronegativity concept. We have empirically established correlations between measured chemical shifts and an atomic charge parameter q_p. This charge parameter is obtained as the sum of the formal charges on the atom and the partial ionic characters of its bonds with neighboring atoms:

$$\underset{\text{charge}}{q_p} = \underset{\text{formal charge}}{Q} + \underset{\text{contribution of ionic character}}{\Sigma I}$$

The ionic bonding component, according to *Pauling*, can be expressed as a function of the electronegativity difference between the atoms of a bond.

$$I_{AB} = 1 - \exp[-0.25(\chi_A - \chi_B)^2]$$

The procedure can be illustrated *e.g.* by the calculation of the charge on the nitrogen in an alkylammonium ion, which carries a positive formal charge:



	$\Delta\chi$	I
$N^{\oplus}$—H	1.2	−0.30
$N^{\oplus}$—C	0.8	−0.15
$N^{\oplus}$		Q 1.00

$$q_p = 1.00 + 2(-0.30) + 2(-0.15) = +0.10$$

In this way it was possible to correlate shifts found in the ESCA spectra for a large number of compounds having very different structures with a calculated charge parameter q_p. Figure 10 shows the result for a series of sulfur groups, based on measurements of the 2p energy for about 100 sulfur compounds. Similar correlations are found for other elements, and this confirms the hypothesis of the charge-dependence of the binding energies. They have proved to be particularly useful in the application of the ESCA method. Some examples of the application of ESCA to special problems in chemistry are described in the following section.

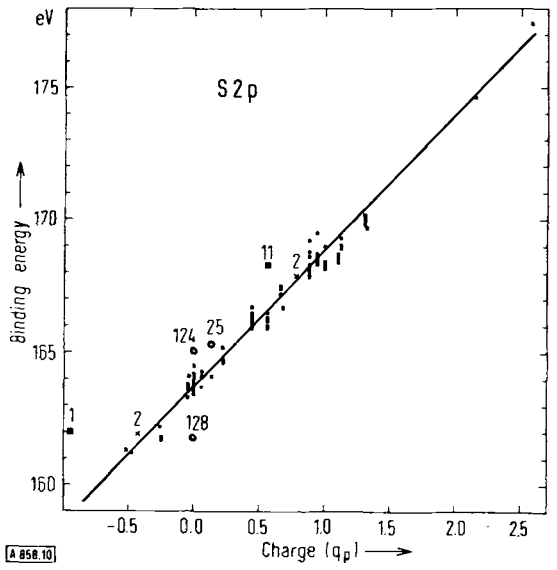


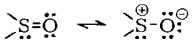
Fig. 10. Correlation of the ESCA shifts for the 2p level of sulfur in various sulfur groups with a charge parameter calculated as the sum of the partial ionic contributions in the bonds. (For assignment of the numbers, cf. [4].)

4. Selected Examples

4.1. Polarity of Chemical Bonds

The charge-dependence of the shifts makes electron spectroscopy particularly suitable for the study of the polarity of chemical bonds. It is possible in this way to investigate the polarity without knowing the bond lengths and bond angles.

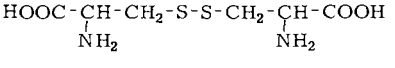
S—O bonds in many sulfur compounds have been intensively studied[4]. The polarity has been found to be fairly structure-dependent for sulfoxides. Its average value lies roughly between the values calculated on the basis of model substances and charge correlations for the two limiting structures.



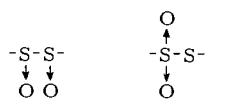
A comparison with the carbonyl group shows that the sulfinyl group has approximately the same polarity. These experimental results help to answer the question whether sulfur expands its valence shell by making use of d orbitals.

4.2. Oxidation of Cystine

The example of doubly oxidized cystine can be used to show how the chemical shifts in the ESCA spectra can help to solve structural problems[5]. The cystine molecule contains two equivalent sulfur atoms and two possible structures



had to be considered for the dioxide, *i.e.* disulfoxide and *S*-thiosulfonate.



Disulfoxide *S*-Thiosulfonate

Analysis of the IR and NMR spectra had yielded no definite answer regarding the occurrence of these isomers. The ESCA spectrum of the dioxide clearly shows, on the other hand, that the compound has a thiosulfonate structure (Fig. 11).

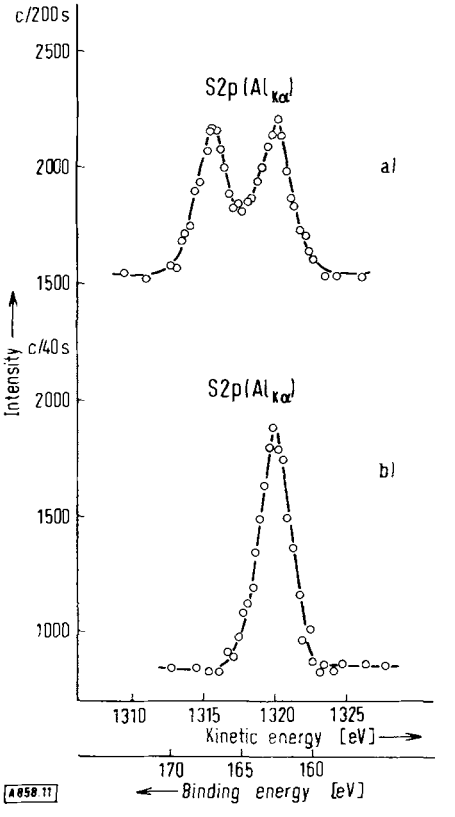


Fig. 11. Structure determination by ESCA. A comparison of the electron spectra from the 2p level of sulfur in cystine *S,S*-dioxide (a) and in unoxidized cystine (b) shows that the dioxide has a thiosulfonate structure.

Instead of a single line, as in the case of unoxidized cystine, two lines are observed for the 2p level of sulfur, one of these showing no shift and the other a shift of 4.0 eV to a more highly oxidized state. The disulfoxide would have given only one line, with the relative intensity doubled and with a shift of ≈ 2 eV.

More complicated structural problems have also been elucidated by the ESCA technique, and it is likely that the further development of the instruments used will lead to increasingly valuable conclusions.

4.3. Valence Problems

The problem of the electron transfer between the metal and the carbon in transition metal carbides was disputed for a long time. For lack of reliable experimental data, no decision could be reached in favor of any of the various theories proposed. ESCA measurements of the energy

shifts for the inner electrons in such compounds and other model substances have now shown that an electron transfer takes place from the metal to the carbon in these carbides (Fig. 12)[6].

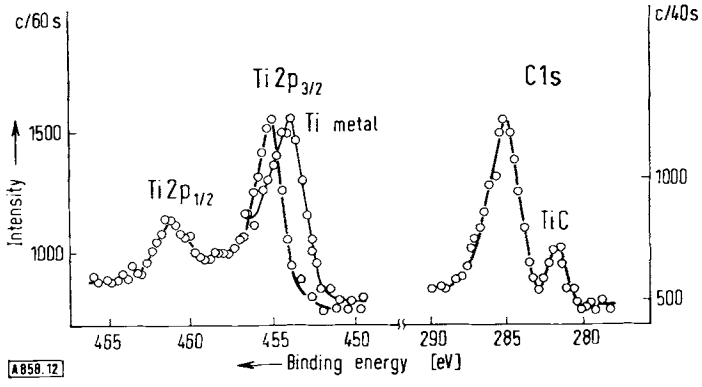


Fig. 12. ESCA spectra of TiC and Ti metal. The line shifts yield information on the charge transfer between the metal and the carbon in the carbide.

In an investigation of the reduced ternary phases in the W—V—O system, the problem of the oxidation state of the tungsten and vanadium atoms was examined. This is associated with the question of the order or disorder of the two types of metal atoms in the crystal structure. The ESCA spectra showed the following distribution of the oxidation states in $W_3V_5O_{20}$ and WV_2O_6, which had already been suggested on the basis of various structures[7]:

$$W^{VI}V^{V}(W^{VI}_{0.25}V^{IV}_{0.75})_2O_{10} \qquad W^{VI}V^{III}_2O_6$$

Figure 13 shows the spectra of vanadium ($2p_{3/2}$) and of tungsten ($4f_{5/2,7/2}$) in $W_3V_5O_{20}$. The positions of the lines obtained with model substances for various oxidation numbers are indicated. It can be seen that tungsten is present exclusively in the hexavalent state, whereas vanadium is present both in the tetravalent and in the pentavalent states.

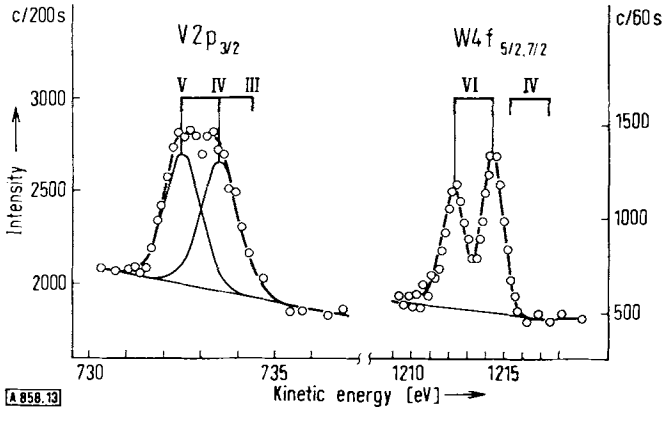


Fig. 13. It can be seen from this ESCA spectrum of $W_3V_5O_{20}$ that tungsten is present as W^{VI} and vanadium in two oxidation states, *i.e.* as V^{IV} and V^{V}.

In the study of many catalytic reactions, the main point of interest is the bonding of the metal in organometallic complexes. We have recently investigated some platinum complexes in which the metal is present in a low formal oxidation state[8]. On the basis of the ESCA data, it was possible to assign relative oxidation states to the central metal, and the investigation confirmed that the coordination of "neutral" ligands can lead to a considerable charge transfer from the metal to the ligands. Figure 14 shows the position of the $4f_{7/2}$ level of platinum in such complexes.

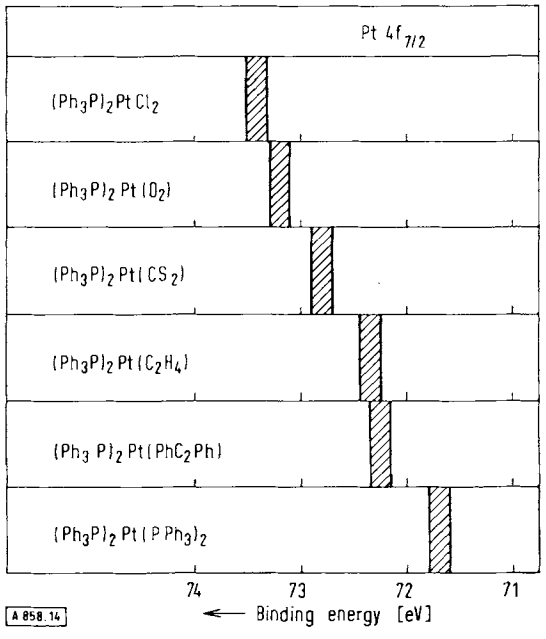


Fig. 14. Chemical shifts for the $4f_{7/2}$ level of platinum in some complexes.

5. Electron Spectra of Free Molecules and Solids

As was mentioned in Section 2, if X-rays are used to excite the electron spectra, the behavior of both the inner electrons and the valence electrons can be investigated. Figure 15 shows an ESCA spectrum of gaseous tetrafluoromethane stimulated with $Mg_{K\alpha}$ radiation. The two lines for binding energies of 696 and 302 eV correspond to the 1s electrons of the fluorine and of the carbon respectively. The K-Auger spectrum of fluorine is observed between kinetic energies of 630 and 660 eV. Molecular orbitals of the valence electrons, which are formed mainly from the atomic 2s and 2p orbitals of the carbon and the fluorine in the CF_4 molecule, are "seen" in the range of binding energies below 50 eV (kinetic energy 1200—1254 eV). The 32 valence electrons of CF_4 are distributed over 16 molecular orbitals, but because of the high symmetry of the molecule, several of the orbitals are degenerate, so that only 7 ionization energies can be distinguished in the spectrum of the valence electrons. Three of these states were investigated earlier on the basis of UV-excited spectra; they can be essentially assigned to non-bonding molecular orbitals.

For a deeper understanding of the chemical bonding, it is necessary also to study the bonding orbitals. These are shown in Figure 15. We used semiempirical (CNDO) and *ab initio* calculations of the valence electron configuration and of the atomic parentage of the molecular orbitals for the interpretation of the MO spectra. A property of the X-ray excited electron spectra that is particularly useful

in this connection is that the cross section for photoemission from a given orbital is strongly dependent on the symmetry of the orbital.

An interesting line splitting is observed in the spectra of the inner electrons of paramagnetic molecules. This splitting is shown in Figure 16 for molecular oxygen in air. The

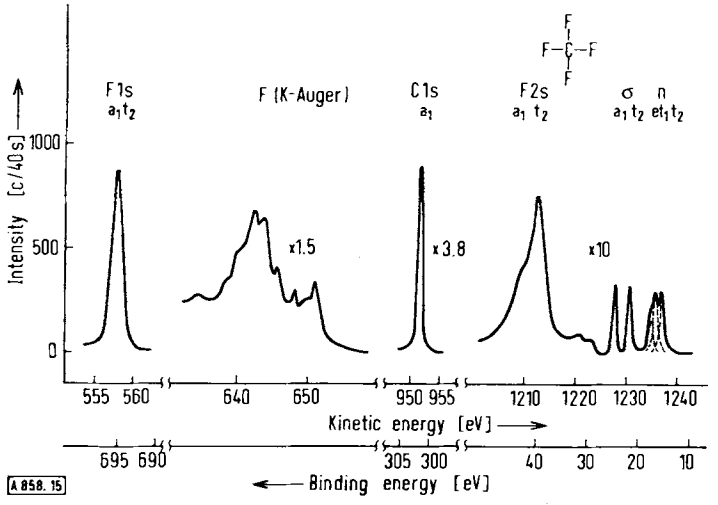


Fig. 15. ESCA spectrum of CF_4. This spectrum shows both the inner electron levels F1s and C1s and the energy levels for the molecular orbitals of the valence electrons. It also shows the K-Auger electrons of fluorine.

spectrum contains the 1s lines of the oxygen and of the nitrogen in the air, as well as the 2p spin doublet of argon, which had a partial pressure of 10^{-3} torr in this case. The 1s line of oxygen is split into two components, with a distance of 1.1 eV between the lines and with an intensity ratio of 1:2. This splitting can be explained as follows. On photoemission of an electron from the 1s level, it is necessary to take into account the interaction between a 1s state with spin $\frac{1}{2}$ and the MO state ($\pi_g 2p$) of oxygen, which is responsible for its paramagnetic properties.

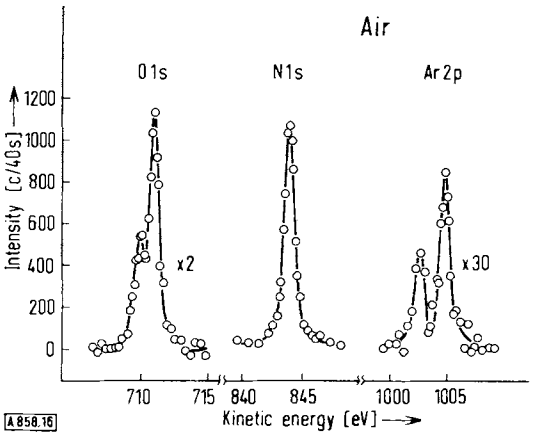


Fig. 16. ESCA spectrum of oxygen, nitrogen, and argon in air. For oxygen, which is paramagnetic, one observes a splitting of the 1s line into two components.

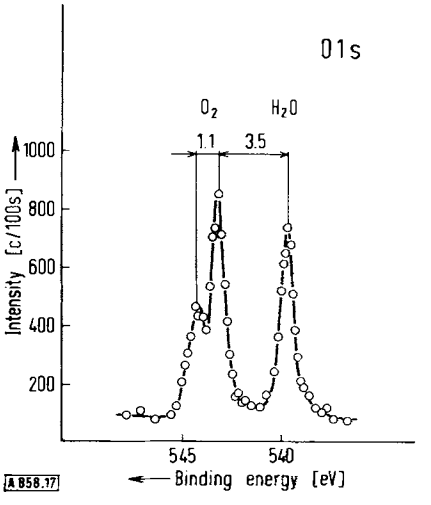


Fig. 17. 1s lines of oxygen in O_2 and H_2O. The line splitting observed for the paramagnetic oxygen molecule disappears when the oxygen is chemically bonded in water vapor. This is accompanied by a considerable chemical shift of the 1s level.

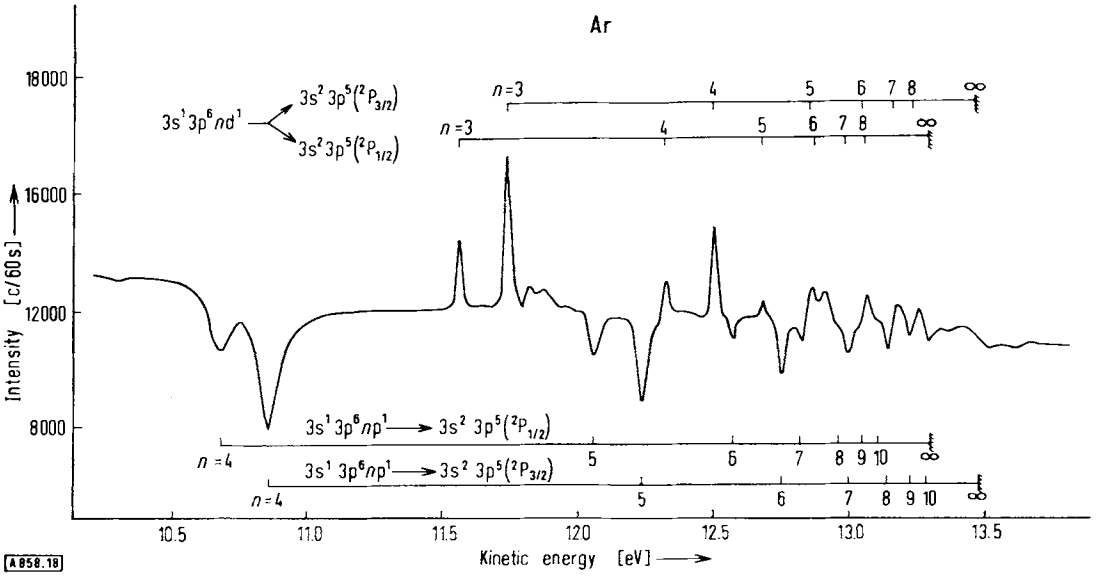


Fig. 18. Autoionization electron spectrum of argon, excited by electron bombardment.

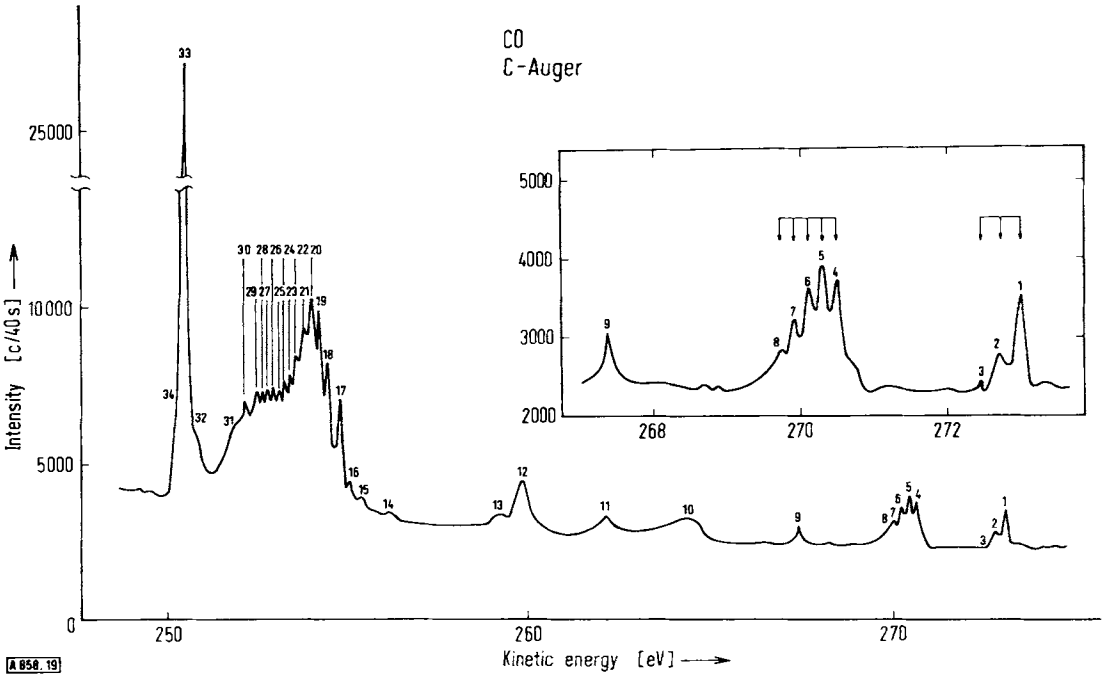


Fig. 19. Auger and autoionization electron spectrum of CO with vibrational structure.

The resultant spin of the two electrons with parallel spin in this orbital is 1. The total spin of the molecule after the emission of a 1s electron will therefore be $\frac{1}{2}$ or $\frac{3}{2}$, *i.e.* the molecule passes into a doublet or quadruplet state. The intensity ratio of the lines thus becomes 2:4, and the calculated magnitude of the energy splitting agrees with that in the electron spectrum (Fig. 16).

This "spin (or exchange) splitting" disappears when the oxygen is chemically bonded to other atoms in diamagnetic molecules, as can be seen from the spectra of O_2 and H_2O (Fig. 17). As discussed earlier, it is replaced by a "chemical shift", which has a magnitude of 3.5 eV in this example between (the quadruplet state of) molecular oxygen and the oxygen bound in H_2O.

The autoionization and Auger electron spectra (cf. Section 2) of free atoms and molecules have not yet been investigated very extensively. We have obtained highly resolved spectra of the inert gases and of molecules by electron bombardment excitation. These spectra contain very large numbers of lines, and can be compared in part with transitions in UV spectra. The autoionization spectrum of argon (Fig. 18) contains several Rydberg series with a series limit that corresponds to the complete separation of a 3s electron in the initial state. The Auger spectrum and the autoionization spectrum of carbon in the CO molecule are shown in Figure 19. The left-hand part of the spectrum is the Auger portion, which shows a pronounced vibration structure in the region around 253 eV. Further to the right in the spectrum, one finds a number of groups of autoionization lines with clearly resolved vibrational components.

We have also extended the scope of the ESCA technique to investigations on solids. Thus the angular distribution of elastically scattered electrons ejected by $Mg_{K\alpha}$ radiation from various levels in an NaCl crystal has recently been

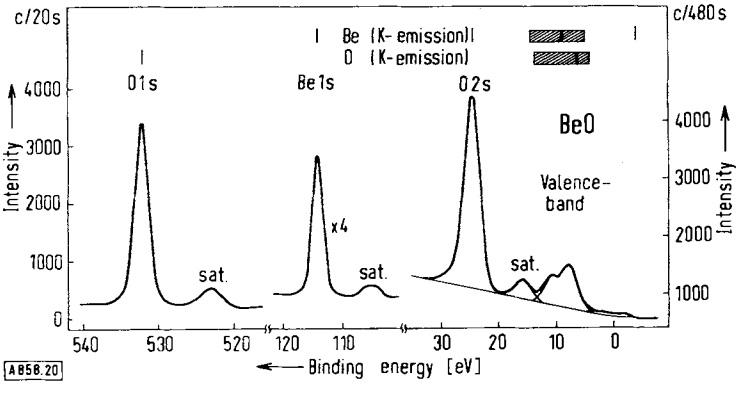


Fig. 20. ESCA spectrum of BeO, excited with $Mg_{K\alpha}$. This spectrum shows both the inner electron levels and the valence bands of the oxide. A comparison with X-ray emission data is shown in the upper part of the figure.

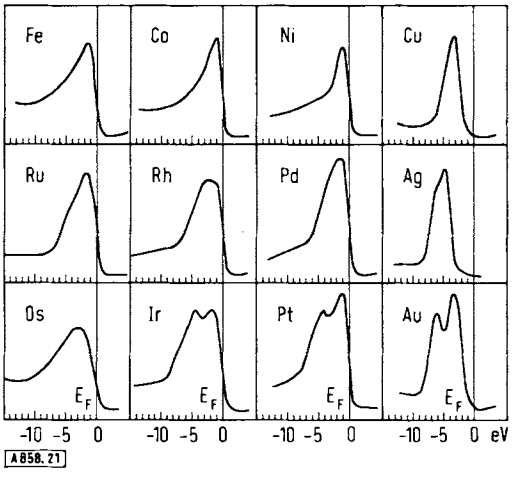


Fig. 21. Band spectra of the transition metals of the first, second, and third series.

investigated[9], and the "escape depth" for electrons liberated from a metal by the action of X-rays has been determined experimentally[10]. The valence bands in LiF, BeO, BN, and graphite have also been studied, and the results compared with X-ray spectroscopic data[11]; see Figure 20.

We have also studied the valence bands in transition metals and other solids[12, 1]. Figure 21 shows electron spectra from the valence bands of twelve transition metals. After certain corrections, these ESCA spectra provide a very good description of the energy distribution in the bands.

It is my pleasure to thank Professor Kai Siegbahn and all the other members of our research group in Uppsala for their contribution to the work that led to the results presented here.

Received: October 28, 1970 [A 858 IE]
German version: Angew. Chem. *84*, 144 (1972)
Translated by Express Translation Service, London

[1] *K. Siegbahn, C. Nordling, A. Fahlman, R. Nordberg, K. Hamrin, J. Hedman, G. Johansson, T. Bergmark, S.-E. Karlsson, I. Lindgren,* and *B. Lindberg*: ESCA: Atomic, Molecular and Solid State Structure Studied by Means of Electron Spectroscopy. Nova Acta Regiae Soc. Sci. Upsaliensis, Ser. IV, Vol. 20 (1967).

[2] *K. Siegbahn, C. Nordling, G. Johansson, J. Hedman, P. F. Hedén, K. Hamrin, U. Gelius, T. Bergmark, L. O. Werme, R. Manne,* and *Y. Baer*: ESCA Applied to Free Molecules. North-Holland, Amsterdam 1969.

[3] *U. Gelius, P. F. Hedén, J. Hedman, B. J. Lindberg, R. Manne, R. Nordberg, C. Nordling,* and *K. Siegbahn*, Physica Scripta *2*, 70 (1970).

[4] *B. Lindberg, K. Hamrin, G. Johansson, U. Gelius, A. Fahlman, C. Nordling,* and *K. Siegbahn*, Physica Scripta *1*, 286 (1970).

[5] *G. Axelson, K. Hamrin, A. Fahlman, C. Nordling,* and *B. J. Lindberg*, Spectrochim. Acta *23*, 2015 (1967).

[6] *L. Ramqvist, K. Hamrin, G. Johansson, A. Fahlman,* and *C. Nordling*, J. Phys. Chem. Solids *30*, 1835 (1969).

[7] *K. Hamrin, C. Nordling,* and *L. Kihlborg*, Ann. Acad. Reg. Sci. Upsaliensis 14 (1970).

[8] *C. D. Cook, K. Y. Wan, U. Gelius, K. Hamrin, G. Johansson, E. Olson, H. Siegbahn, C. Nordling,* and *K. Siegbahn*, J. Amer. Chem. Soc. *93*, 1904 (1971).

[9] *K. Siegbahn, U. Gelius, H. Siegbahn,* and *E. Olson*, Physica Scripta *1*, 272 (1970).

[10] *Y. Baer, P. F. Hedén, J. Hedman, M. Klasson,* and *C. Nordling*, Solid State Commun. *8*, 1479 (1970).

[11] *K. Hamrin, G. Johansson, U. Gelius, C. Nordling,* and *K. Siegbahn*, Physica Scripta *1*, 277 (1970).

[12] *Y. Baer, P. F. Hedén, M. Klasson, C. Nordling,* and *K. Siegbahn*, Physica Scripta *1*, 55 (1970).

The Electronic Properties of Diradicals

By Lionel Salem and Colin Rowland[*]

A review of the various possible definitions of diradicals leads the authors to describe these systems as having two odd electrons in degenerate or nearly-degenerate molecular orbitals. A study of the wave-function for the two odd electrons shows that its form depends entirely on whether the diradical is homo- or heterosymmetric. Energy schemes are given in these two cases, as well as in the intermediate "non-symmetric" case. The extent of zwitterionic character in diradical states is also investigated. This is followed by a discussion of intersystem crossing between singlet and triplet diradical states via spin-orbit coupling and other mechanisms. The electronic matrix elements for spin-orbit coupling are calculated and evaluated numerically for various model cases. It is then possible to establish general rules for favorable (electronic) intersystem crossing. In 1,3 or 1,4 diradicals its efficiency is estimated to be comparable with that in aromatics. The role of the electron-nuclear hyperfine interaction in mixing singlet and triplet states, particularly in CIDNP, is explained.

Finally the question of whether diradicals actually occur as secondary minima on potential energy surfaces is examined. Recent quantum-mechanical calculations, in contradiction to some thermochemical and kinetic evidence, lead to flat singlet surfaces without significant minima.

1. Introduction: What is a Diradical?

The purpose of this article is to study the qualitative and quantitative properties of those molecular species which Organic Chemists call diradicals. The recent progress in the understanding of concerted reactions[1] has been accompanied by an increased interest in the Chemistry of species with non-concerted behavior[2]. Although, as we shall see, it is difficult to rigorously define the boundaries of the "diradical" family, it is possible to specify fundamental electronic properties which are typical of this family (Section 1). Following that, we shall study successively the wave functions of diradicals and their covalent *versus* ionic character (Section 2), general rules for the spin-orbit induced intersystem crossing between singlet and triplet states (as a function of geometry) and other mixing mechanisms (Sec-

[*] Prof. Dr. L. Salem and Dr. C. Rowland
Laboratoire de Chimie Théorique
Centre Scientifique d'Orsay
Université de Paris-Sud, 91-Orsay (France)
The Laboratoire de Chimie Théorique is also part of the Laboratoire de Physico-Chimie des Rayonnements, associated with the CNRS.

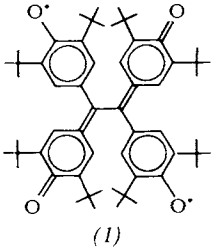
tion 3), and finally the kinetic and thermochemical *versus* quantum-chemical evidence for diradicals as "intermediates", *i.e.* metastable species in secondary minima on the potential energy surface (Section 4).

The term diradical has generally been used loosely to describe systems which can be formally written with two unpaired electrons. A closer look shows that this concept includes a wide variety of species and that the degree of "non-pairing" depends on the type of experiment which is being performed.

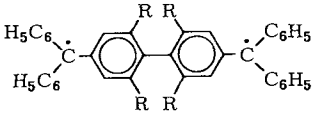
1.1. "Two Odd Electrons Far Apart"

The ESR spectroscopist might strictly call a "diradical" any single species which gives an ESR spectrum characteristic of two doublet states, rather than one characteristic of a triplet state. This is true if the interaction between odd electrons is smaller than the hyperfine interaction between odd electron spin and nuclear spin. Thus it escapes measurement by the ESR probe (see Section 3.5). The simplest way to weaken the electronic interaction to this extent is to push the two electrons very far away from each other. For instance bisgalvinoxyl *(1)* shows an ESR spectrum characteristic of two doublet states[3].

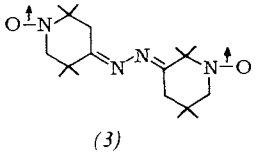
Chichibabin's hydrocarbon[4] (R = H) was long considered to be borderline between the case where the system can be described as two doublet states and where the interaction is sufficient so that triplet and singlet states are well defined. The two electrons interact weakly *via* a small residual con-



(1)



(2)

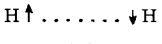


(3)



(4)

jugation. However, in the nitroxide *(3)* the odd electron interaction is already greater than the hyperfine interaction and the ESR spectrum is that of a well-defined triplet state[5]. In *o*-dihydrobenzene *(4)* the odd-electron interaction is finally so large that the ground state is probably best described as a closed-shell singlet[6].

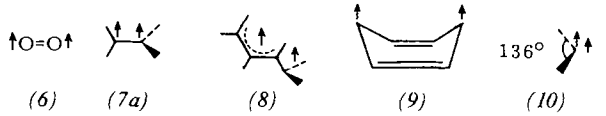


(5)

In this line of thought the simplest diradical of all would be a greatly stretched H_2 molecule *(5)*.

1.2. "Two Odd Electrons with Parallel Spins"

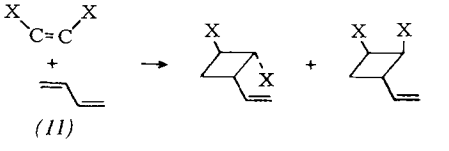
A second common way of thinking of unpaired electrons is to give them parallel spins. It was suggested long ago[7] that the triplet states responsible for phosphorescence should be identified with diradical species familiar to Organic Chemists. Triplet diradicals have been invoked in innumerable photochemical reactions[2c]. Outstanding triplet diradicals are oxygen *(6)*, the ground state of twisted ethylene[8] ("dimethylene") *(7a)*, the lowest $\pi \rightarrow \pi^*$ triplet states of dienes *(8)* and of benzene *(9)* and the ground state of methylene[9] *(10)*.



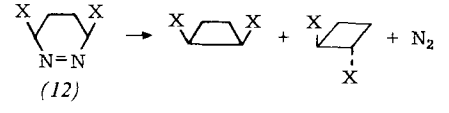
(6) *(7a)* *(8)* *(9)* *(10)*

1.3. "Non-polar Bifunctional Species in which Loss of Configuration Arises from Internal Rotation"

The Organic Chemist generally recognizes a biradical[2b] by the loss of configuration such as occurs in reactions of molecules *(11)* and *(12)*. A total loss of configuration such

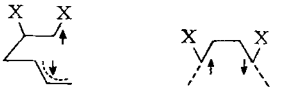


(11)



(12)

as shown would imply the formation of intermediate species such as *(13)* or *(14)* in which rotation about the terminal

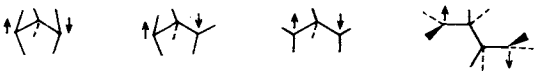


(13) *(14)*

single bonds is faster than carbon-carbon bond reclosure. In fact the extent of approach to equal proportions of product isomers is often used to measure the extent of diradical pathway in the reaction—although it is recognized[2b] that a diradical may be created, but configuration still maintained, if there is a large steric barrier to internal rotation. Triplet diradicals, for which spin inversion is required before closure, are often chosen as reference systems for the loss of configuration. Singlet diradicals are expected to exhibit at least some facets of triplet diradical behavior.

Typical diradicals which have been invoked in this family are trimethylene *(15)*—in several possible geo-

metries[10–14][*]—tetramethylene *(16)*, 1-hexenylene *(13)*, *etc.*



(15a) *(15b)* *(15c)* *(16)*

1.4. Limitations of the Previous Viewpoints

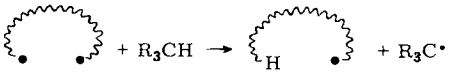
The previous definitions all carry a certain degree of arbitrariness. As concerns the first point of view it is clear that in many cases the two electrons are not totally uncoupled; they conserve a weak residual interaction. The appropriate states are then the singlet, triplet pair. Furthermore, to obtain such weak interaction it is not necessary that the electrons be far apart. Singlet ethylene twisted at 90°, *(7b)*, is a case in point. Thus distance does not seem to be a useful criterion.



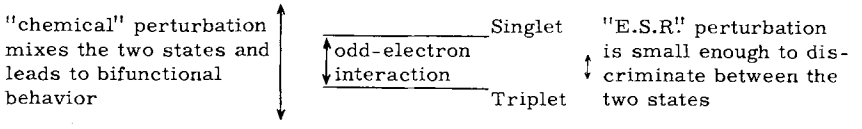
(7b)

The restriction of diradicals to a single spin state—the second point of view—is also a severe limitation. Bifunctional behavior occurs equally well in singlet diradicals and in triplet diradicals, even though the former species have generally a much shorter life-time. Finally the third viewpoint is also arbitrary insofar as it describes the behavior of the intermediate system from an observation of the reaction products. Borderline cases, in which the percentage of isomers lies between that expected for a concerted process and that expected for a diradical process are often interpreted in terms of two competing pathways whereas they may reflect the behavior of some single species in which two electrons are only partially unpaired.

Let us try then and sort out the common features of the diradical species described so far. In only one extreme—molecule *(1)*—is there rigorously no interaction left between the odd electrons. Such a species is truly a "double radical"[**] in the sense that the spin states observed by ESR spectroscopy are those for the separate electrons (doublets) rather than those for the pair (singlet and triplet). In the great majority of systems, however—*(3)* to *(16)*—the odd electron interaction is *sufficient* at least for two distinct states to be recognized by the electron-nuclear hyperfine probe of ESR spectroscopy. At the same time it is expected that it is *not so large* that gross chemical perturbations (such as the approach of a reactant) will discriminate entirely between the two states. Rather, the chemical perturbation will create a "mixture" of the two states, with typical bifunctional behavior. For instance, in the abstraction reaction:



the perturbation due to R_3CH effectively leads to two totally uncoupled odd electrons. This uncoupling is brought about by the mixing of the singlet and triplet states of the starting diradical, leading to two doublet states. Scheme 1 summarizes the relative sizes of the various interactions.

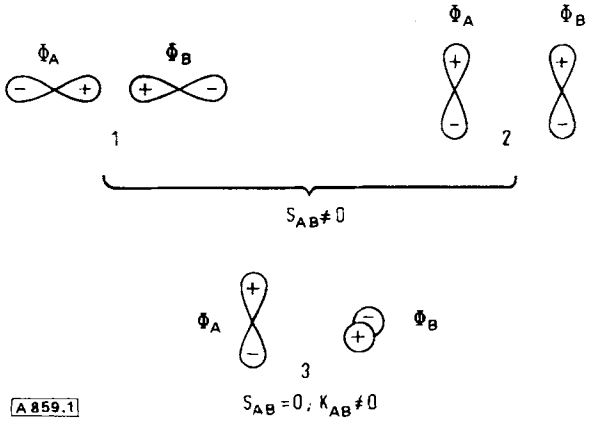


Scheme 1. Relative sizes of various interactions.

Thus systems *(3)* to *(16)* share the common feature of two weakly interacting electrons (*nearly* independent). Another characteristic is that the two electrons have similar energy. Both these properties appear to be required of a system in which two radical centers can effectively behave as if they were independent and equally reactive in the presence of an external reagent. We shall now try and establish a better theoretical understanding of these properties.

1.5. A Localized Picture

The simplest way of describing the odd-electron pair is to assign each electron to a *localized* (for instance, atomic) orbital. Let ϕ_A and ϕ_B be respectively the localized orbitals occupied by the two electrons. These orbitals can interact in varying manners, as shown in Figure 1: *via* a weak one-electron overlap integral S_{AB}, or *via* a two-electron exchange



A 859.1

Fig. 1. One- and two-electron interactions between odd electrons in ϕ_A and ϕ_B.

[*] The role of these different diradical configurations in the geometrical and optical isomerization reactions of cyclopropane is established and the transition state for geometrical isomerization is described in [14].

[**] Molecule *(2)* with R = Cl is also a double radical [16].

integral[*] K_{AB}. Case (1) occurs in face-to-face trimethylene *(15a)* and in face-to-face tetramethylene *(16a)*[15]. Similarly, case (2) occurs in edge-to-edge trimethylene *(15c)* and in edge-to-edge tetramethylene *(16c)*[17]. Case (3), in which the interaction is of bielectronic nature, occurs in *(7)* or *(15b)*.



(16a) *(16c)*

In all cases, therefore, a weak interaction is conserved between the two odd electrons. The *type* of interaction (one-electron or two-electron) is irrelevant as far as diradical *character* is concerned—although the chemical behavior will vary from one case to another.

This simple picture of weakly interacting, equi-energetic odd electrons is lost:

1. if the overlap integral S_{AB} becomes too large (bond formation)

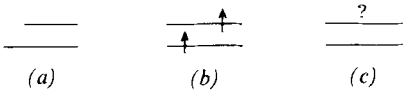
2. if the energy difference between ϕ_A and ϕ_B is too large (localized electron-pair formation in the lower orbital).

These points will be developed further in Section 1.6 (see Figure 2).

1.6. A Delocalized Picture: "Two Odd Electrons in Degenerate or Nearly-Degenerate Molecular Orbitals"

In the previous Section we gave a classical picture of two weakly interacting odd electrons localized in two atomic orbitals. The size of the interaction was measured by K or S. These quantities are very sensitive to geometry and there is no simple way to define limiting values of S, and eventually K, beyond which diradical character is lost. A useful measure of such interactions, which avoids all reference to geometry, is based on *energetic* considerations. This measure is provided by the energy difference between the molecular orbitals occupied by the two electrons or between the lowest triplet and singlet states.

In Section 2.1 and 2.2 we shall see that cases (1) to (3) can be conveniently described by a molecular orbital picture in which the odd electrons are distributed in a pair of molecular orbitals, which are generally delocalized over ϕ_A and ϕ_B (Section 2.1) but which are sometimes nearly localized (Section 2.2). *If* the overlap between ϕ_A and ϕ_B is very weak and *if* the local energies E_A and E_B of ϕ_A and ϕ_B are nearly the same, these two orbitals are degenerate or nearly degenerate (Scheme 2)[18][**].

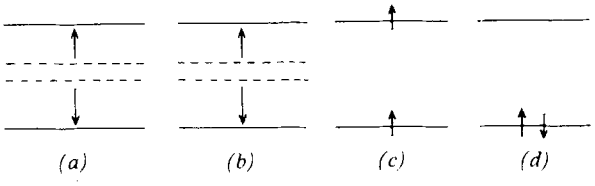


(a) *(b)* *(c)*

Scheme 2. (a) Non-bonding molecular orbitals; (b) triplet; (c) singlet [***].

The lowest states of the system are a (triplet, singlet) pair with nearly equal energies[***]. Both states describe the diradical; they differ only in the manner in which the electron spins couple. If the separation of the molecular orbitals is sufficiently small, Hund's rule requires the triplet to be the ground state.

Now if the overlap between ϕ_A and ϕ_B increases, the two molecular orbitals cease to have non-bonding character: one orbital becomes bonding and is lowered, while the other becomes anti-bonding and is raised. A lowering of the local energy E_A, while E_B is raised, would lead to similar consequences: one molecular orbital acquires essentially ϕ_A character and is stabilized, and the other one is raised:



(a) *(b)* *(c)* *(d)*

Scheme 3. (a) Increase overlap; (b) increase difference in local energies; (c) triplet; (d) singlet.

In both cases the induced splitting causes a reversal in the ordering of states. The triplet state rises while the system tends to adopt as ground state the closed-shell singlet configuration in which the two electrons are paired in the lower orbital. Thus the nature of the singlet wave function changes progressively from "open-shell" to "closed-shell". Figure 2 illustrates the variation of the state energies for both cases.

In case (a)—increase of overlap—the singlet state acquires covalent bonding character; in case (b)—increase of local energy difference—the singlet state acquires ionic character.

As one advances along the x axis of both diagrams, diradical character is lost. The region where the triplet becomes strongly destabilized and where the singlet becomes a closed shell is of course ill-defined (shaded region). It is reasonable to restrict the diradical region proper to that portion of the diagrams, where the triplet-singlet spacing is small and, *a fortiori*, where the molecular orbitals are reasonably close[19][****] (see also Section 1.4).

We would like to emphasize that strong overlap between ϕ_A and ϕ_B, with the singlet well below the triplet, preclude diradical character even in the triplet state. Consider for instance planar triplet ethylene *(7c)*.

[*] There is a two-electron Coulombic interaction, but it does not discriminate between triplet and singlet. The integrals $S_{AB}=\int\phi_A\phi_B d\tau$ and $K_{AB}=\int\phi_A(1)\phi_B(1)\frac{1}{r_{12}}\phi_A(2)\phi_B(2)d\tau_1 d\tau_2$.

[**] The lower of the two molecular orbitals need not be that in which ϕ_A and ϕ_B overlap positively. The negative combination may be stabilized by through-bond interactions [18].

[***] In the triplet state, of course, one electron occupies each orbital. The singlet state, however, may be either a single configuration with the same spatial occupation (Section 2.2) or a mixture of configurations (Section 2.1).

[****] *G. R. Freeman* [19] has suggested a maximum value of kT for the singlet-triplet energy difference.

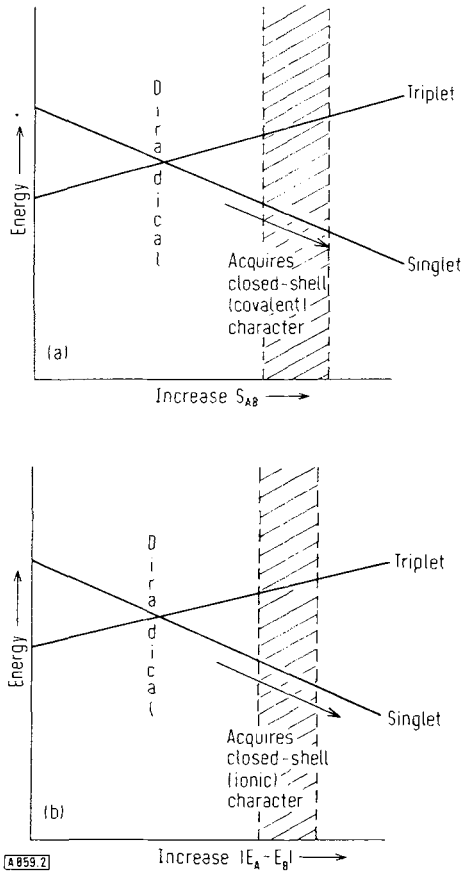


Fig. 2. Energies of (triplet, singlet) pair as the molecular orbital splitting increases. Cases (a) and (b), see text.

Because of the large overlap between the atomic pπ orbitals, the bonding molecular orbital ($\phi_A+\phi_B$) is much more stable than the antibonding orbital ($\phi_A-\phi_B$). In the triplet state one electron occupies each orbital, so that the antibonding electron should be much more labile than the bonding one. Such a system is at best a diradical *precursor*



(7c)

since the more stable electron would be expected to react only after an initial step involving the excited electron. It may be difficult to conceive of triplet ethylene as being a diradical in some phases of its twisting vibration [*(7a)*] and not in others [*(7c)*][*]. Yet clearly *(7a)* can have bifunctional behavior whereas *(7c)* can have only monofunctional behavior. Similarly, H_2 or Li_2 are closed shells in some phases of certain stretching vibrations and open-shell diradicals in others. Also, it is doubtful whether triplet cyclobutene will show bifunctional behavior of the type described in Section 1.3. Even the two odd electrons in a highly bent ($\approx 90°$) methylene triplet [cf. *(10)*] would cease to be equally available, and it could be argued at some length whether it is proper to call such a system a diradical. The electronic characteristics of diradicals may be summarized as follows:

A) Localized Description

a) Weak, but non-zero, interaction between the odd atomic orbitals (*nearly independent* electrons).

b) Similar energy of the odd atomic orbitals (*equally available* electrons).

B) Delocalized Description

a) Degenerate or nearly-degenerate molecular orbitals for the odd electrons.

b) A pair of lowest triplet and singlet states ("diradical" states) with a small separation. Diradical states occur in pairs or not at all.

In the following, the Organic Chemist should constantly remind himself *that the description of diradicals is that of states and two-electron properties rather than orbitals and one-electron properties.* The one-electron model is no longer sufficient (Section 2). Furthermore *these states may represent strongly distorted molecular geometries, not necessarily stable minima* (Section 4).

2. Wave Functions for Diradicals. Covalent *versus* Zwitterionic Character

We now turn to the accurate quantum-mechanical description of diradicals. This description is relatively simple in the "valence-bond" approach: for two odd electrons localized on ϕ_A and ϕ_B the appropriate wave functions are:

$$\begin{aligned} &\text{singlet:} \quad (2 + 2S_{AB}^2)^{-\frac{1}{2}}[\phi_A(1)\phi_B(2) + \phi_B(1)\phi_A(2)] \\ &\text{triplet:} \quad (2 - 2S_{AB}^2)^{-\frac{1}{2}}[\phi_A(1)\phi_B(2) - \phi_B(1)\phi_A(2)] \end{aligned} \tag{1}$$

Similarly two ionic states exist which can serve to describe zwitterions:

$$\begin{aligned} &(2 + 2S_{AB}^2)^{-\frac{1}{2}}[\phi_A(1)\phi_A(2) + \phi_B(1)\phi_B(2)] \\ &(2 - 2S_{AB}^2)^{-\frac{1}{2}}[\phi_A(1)\phi_A(2) - \phi_B(1)\phi_B(2)] \end{aligned} \tag{2}$$

However the vast majority of quantitative calculations of molecular systems are based on molecular orbitals. It is therefore useful to obtain the proper diradical wave functions in the molecular orbital framework. The main difficulty will arise from the requirement that several molecular orbital configurations be *superposed*[20] to obtain functions such as (1) or (2). We shall study successively three limiting cases.

2.1. Homosymmetric Diradicals

We call "homosymmetric" diradical any species in which the odd orbitals ϕ_A and ϕ_B are related by some symmetry element (axis, or plane). The two orbitals may overlap [*(4)*, *(5)*, *(15a)*, *(15c)*, *(16a)*, *(16c)*] or be orthogonal [*(7a)*, *(7b)*]. In either case the proper normalized molecular orbitals are

$$\begin{aligned} \psi_+ &= (\phi_A + \phi_B)/\sqrt{2 + 2S_{AB}} \\ \psi_- &= (\phi_A - \phi_B)/\sqrt{2 - 2S_{AB}} \end{aligned} \tag{3}$$

[*] This feature has been humorously called an "ugly fact" by *G. S. Hammond* (private communication to the authors, 1970).

in a first approximation in which only the through-space interaction of ϕ_A and ϕ_B is considered[18], cf. Footnote [**] on p. 95). From eq. (3) can be constructed the three configurations[*]

$$\psi_+^2, \quad \psi_+\psi_-, \text{ and } \psi_-^2$$

The first and third configurations correspond to singlet spin states. For the configuration $\psi_+\psi_-$ we will specify whether the spin state is a singlet ($^1\psi_+\psi_-$) or a triplet ($^3\psi_+\psi_-$). The spatial symmetry of these three configurations relative to the symmetry element relating ϕ_A and ϕ_B is respectively $+$, $-$, and $+$. The triplet has spatial symmetry $-$.

Configuration ψ_+^2 is a good description of the ground singlet state function when ϕ_A and ϕ_B are strongly bound. (In the following we assume $S_{AB}>0$.) However, if ϕ_A and ϕ_B overlap only weakly or not at all, ψ_+^2 ceases to describe the ground state correctly. Indeed, in terms of the basic atomic orbitals

$$(2+2S_{AB})\psi_+^2 \equiv [\phi_A(1)\phi_B(2)+\phi_B(1)\phi_A(2)] + [\phi_A(1)\phi_A(2)+\phi_B(1)\phi_B(2)] \quad (4)$$

Because of the ionic terms in (4), the energy of the single configuration ψ_+^2 rises much faster than does the true energy of the ground state when the overlap S_{AB} decreases. The correct manner to decrease—and eventually eliminate—the weight of the ionic terms is to mix with ψ_+^2 the second configuration of *same symmetry*

$$(2-2S_{AB})\psi_-^2 \equiv -[\phi_A(1)\phi_B(2)+\phi_B(1)\phi_A(2)] + [\phi_A(1)\phi_A(2)+\phi_B(1)\phi_B(2)] \quad (5)$$

in such a manner that the ionic terms subtract. This is done by taking the negative combination

$$\lambda\psi_+^2 - \sqrt{1-\lambda^2}\,\psi_-^2 \qquad (1 \geq \lambda \geq 1/\sqrt{2})$$

This mixture still contains a small fraction of ionic character. At the limit where the two configurations have *equal energy*, $\lambda = 1/\sqrt{2}$. This can happen in two cases:

a) $S_{AB}=0$. Then we recover the purely covalent singlet (1)

$$\frac{1}{\sqrt{2}}(\psi_+^2-\psi_-^2) \equiv 2^{-\frac{1}{2}}[\phi_A(1)\phi_B(2)+\phi_B(1)\phi_A(2)] \qquad (S_{AB}\equiv 0) \quad (6)$$

b) the degeneracy is *accidental*. This can occur in systems such as *(4)*, *(15a)*, *(15c)* or *(16a)*, *(16c)* where the orbital description (3) is only approximately valid, other components mixing in to ψ_+ or ψ_- *via* through-bond interactions[18]. Then the residual ionic character can easily be verified to be roughly proportional to S_{AB}, which is not necessarily zero.

In a similar fashion ψ_-^2, which is an appropriate representation of the doubly excited state in a closed-shell system, becomes inappropriate for small S_{AB} and the correct description is

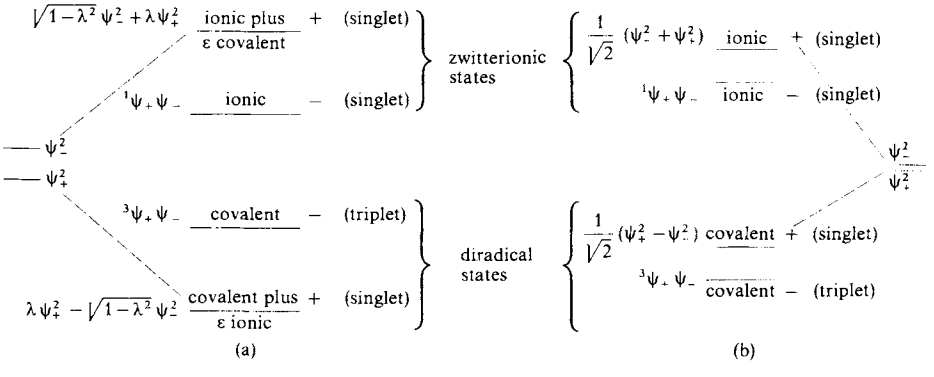
$$\sqrt{1-\lambda^2}\,\psi_+^2 + \lambda\psi_-^2$$

which still contains some covalent character. At the limit $S_{AB}=0$ we have:

$$\frac{1}{\sqrt{2}}(\psi_+^2+\psi_-^2) \equiv 2^{-\frac{1}{2}}[\phi_A(1)\phi_A(2)+\phi_B(1)\phi_B(2)] \qquad (S_{AB}\equiv 0) \quad (7)$$

As to the other two configurations, $^1\psi_+\psi_-$ and $^3\psi_+\psi_-$, they remain appropriate descriptions of the singly-excited singlet state and of the lowest triplet state whatever the value of S_{AB}. The reason is that their spatial and spin symmetry is different from that of the two other configurations. The configuration $^1\psi_+\psi_-$ is purely ionic, *whatever* the value of S_{AB}:

$$^1\psi_+\psi_- \equiv (2-2S_{AB}^2)^{-\frac{1}{2}}[\phi_A(1)\phi_A(2)-\phi_B(1)\phi_B(2)] \quad (8)$$



Scheme 4. Homosymmetric diradical: Electronic configurations and energies (for the zwitterionic states see Footnote [***] on p. 98). (a) $S_{AB}>0$ ($1 \geq \lambda \geq 1/\sqrt{2}$); (b) $S_{AB}\approx 0$ ($\lambda = 1/\sqrt{2}$).

while the triplet configuration $^3\psi_+\psi_-$ describes correctly the triplet state (1):

$$^3\psi_+\psi_- \equiv (2-2S_{AB}^2)^{-\frac{1}{2}}[\phi_A(1)\phi_B(2)-\phi_B(1)\phi_A(2)] \quad (9)$$

The orbital energies, energy levels of the states, appropriate wave functions and spatial symmetries ($+$ or $-$) are summarized below (Scheme 4) for a homosymmetric diradical a) with $S_{AB}>0$; b) with $S_{AB}\approx 0$ (degenerate molecular orbitals). The covalent and/or ionic character is also indicated.

[*] In the following, the notation $\psi_\pm^2$ will be used to denote both the conventional configuration and the singlet wave function $|\psi_+\bar{\psi}_-|$. In the case of the open-shell configuration $\psi_\pm\psi_-$ we denote $^1\psi_+\psi_- \equiv (|\psi_+\bar{\psi}_-|+|\psi_-\bar{\psi}_+|)/\sqrt{2}$ and $^3\psi_+\psi_- \equiv (|\psi_+\bar{\psi}_-|-|\psi_-\bar{\psi}_+|)/\sqrt{2}$.

For negative overlap ([18], cf. Footnote [**] on p. 95) the character of the states is the same but the role of the configurations ψ_+^2 and ψ_-^2 is reversed. Cases (a) and (b) are illustrated in Figure 3 by a) a stretched H_2 molecule; b) the twisting of ethylene to 90°.

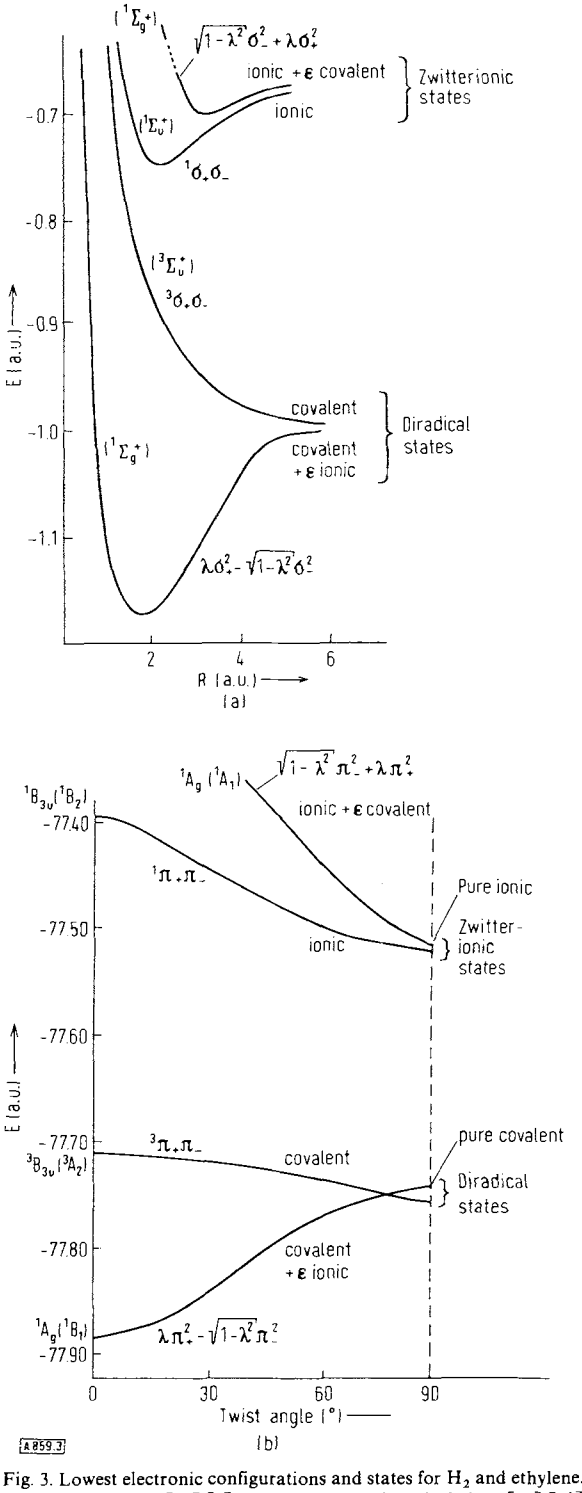


Fig. 3. Lowest electronic configurations and states for H_2 and ethylene. a) Stretching of H_2 [21] [*] ($S_{AB}>0$), b) Twisting of ethylene [22] [**] ($S_{AB}=0$ at 90°).

[*] The higher $^1\Sigma_g^+$ state actually has a second minimum at short R due to the mixing of σ_-^2 with the σ_+2s configuration [21].

[**] The energy curves are obtained from *U. Kaldor* and *I. Shavitt*, J. Chem. Phys. *48*, 191 (1968). The nomenclature of states in parentheses corresponds to the 90° situation (D_{2d} symmetry). For the ionic *vs.* covalent character of the excited states of ethylene, see also [22].

In the first case the overlap remains non-zero though very weak; in the second case S_{AB} is 0 for a twist of 90°.

The common feature in both cases is the existence of a *(singlet, triplet)* low-lying pair of degenerate *diradical* states of covalent nature, together with a second *(singlet, singlet)* pair of states of ionic nature. The latter pair of states, with high energy, are the "zwitterionic"[***] states for the system. For H_2 they correspond to the interaction of the classical structures

$$(H^{\oplus}\ H^{\ominus}),\quad (H^{\ominus}\ H^{\oplus})$$

In twisted ethylene, the zwitterionic states correspond to the mixing of the structures[22][**].



The relative triplet-singlet spacing of the diradical states is an interesting feature which discriminates between stretched H_2 (Fig. 3a) and twisted ethylene (Fig. 3b). In H_2, even at infinite distance, the singlet state lies under the triplet state[23, 24]. A naive explanation is that the one-electron energy terms dominate the two-electron exchange terms at all distances. Thus Hund's rule can never be satisfied. In 90° twisted ethylene, however, the triplet state is the ground state. The overlap S_{AB} vanishes so the two-electron exchange integral automatically puts the triplet state (two-electron energy: $J_{AB}-K_{AB}$) under the singlet state (two-electron energy: $J_{AB}+K_{AB}$). The relative energies of the diradical states and of the zwitterionic states are shown in Scheme 5 below for the case $S_{AB}=0$.

This pattern is also valid for $S_{AB}\neq 0$ in those cases where the molecular orbitals ψ_+ and ψ_- are accidentally degenerate [see the discussion of eq. (6)].

We have not dealt with the magnitude or sign of the singlet-triplet separation. It depends on the relative size of the one-electron energy difference between ψ_+ and ψ_- (approximately measured by S_{AB})—a large difference favoring the singlet—and of the two-electron exchange energy K_{AB}, which favors the triplet (Scheme 5). Generally, when ϕ_A and ϕ_B are strictly localized on different centers, K_{AB} is very small and the triplet never falls more than ≈ 5 kcal/mol below the singlet. The difference calculated for ethylene—8.5 kcal/mol—seems to be an upper limit. In other types of diradicals, however (Section 2.2), the singlet-triplet energy difference can become larger.

To summarize, the lowest singlet state of a homosymmetric diradical is a mixture of two configurations. The triplet state generally does not fall more than a few kcal/mol below this singlet state.

[***] In the "zwitterionic" states the homosymmetric species (H_2 or ethylene) has *no net dipole moment*. The term "zwitterionic" is used because one of these states is the correct description of the ground state of true zwitterions (Section 2.4). Similarly loose language is used in describing "1.3 dipoles", in which there is also resonance between two polar structures but where the net dipole moment is *small* and the polar characteristics revealed only during reaction processes.—The authors are grateful to Professors *E. Heilbronner* and *R. Huisgen* for discussions on this point.

$\frac{1}{\sqrt{2}}(\uparrow\downarrow -)$ minus $\frac{1}{\sqrt{2}}(-\uparrow\downarrow)$;	$\uparrow\uparrow$	$\downarrow\downarrow$	$\frac{1}{\sqrt{2}}(\uparrow\downarrow -)$ plus $\frac{1}{\sqrt{2}}(-\uparrow\downarrow)$
$J_{AB}+K_{AB}$	$J_{AB}-K_{AB}$	$\frac{1}{2}(J_{AA}+J_{BB})-K_{AB}$	$\frac{1}{2}(J_{AA}+J_{BB})+K_{AB}$
Diradical Singlet	Diradical Triplet	Zwitterionic Singlet [*]	Zwitterionic Singlet [*]

Scheme 5. Energies for the homosymmetric diradical ($S_{AB}=0$); the two orbitals are ψ_+ and ψ_-.
J_{AB} = Coulomb repulsion integral between ϕ_A and ϕ_B
J_{AA} = Self-repulsion integral for ϕ_A
K_{AB} = Exchange integral between ϕ_A and ϕ_B.

2.2. Heterosymmetric Diradicals

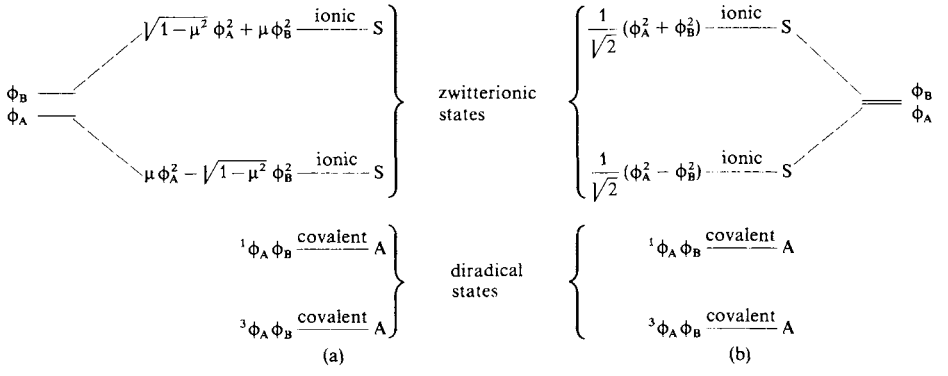
In "heterosymmetric" diradicals the orbitals ϕ_A and ϕ_B, though not necessarily localized, belong to different symmetry representations of the molecular point group. Typical examples are *(8)*, *(10)*, and *(15b)*, which all have a plane of symmetry, and where one odd electron occupies a σ orbital while the other one occupies a π orbital. It follows immediately that ϕ_A and ϕ_B can be used as such to construct the diradical and zwitterionic states in the same manner that ψ_+ and ψ_- were used previously. Thus the starting configurations are:

ϕ_A^2, $\phi_A\phi_B$, and ϕ_B^2

with ϕ_A^2 and ϕ_B^2 representing paired electrons respectively on A and B and $\phi_A\phi_B$ (singlet or triplet) representing one electron on each orbital.

tions are defined by a mixing parameter $\mu(1\geq\mu\geq 1/\sqrt{2})$ similar to λ. For $\mu=1/\sqrt{2}$ (Scheme 6b)—this can only occur accidentally since the local fields surrounding ϕ_A and ϕ_B are generally different in a heterosymmetric species—the two-electron energies of all four states are identical to those at the end of Section 2.1 (Scheme 5). Indeed the wave functions of Scheme 4b and 6b are identical when expressed in terms of the local orbitals ϕ_A and ϕ_B. Even if $\mu>1/\sqrt{2}$, the ground state is a triplet, since the configuration $^3\phi_A\phi_B$ always lies below $^1\phi_A\phi_B$. Note that the symmetries in Scheme 6 have been written by assuming one orbital to be S and the other A.

There is an exceptional heterosymmetric diradical—methylene—where the large size of the interorbital repulsion energy J_{AB} (between two atomic orbitals on the same center) together with the significant exchange energy K_{AB} cause the covalent singlet state to rise above the lower ionic



Scheme 6. Heterosymmetric diradical: Electron configurations and energies. (a) $E_A-E_B<0$ $(1\geq\mu>1/\sqrt{2})$; (b) $E_A=E_B$ (accidental degeneracy) $(\mu=1/\sqrt{2})$.

The difference with the homosymmetric case is the manner in which the configurations are used to build the correct wave functions. The negative combination of ϕ_A^2 and ϕ_B^2 gives directly the same ionic state which was obtained previously from the single configuration $^1\psi_+\psi_-$. Similarly, configuration $^1\phi_A\phi_B$ describes the covalent diradical state which previously required combining ψ_+^2 with ψ_-^2. Thus the energy pattern in Scheme 6 resembles that in Scheme 4 for the nature of the states but not for the number of configurations involved in describing each one. Furthermore, the weights of ϕ_A^2 and ϕ_B^2 in the two ionic wave functions are not necessarily the same: although $S_{AB}=0$, the local energies of ϕ_A and ϕ_B are generally different and the orbitals not perfectly degenerate (Section 1.6). The proper combination of singlet state. For an HCH angle of 140° the ordering of states in methylene is roughly[25,26] as given in Scheme 7.

$(^1A_1)$ $\sqrt{1-\mu^2}\,\sigma^2+\mu\pi^2$	ionic	zwitterionic states
$(^1B_1)$ $^1\sigma\pi$	covalent	
$(^1A_1)$ $\mu\sigma^2-\sqrt{1-\mu^2}\,\pi^2$	ionic	diradical states
$(^3B_1)$ $^3\sigma\pi$	covalent	

Scheme 7. Ordering of states in methylene [25, 26]. (Note that σ and π are localized on the same center.)

The triplet lies well below the lowest singlet. The energy difference is 24 kcal/mol between the minima of the two states, 31 kcal/mol for linear methylene[25]. Similarly the ground $^3\Sigma_g^-$ state of O_2 lies 22 kcal/mol below the first

[*] See Footnote [***] on p. 98.

singlet $^1\Delta_g$ because of the large one-center exchange terms between π_x^* and π_y^* orbitals.

We note finally that, whereas in the homosymmetric diradical the extent to which λ deviates from $1/\sqrt{2}$ is roughly a measure of the overlap S_{AB}[*], in heterosymmetric diradicals the deviation of μ from $1/\sqrt{2}$ measures the extent to which the local energies E_A of ϕ_A and E_B of ϕ_B differ.

2.3. The "Non-symmetric" Case

The question now arises as to the behavior of the wave function and energies along a geometrical transformation which brings a homosymmetric diradical into a heterosymmetric diradical. Consider, as an example, the internal rotation of a methylene group which transforms edge-to-edge trimethylene *(15c)* into edge-to-face trimethylene *(15b)*:



(15c) *(15b)*

Clearly along the "reaction" coordinate—except at the start and at the end—the system has no symmetry whatsoever. Thus at any intermediate point the orbitals ϕ_A and ϕ_B overlap but there are no symmetry restrictions on the way in which they combine. The two non-bonding molecular orbitals, which we call ψ and ψ', have different weights on A and B. Orbital ψ localizes more and more on A while ψ' localizes on B, as the reaction proceeds. Furthermore during the rotation *both* molecular orbitals develop an in-plane component (formally called σ) and keep an out-of-plane component (formally called π)[**]. The initial, intermediate and final forms of ψ and ψ' are shown in Figure 4.

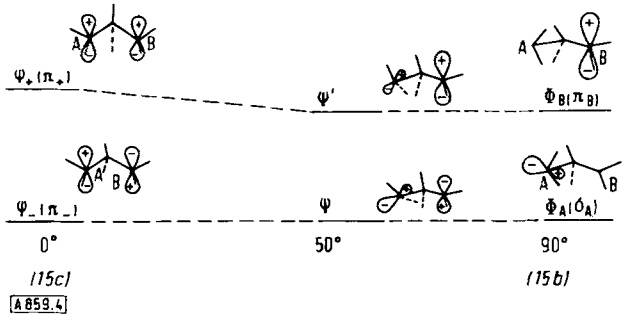


Fig. 4. Transformation of *(15c)* into *(15b)* *via* methylene rotation.

At the intermediate point shown (rotation of 50°) ψ and ψ' are given approximately by

$$\begin{cases} \psi \approx (0.72\sigma_A + 0.55\pi_A) - 0.45\pi_B \\ \psi' \approx (0.34\sigma_A + 0.26\pi_A) + 0.87\pi_B \end{cases} \quad (10)$$

[*] One can even think of $2(1-\lambda^2)$ as a "measure" of diradical character; see [27].

[**] Hence to describe the evolution of both molecular orbitals by perturbation theory would require other than the two initial orbitals themselves.

where the terms σ and π refer to partial in or out-of plane components.

The most interesting feature is the manner in which the energy scheme of 4a is transformed into an energy scheme of type 6a. We will restrict ourselves to the three singlets, for which the configurational description varies along the path. Essentially:

1. There is a cross-over (Fig. 5) of the energies of configurations ψ^2 and ψ'^2 with that of configuration $^1\psi\psi'$. Indeed

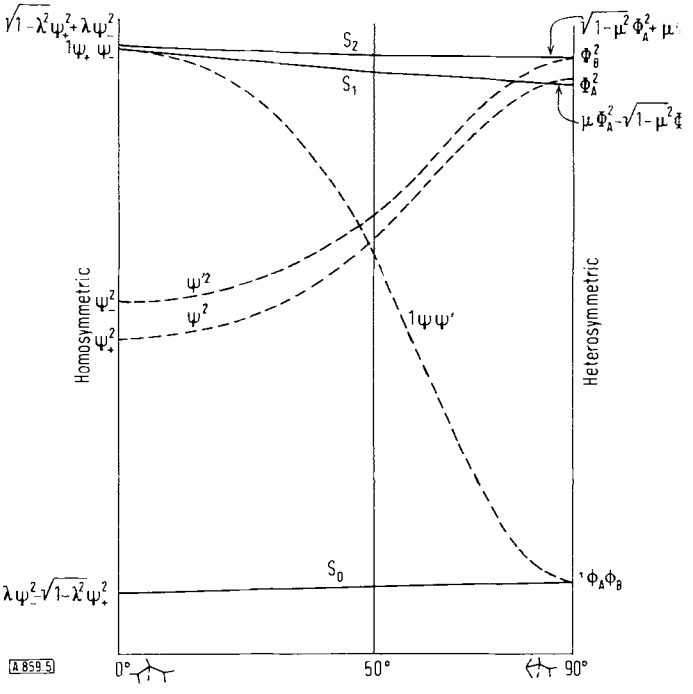


Fig. 5. Singlet configurations and singlet states for internal rotation in the trimethylene diradical [28].

this "open-shell" configuration describes a highly excited ionic state of the starting diradical *(15c)* (Scheme 4a) but correlates with $^1\phi_A\phi_B$ which describes the low-lying covalent diradical state in the final system *(15b)* (Scheme 6a). Thus its energy decreases steadily. Similarly the pair of nearly-degenerate, relatively low-lying configurations ψ_+^2 and ψ_-^2 which initially served to build the ground singlet and top singlet by configuration interaction correlate with the ionic configurations ϕ_A^2 and ϕ_B^2 which interact weakly to give the two ionic states of *(15c)*.

2. The energy levels of the *states* stay nearly constant.

3. The coefficient λ at the start ≈ 0.74 (*i.e.* ψ_+^2 and ψ_-^2 mix almost equally). However the energy difference between ϕ_A^2 and ϕ_B^2 and their weak mixing *via* K_{AB} are such that μ is nearly equal to 1.

Let us write out the wave functions of the three states at 50°, near the crossing point of the three configurations. The three states are:

$$\begin{cases} S_0 = -0.60\,(^1\psi\psi') + 0.58\,(\psi^2) - 0.55\,(\psi'^2) \\ S_1 = -0.69\,(^1\psi\psi') - 0.72\,(\psi^2) - 0.01\,(\psi'^2) \\ S_2 = -0.40\,(^1\psi\psi') + 0.37\,(\psi^2) + 0.84\,(\psi'^2) \end{cases} \quad (11)$$

Although the ground singlet S_0 appears as a nearly equal mixture of all three configurations, at this intermediate

stage, it is possible to show that it actually retains nearly *pure covalent* character. Indeed expansion of (11) in terms of (10) gives:

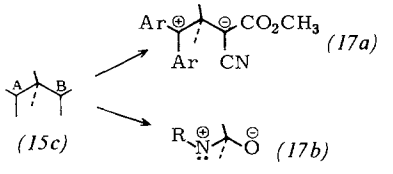
$$S_0 = 0.55\,[\sigma_A(1)\pi_B(2) + \pi_B(1)\sigma_A(2)] + 0.42\,[\pi_A(1)\pi_B(2) + \pi_B(1)\pi_A(2)] + \text{terms with coefficient} \leq 0.03$$

At the same time S_1 and S_2 remain nearly purely ionic. Thus the three states keep their covalent, or ionic character throughout, and Scheme 4 goes smoothly into Scheme 6.

To summarize, in the "non-symmetric" case the diradical singlet state is generally a mixture of *three* configurations.

2.4. Introduction of Zwitterionic Character in a Diradical

An important conclusion of our study in 2.2 and 2.3 is that to each pair of diradical states is associated a pair of zwitterionic states. Now it is well-known to Organic Chemists that, for instance, a diradical such as *(15b)* or *(15c)* can be transformed into a zwitterion either by appropriate substitution on the terminal carbon atoms [*(17a)*][29] or formally by exchange of the C atoms with suitable heteroatoms [*(17b)*].



What do such changes imply as to the behavior of the pairs of diradical and zwitterionic states of Schemes 4 or 6? Substitution of a hydrogen atom attached to C_A by an electropositive substituent while an electron attracting substituent is put at C_B, or formal replacement of C_A by N and C_B by O lowers the local energy E_B relative to the local energy E_A.

In the homosymmetric case the ionic component

$$\phi_B(1)\phi_B(2)$$

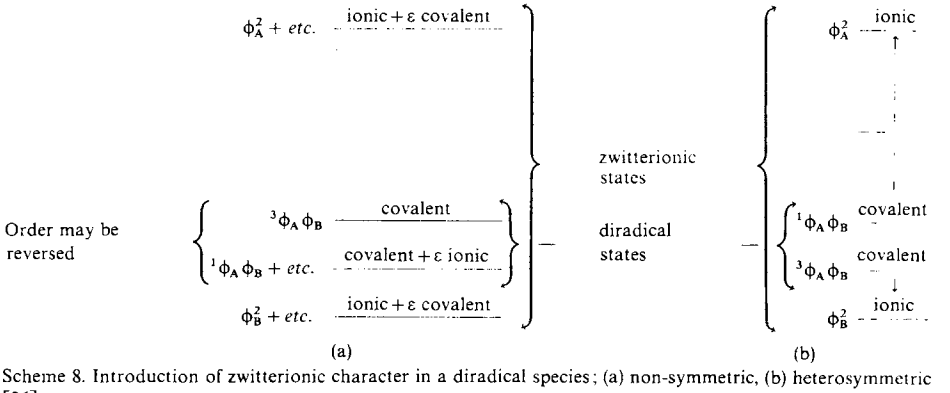
is significantly stabilized while the other component

$$\phi_A(1)\phi_A(2)$$

is destabilized. The proper ionic wave functions are no longer given by (2). One ionic wave function has essentially ϕ_B^2 character and little ϕ_A^2 character ($A^+ B^-$), with a very low energy[30]. The other wave function, which contains nearly all the ϕ_A^2 character ($A^- B^+$), has a high energy. The final energy pattern is shown in Scheme 8. The ground *state*, which was nearly purely covalent, has built in more and more ionic character to become nearly ionic. The second singlet state, which was ionic, is now the diradical state. Not only has the energy pattern changed, but also the characteristics of the singlet wave functions. Indeed substitution on species *(15c)* destroys the symmetry element which related ϕ_A and ϕ_B. The situation becomes similar to that in the "non-symmetric" case (Section 2.3) with all three singlet configurations being allowed to mix. Actually the lower configuration is strongly localized on ϕ_B and the highest one on ϕ_A so that the mixing will be relatively small. Hence there will be only residual mixing between the lowest configuration $\psi^2 (\approx \phi_B^2)$, the intermediate one $^1\psi\psi' (\approx \phi_A\phi_B)$ and the upper one $^1\psi'^2 (\approx \phi_A^2)$.

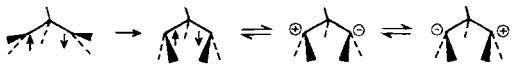
In the heterosymmetric case the components ϕ_A^2 and ϕ_B^2 are of course affected in the same manner as in the homosymmetric case. The only difference lies in the nature of the singlet states: the substitution does not necessarily destroy the element of symmetry which caused ϕ_A and ϕ_B to belong to different representations. Thus all states can remain "pure" ionic or "pure" covalent.

In Scheme 8 we have drawn the zwitterionic state as the ground state of both systems. The nature of the ground state depends on several factors: the difference $E_A - E_B$ of course, but also the extent of overlap between ϕ_A and ϕ_B. Strongly asymmetric substitution on A and B may reduce this overlap by introducing a difference in size in the lobes of ϕ_A and ϕ_B, thereby helping to raise the covalent singlet.



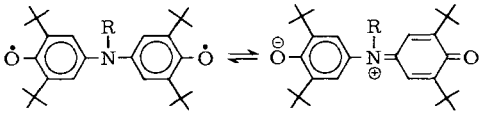
Scheme 8. Introduction of zwitterionic character in a diradical species; (a) non-symmetric, (b) heterosymmetric [26].

The reader will not fail to observe that in the general, non-symmetric case, *the lowest zwitterionic state involves some covalent character just as the lowest diradical state involves some ionic character*. Thus, the familiar terms "diradical" or "zwitterion" are only simplifications of the real situation. Sometimes the "unmentioned" character can become important or predominant *via* a simple geometric change. Thus a significant increase in zwitterionic character of the ground diradical state can occur in face-to-face trimethylene *(15a)*[10] by simple inwards pyramidalization of the terminal methylene groups:



(15d) *(15a)*

An interesting case is the interconversion of a homosymmetric species with a diradical ground state into a species with a zwitterionic ground state *via* a change in hybridization at a single atom, again obtained *via* a simple pyramidalization or depyramidalization process[31]:



(18a) *(18b)*

Diradical *(18a)* has a triplet ground state and is paramagnetic, while the closed-shell species *(18b)* is diamagnetic. The kinetics of the interconversion can be investigated by studying the variation in the line width of the NMR peaks of the zwitterions.

3. Geometrical Selection Rules for Intersystem Crossing between Singlet and Triplet Diradical States *via* Spin-Orbit Coupling

3.1. Introduction: Conditions for Perfect Vibronic Degeneracy between Triplet and Singlet States

It is well known that singlet and triplet states are not proper stationary states of a system when certain intramolecular magnetic interactions are allowed for. In the presence of these interactions the proper states are mixtures of the "pure" spin triplet and singlet states. Time-dependent perturbation theory shows that a system prepared in one of the pure states—as would be a singlet diradical by bond rupture—can evolve by an appropriate interaction, into an oscillatory *mixture* of the two (singlet and triplet) states. If the triplet component can further be stabilized energetically, the entire system can end up in the triplet state[*]. This process is known as intersystem crossing and is illustrated in Figure 6.

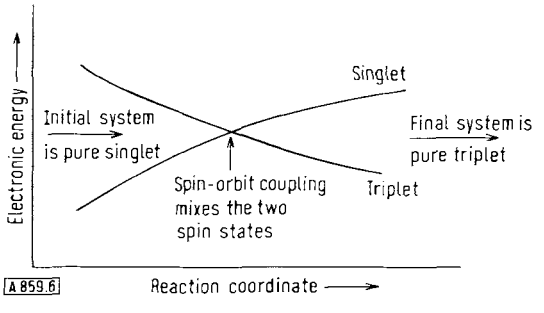


Fig. 6. Intersystem crossing.

[*] For an interesting discussion of intersystem crossing in diradicals, see [32].

Spin-orbit coupling is the most common mechanism *via* which intersystem crossing can occur. The two fundamental prerequisites for the crossing to be effective are:

1. There must be non-zero mixing, *via* the appropriate operator, of the *electronic* wave functions. Essentially the orbital transition between the electronic wave function for the singlet and the electronic wave function for the triplet must create a torque which can flip the electron spin. We shall return to this electronic factor in great detail in the further sections.

2. The separation between the singlet and triplet levels must not be larger than the size of the interaction. In the carbon atom, for instance, the spin-orbit induced splitting between $^3P_1$ and $^3P_0$ states is 16.4 cm^{-1}[33]. Since this is significantly smaller than vibrational spacings in molecules, intersystem crossing will require nearly perfect degeneracy between the vibronic (*i. e.* electronic plus vibrational) levels of singlet and triplet states.

Let us discuss the conditions under which such vibronic degeneracy can occur. Figure 7 shows the calculated spacings for the vibrational levels of the lowest singlet-triplet

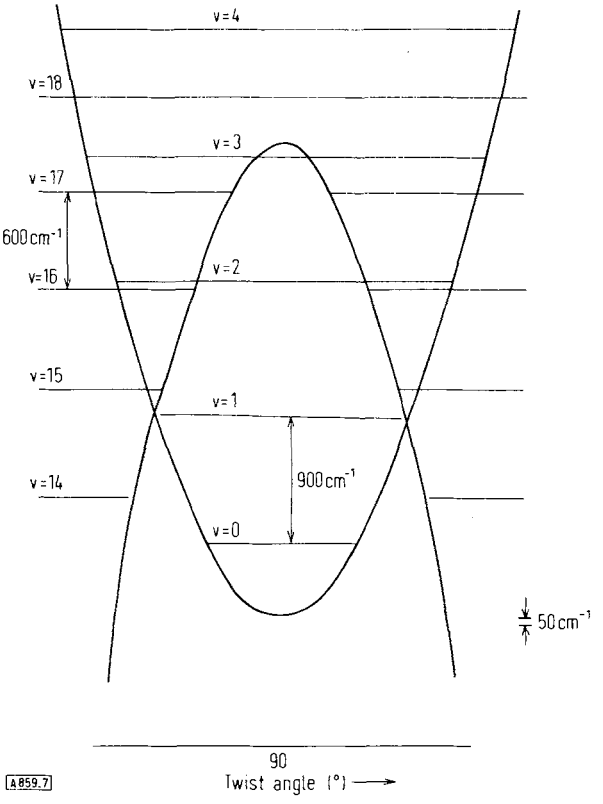


Fig. 7. Estimated vibrational spacings in twisted ethylene. (The electronic energy difference of 3000 cm^{-1} at 90° is obtained from Ref. [**] on p. 98.)

pair of states in twisted ethylene. We have calculated the spacings between the singlet vibrational levels by solution of Mathieu's equation for a barrier height of 16000 cm^{-1} (the value of 45 kcal/mol required to fit the experimental separation of 1023 cm^{-1}[8] between the two lowest twisting levels in planar ethylene). For the triplet the spacings are obtained by using the potential energy curve of Ref. [**] on p. 98.

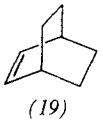
Clearly the coincidence of vibrational levels is insufficient to ensure that singlet ethylene can cross to triplet ethylene. Although there are pairs of vibrational levels which are relatively close, and which may in fact be nearly perfectly degenerate, the chances of creating singlet ethylene in just the appropriate high vibrational level [for instance v = 16, which coincides with the triplet (v = 2)-level] are extremely small. A much greater density of vibrational levels would be required for a significant probability of intersystem crossing.

What is required for efficient intersystem crossing is that the levels of the initial state interact, not with a sparse manifold (as in Fig. 7) of highly discrete vibrational levels, but with a dense continuum of vibrational levels[34]. It is well-known that in the equilibrium regions of bound states (triplet in Fig. 7) such a dense continuum exists only for sufficiently large molecules, of the size of benzene say[35].

Thus for *small isolated diradicals*—for instance *(7)*, *(8)*, *(10)*, *(15)*, *(16)* in a rigid matrix—*intersystem crossing should not be efficient*. However, the necessary continuum of energy states may be provided in different ways for the *non-isolated* system:

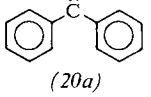
1. By collision with a rare gas. *Eder* and *Carr* have shown[36][*] that singlet methylene intersystem-crosses efficiently in the presence of inert gases. The collision partner effectively couples singlet methylene with the required continuum of states. Similarly the conversion of triplet ethylene to *cis* and *trans* singlet products follows bimolecular kinetics[37a].

2. By linking the small diradical in which intersystem crossing is sought to a large chain which plays the role of a collisional "solvent" with a vast number of vibronic levels. The facile intersystem crossing to the ground singlet state in triplet-sensitized olefins such as bicyclo[2.2.2]oct-2-ene *(19)*[37b] can probably be explained in this manner. In certain cases the continuum which is provided may involve

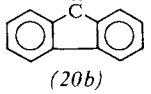


(19)

internal rotational levels. For instance diphenyl carbene *(20a)* decays very efficiently from singlet to triplet while *(20b)*, in which the rotation of the phenyl groups is blocked, arrives much less efficiently in the triplet state[38], judging by its reactivity.



(20a)



(20b)

[*] It has been suggested that the collision also serves to enhance the electronic coupling proper *via* methylene spin-gas orbital angular momentum interactions (*M. Y. Chu* and *J. S. Dahler*, Chem. Phys. Lett. *8*, 369 (1971)). However (Section 3.4) the electronic factor in isolated methylene is already very large and, although it is difficult to assess the importance of the large collision-induced orbital distortions, it is doubtful that the collision does anything but actually decrease the electronic term.

3. Even in gaseous "unimolecular" reactions collisions are required to activate and deactivate the reactant molecules; these collisions may suffice to ensure intersystem crossing in small diradicals such as *(15)* or *(16)*.

In the following sections we shall assume that the problem of level degeneracy has been taken care of in some manner. It must therefore be kept in mind that the electronic factors which we shall calculate can be used for meaningful predictions only if this degeneracy is *effectively* ensured.

3.2. The Electronic Factor in Homosymmetric Diradicals

Let us first consider the mixing induced by the spin-orbit coupling operator $H_{sp.orb.}$, between the singlet diradical wave function:

$$S_0 \equiv \lambda\psi_+^2 - \sqrt{1-\lambda^2}\,\psi_-^2 \tag{12}$$

(see Scheme 4a) and the triplet diradical wave function

$$T_0 \equiv {}^3\psi_+\psi_-$$

The orbitals ψ_+ and ψ_- are given by eq. (3). Thus the matrix element is

$$\langle\lambda\psi_+^2 - \sqrt{1-\lambda^2}\,\psi_-^2 | H_{sp.orb.} | {}^3\psi_+\psi_-\rangle \tag{13}$$

In the triplet state *all three spin components* must be considered; there are three matrix elements.

In a first approximation in which two-electron terms are neglected the spin-orbit operator $H_{sp.orb.}$ can be reduced to a sum of one-electron terms each involving a product of orbital angular momentum **l** and spin angular momentum **s**[39][**].

$$H_{sp.orb.} = \frac{e^2}{2mc^2}\sum_{\substack{\text{nuclei}\\ i}}\sum_{\substack{\text{electrons}\\ k}}\frac{Z_i}{r_{ik}^3}\,\mathbf{l}_k\cdot\mathbf{s}_k = H_x + H_y + H_z \tag{14}$$

where H_x is the x component of the operator, H_y its y component and H_z its z component. The calculation of the matrix elements of $H_{sp.orb.}$ between two determinantal functions such as ψ_+^2 and $\psi_+\psi_-$ is straightforward[39][**] and leads to Table 1 for the matrix elements between S_0 and T_0. In the present case

$$H'_{lx} = \frac{\hbar e^2}{4m^2c^2}\left(\frac{Z_A|_x^A}{r_A^3} + \frac{Z_B|_x^B}{r_B^3}\right) \tag{15}$$

with $Z_A = Z_B = Z$.

We now assume that the symmetry element relating ϕ_A and ϕ_B is either a $C_2(x)$ axis or a $\sigma(xz)$ plane as shown in Figure 8. Finally in the matrix elements of Table 1 we restrict our-

[**] The numbers in the Table 5.4 of *McGlynn et al.* [39], which refer to an open-shell singlet configuration, must be multiplied by $\sqrt{2}$ to give correct results for a closed-shell configuration such as ψ_+^2. For the doubly-excited configuration ψ_-^2, a minus sign must be introduced. Note that eq. (5.42) of *McGlynn et al.* is incorrect: the numerical factor should be 1 rather than $1/\sqrt{2}$ (the latter would be correct only if |a c| were to replace (a c)). The equations which follow, however, are correct.

Table 1. Spin-orbit coupling matrix elements between S_0 and T_0.

Component of $H_{sp.orb.}$	$\langle S_0\|H_{sp.orb.}\|T_0^{(1)}\rangle$	$\langle S_0\|H_{sp.orb.}\|T_0^{(0)}\rangle$	$\langle S_0\|H_{sp.orb.}\|T_0^{(-1)}\rangle$
H_x	$\lambda\langle\psi_+\|H'_{ix}\|\psi_-\rangle + \sqrt{1-\lambda^2}\langle\psi_-\|H'_{ix}\|\psi_+\rangle$	0	$-\lambda\langle\psi_+\|H'_{ix}\|\psi_-\rangle - \sqrt{1-\lambda^2}\langle\psi_-\|H'_{ix}\|\psi_+\rangle$
H_y	$i[\lambda\langle\psi_+\|H'_{iy}\|\psi_-\rangle + \sqrt{1-\lambda^2}\langle\psi_-\|H'_{iy}\|\psi_+\rangle]$	0	$i[\lambda\langle\psi_+\|H'_{iy}\|\psi_-\rangle + \sqrt{1-\lambda^2}\langle\psi_-\|H'_{iy}\|\psi_+\rangle]$
H_z	0	$-\sqrt{2}[\lambda\langle\psi_+\|H'_{iz}\|\psi_-\rangle + \sqrt{1-\lambda^2}\langle\psi_-\|H'_{iz}\|\psi_+\rangle]$	0

Table 2. Spin-orbit-coupling matrix elements between singlet and triplet in a homosymmetric diradical: These matrix elements must be multiplied by the proportionality constant $\hbar e^2/(4m^2c^2)$ [see (19)]. $N=(4-4S_{AB}^2)^{-\frac{1}{2}}$.

The coefficients a, b, c give the orientation of the odd orbitals ϕ_A and ϕ_B [eq. (16)]; λ is a measure of the degree of ionic character [eq. (12)]; the integrals ξ_{AB}^{σ} and ξ_{AB}^{π} are defined in eq. (17) and are tabulated in Table 3. The overall singlet-triplet splitting is obtained by solving the 4-by-4 secular determinant involving the overall matrix elements of $H_{sp.orb.}$ between S_0, $T_0^{(1)}$, $T_0^{(0)}$, and $T_0^{(-1)}$ [see (20)].

Component of $H_{sp.orb.}$	$\langle S_0\|H_{sp.orb.}\|T_0^{(1)}\rangle$	$\langle S_0\|H_{sp.orb.}\|T_0^{(0)}\rangle$	$\langle S_0\|H_{sp.orb.}\|T_0^{(-1)}\rangle$
	Case I (C_2 axis)		
H_x	0	0	0
H_y	$-4NZ\hbar ac(\lambda-\sqrt{1-\lambda^2})(2\xi_{AB}^{\pi})$	0	$-4NZ\hbar ac(\lambda-\sqrt{1-\lambda^2})(2\xi_{AB}^{\pi})$
H_z	0	$4\sqrt{2}NZ\hbar abi(\lambda-\sqrt{1-\lambda^2})(\xi_{AB}^{\sigma}+\xi_{AB}^{\pi})$	0
	Case II (C_s plane)		
H_x	$4NZ\hbar bci(\lambda-\sqrt{1-\lambda^2})(\xi_{AB}^{\sigma}+\xi_{AB}^{\pi})$	0	$-4NZ\hbar bci(\lambda-\sqrt{1-\lambda^2})(\xi_{AB}^{\sigma}+\xi_{AB}^{\pi})$
H_y	0	0	0
H_z	0	$4\sqrt{2}NZ\hbar abi(\lambda-\sqrt{1-\lambda^2})(\xi_{AB}^{\sigma}+\xi_{AB}^{\pi})$	0

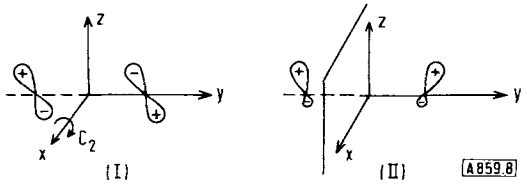


Fig. 8. Symmetry elements which couple ϕ_A and ϕ_B: (I) $C_2(x)$ axis, (II) $\sigma(xz)$ plane.

selves to the p_x, p_y, and p_z components involved in ϕ_A and ϕ_B. (The expectation value of l_x, l_y, and l_z acting on an s orbital is zero.) Then we can write, for (I) and (II):

$$\text{I}\begin{cases}\phi_A = ax_A + by_A + cz_A\\ \phi_B = ax_B - by_B - cz_B\end{cases}\qquad \text{II}\begin{cases}\phi_A = ax_A + by_A + cz_A\\ \phi_B = ax_B - by_B + cz_B\end{cases}\tag{16}$$

where $x \equiv p_x$, *etc.* The only non-vanishing matrix elements of $(1/r_A^3)l_x^A$, for instance, involve coordinate components on the same atom or coordinate components on both A and B:

$$\begin{cases}\left\langle z_A\left|\frac{1}{r_A^3}l_x^A\right|y_A\right\rangle \equiv -\left\langle y_A\left|\frac{1}{r_A^3}l_x^A\right|z_A\right\rangle;\ \left\langle z_B\left|\frac{1}{r_A^3}l_x^A\right|y_B\right\rangle \equiv -\left\langle y_B\left|\frac{1}{r_A^3}l_x^A\right|z_B\right\rangle\\ \left\langle z_B\left|\frac{1}{r_A^3}l_x^A\right|y_A\right\rangle \equiv -\left\langle y_A\left|\frac{1}{r_A^3}l_x^A\right|z_B\right\rangle \equiv i\hbar\xi_{AB}^{\pi}\\ \left\langle y_B\left|\frac{1}{r_A^3}l_x^A\right|z_A\right\rangle \equiv -\left\langle z_A\left|\frac{1}{r_A^3}l_x^A\right|y_B\right\rangle \equiv -i\hbar\xi_{AB}^{\sigma}\end{cases}\tag{17}$$

where ξ_{AB}^{π} and ξ_{AB}^{σ} are parameters which we will discuss later. Similar results hold for $(1/r_A^3)l_z^A$ and for $(1/r_A^3)l_y^A$, except that for this last operator only ξ_{AB}^{π} intervenes.

Simple algebra shows that, in terms of the ϕ's, only the off-diagonal elements between ϕ_A and ϕ_B are non-zero. The results are:

$$\left\langle\phi_A\left|\frac{1}{r_A^3}l_x^A\right|\phi_B\right\rangle = \left\langle\phi_B\left|\frac{1}{r_A^3}l_x^A\right|\phi_A\right\rangle^* =$$

$$-i\hbar bc(\xi_{AB}^{\sigma}-\xi_{AB}^{\pi}) = \left\langle\phi_B\left|\frac{1}{r_B^3}l_x^B\right|\phi_A\right\rangle \quad \text{(case I)}$$

$$-i\hbar bc(\xi_{AB}^{\sigma}+\xi_{AB}^{\pi}) = -\left\langle\phi_B\left|\frac{1}{r_B^3}l_x^B\right|\phi_A\right\rangle \quad \text{(case II)}$$

$$\left\langle\phi_A\left|\frac{1}{r_A^3}l_z^A\right|\phi_B\right\rangle = \left\langle\phi_B\left|\frac{1}{r_A^3}l_z^A\right|\phi_A\right\rangle^* =$$

$$i\hbar ab(\xi_{AB}^{\sigma}+\xi_{AB}^{\pi}) = -\left\langle\phi_B\left|\frac{1}{r_B^3}l_z^B\right|\phi_A\right\rangle \quad \text{(cases I, II)}\tag{18}$$

$$\left\langle\phi_A\left|\frac{1}{r_A^3}l_y^A\right|\phi_B\right\rangle = \left\langle\phi_B\left|\frac{1}{r_A^3}l_y^A\right|\phi_A\right\rangle^* =$$

$$-i\hbar ac(2\xi_{AB}^{\pi}) = -\left\langle\phi_B\left|\frac{1}{r_B^3}l_y^B\right|\phi_A\right\rangle \quad \text{(case I)}$$

$$0 = \left\langle\phi_B\left|\frac{1}{r_B^3}l_y^B\right|\phi_A\right\rangle \quad \text{(case II)}$$

The final results for the singlet-triplet matrix elements in cases (I) and (II) are shown in Table 2. All these results must be multiplied by the proportionality constant written in (15), *i.e.* $\hbar e^2/(4m^2c^2)$. The product of this constant by $\hbar$ is the conversion factor

$$\frac{\hbar^2 e^2}{4m^2c^2} \rightarrow 2.9\ \text{cm}^{-1}\tag{19}$$

if ξ is calculated in atomic units.

3.3. General Rules for Favorable Intersystem Crossing

Table 2 yields the favorable conditions for intersystem crossing. Consider for instance a system of type (II), where ϕ_A and ϕ_B are related by a symmetry plane. The extent of spin-orbit coupling induced by the *x component* of the Hamiltonian is proportional

1. To bc, *i.e.* to the product of the y and z components of ϕ_A (or ϕ_B). The maximum value of bc occurs when ϕ_A points parallel to the diagonal of the yz axis system (Figure 9). It is clear that a transition of an electron from ϕ_A to ϕ_B in-

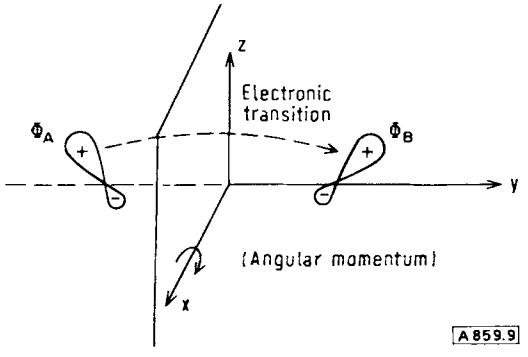


Fig. 9. Creation of orbital angular momentum by electronic transition from ϕ_A to ϕ_B (case II).

volves a rotation of 90° of (the p component of) the orbital which the electron occupies. This is precisely what is required to create an orbital angular momentum around the x axis which can "flip" the electron spin. This situation cannot occur, however, if ϕ_A and ϕ_B were to be related by the x axis as C_2 axis—whence the 0 matrix elements for H_x in case (I). (Similarly in case (II) H_y yields 0.)

In general, therefore, *the orbital axes must be orthogonal to each other and to the axis around which orbital angular momentum is being created.* Figure 10 shows the three different possible favorable cases illustrated for pure p orbitals.

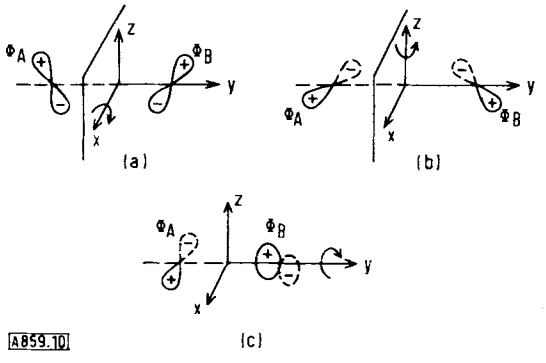


Fig. 10. Favorable orbital orientations for intersystem crossing in diradicals. Arrow shows angular momentum which is created.—The favorable orientation is not enough to ensure intersystem crossing. (a) Case II, C_s symmetry, orbitals in the yz plane; (b) cases I, II, $C_2^{(x)}$ or C_s symmetry, orbitals in the xy plane; (c) $C_2^{(x)}$ symmetry, orbital directions parallel to xz plane.

For angular momentum around z, the optimum value of the matrix element in Table 2 corresponds to a common situation for C_2 symmetry and C_s symmetry. Thus *orbital orientation* is an essential factor for intersystem crossing in diradicals. A triplet diradical in which the odd orbitals point straight at each other is in an unfavorable situation for rebonding.

2. To $\lambda - \sqrt{1-\lambda^2}$, *i.e. to the degree of ionic character* in the singlet wave function (16). Indeed, if the singlet is purely covalent, with one electron on each atomic orbital at all instants, the triplet to singlet transition cannot take one electron from ϕ_A into ϕ_B since the triplet is always purely covalent. No torque can be created to flip the spin since each electron stays in the *same* atomic orbital. Intersystem crossing is effective only if there is some probability of finding both electrons on the same orbital in the singlet. In homosymmetric diradicals the degree of ionic character increases with overlap; thus this second factor is roughly proportional to S_{AB} (see below). In the light of paragraphs 1 and 2, molecule *(15c)*—which is the transition state for optical isomerization of cyclopropane[12, 14]—is hardly prone to intersystem crossing and should remain in the singlet manifold. On the one hand the orbitals ϕ_A and ϕ_B are parallel, and on the other hand the singlet state is nearly covalent.

3. To the sum $\xi^{\sigma}_{AB} + \xi^{\pi}_{AB}$ of two-center integrals. From (17) it is clear that these integrals decrease rapidly with increasing distance AB or decreasing overlap.

Good overlap S_{AB} would therefore seem to be a favorable factor for two reasons [see (2) and (3)]. However, too strong an overlap automatically destroys the degeneracy between the singlet and triplet diradical states (see for instance Figure 3a) and often implies a poorer orbital axis orthogonality. This is illustrated below for ethylene, where we have plotted triplet-singlet energy difference, ionic character and orbital axis orthogonality (ac) against twist angle[*]. The maximum value of the matrix element of H_y is found to occur near 60°. A numerical estimate can

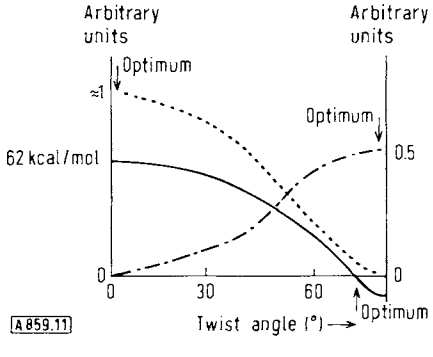


Fig. 11. Terms involved in the H_y induced spin orbit coupling in twisted ethylene (y axis = CC axis; x axis = C_2 axis relating the orbitals). The component ac behaves as $\frac{1}{2}\sin\theta$. —: $E_T - E_S$; ···: $\lambda - \sqrt{1-\lambda^2}$; — · — ·: ac.

be obtained for the intersystem crossing matrix element at this angle by using the values:

[*] In ethylene, in which the spin-orbit coupling is induced by H_y (case I) the integral ξ^{π}_{AB} is insensitive to twisting. Thus the overlap intervenes through λ and through the product ac.

$$(Z=3.25,\text{ effective value})\quad\begin{cases} Z\xi^{\pi}_{AB}=0.7186\,cm^{-1}\,[40][*] \\ S_{AB}\ =0.1321 \\ \lambda\ =0.93 \\ ac\ =\tfrac{1}{2}\sin 60^\circ \end{cases}$$

in Table 2 (Case I, H_y).

We find for the matrix elements of H_y between S_0 and $T_0^{(-1)}$ or $T_0^{(+1)}$ $A=0.70\,cm^{-1}$. Whence, by solving the 3 by 3 secular determinant

$$\begin{vmatrix} -E & A & A \\ A & -E & 0 \\ A & 0 & -E \end{vmatrix}=0 \qquad (20)$$

the splitting between singlet and triplet is:

$$\text{Singlet-triplet splitting}=\sqrt{2}A=1\ cm^{-1} \qquad (21)$$

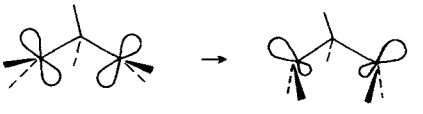
This value is an upper limit for the actual electronic factor in the intersystem crossing since our calculation assumes that the vibronic degeneracy can still be maintained or induced for an electronic energy difference already as large as 1.1 eV. If this is not the case, the actual optimum mixing will occur for larger angles and thereby smaller values of the overall matrix element. Of course (20) will have to be multiplied by a Franck-Condon factor to yield the overall intersystem crossing probability.

Table 3. Values of $Z\xi^{\sigma}_{AB}$ and $Z\xi^{\pi}_{AB}$ for various distances R_{AB} ($Z=3.25$) [40] [*]. Values in cm^{-1} [the conversion factor (19) has been included].

R_{AB}	$Z\xi^{\sigma}_{AB}$	$Z\xi^{\pi}_{AB}$
0	13.5	13.5
1 Å	1.99	1.98
1.5 Å	1.37	0.528
2 Å	0.498	0.133
2.5 Å	0.152	0.032
3.0 Å	0.042	0.0076

Table 3 shows that in 1,3 or 1,4 diradicals the intersystem crossing matrix element drops to 0.5—0.1 cm^{-1}. By comparison the matrix elements for intersystem crossing between the low-lying excited states of benzene are 0.3 cm^{-1}[41]. A tentative comparison of the overall intersystem crossing rates in aromatics and in small diradicals requires knowledge of the vibrational overlap factors. In aromatics the vibrational interaction is characterized by overlap between the lowest level of the higher electronic state and a dense but *strongly oscillatory* manifold of levels from a lower state of similar geometry. In diradicals the situation is similar insofar as the flat or even convex nature of the singlet surface also creates a manifold of *oscillating* vibrational wave functions which must mix with those of the triplet. In aromatics intersystem crossing requires 10^{-8} to 10^{-6} seconds; intersystem crossing rates in diradicals should be of the same order. Only for a singlet diradical lying in a secondary minimum, for which the Franck-Condon overlap with triplet levels (that of two displaced oscillators) might be significant, could the intersystem crossing be enhanced.

Thus introduction of significant overlap occurs at the expense of the intersystem crossing probability, because of the destruction of diradical state pair degeneracy and orbital axis orthogonality. There are, however, cases where ionic character can be significant even though the overlap is small or zero, and in spite of the triplet-singlet proximity. These cases correspond to zwitterionic states (Section 2.4) which are not too far removed from the covalent triplet. One such example is pyramidalized face-to-face trimethylene *(15a)*. The pyramidalization does not destroy the singlet-triplet degeneracy[10] and introduces ionic character into the ground-state singlet. Unfortunately, however, the odd orbitals axes now point nearly toward each other, a less favorable orientation than in *(15d)* trimethylene (compare with Figure 10b).



(15d) good orbital orientation, poor ionic character → *(15a)* poor orbital orientation, good ionic character

A second obvious example is the one-center heterosymmetric diradical methylene where ionic character is predominant in the lowest singlet, the odd orbitals are orthogonal, and where the matrix element ξ^{π}_{AB} is a large one-center term (see Section 3.4).

3.4. The Electronic Factor in the Heterosymmetric Case

In the heterosymmetric case (Section 2.2) the spin-orbit coupling matrix elements vanish between the covalent diradical singlet and the covalent diradical triplet. The reason is simply (Section 3.2) that no angular-momentum-inducing electronic transition is possible from ϕ_A to ϕ_B. For instance in the face-to-edge trimethylene *(15b)*, even though the orbital orientation is favorable, the lack of ionic character in the singlet forbids intersystem crossing.

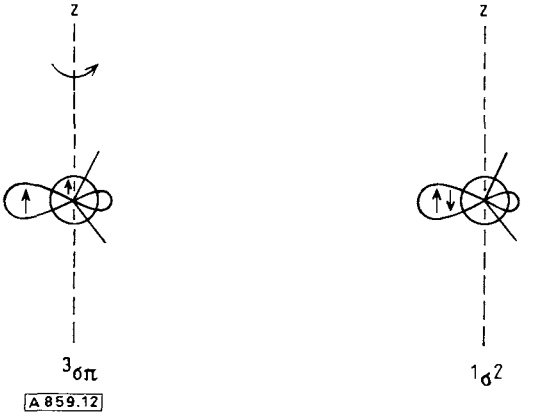


Fig. 12. Spin orbit coupling in methylene.

[*] This value has been calculated according to the procedure of *Coulson* [40] (see also Table 3). The constant (19) is included in this value of $Z\xi^{\pi}_{AB}$.

Non-zero matrix elements occur only between the diradical triplet and a *zwitterionic* singlet. Thus intersystem crossing should be relatively facile in species such as *(17a)* and *(17b)* in an edge-to-face configuration [similar to *(15b)*, see Scheme 8b].

A particularly favorable situation holds in methylene, where the lower singlet has strong ionic character (Scheme 7) and where the orthogonality of the σ and π odd orbitals ensures the creation of angular momentum around the axis which is perpendicular to both orbital directions. We chose this axis as z axis (Figure 12). A calculation similar to that in Section 3.2 then yields (see Table 2, H_z) a spin-orbit coupling matrix element

$$A = 2\sqrt{2}\,Z\hbar(\mu - \sqrt{1-\mu^2})\,\xi_{AA} \tag{22}$$

where $100\,\mu^2$ is the percentage of σ^2 character in the lowest singlet and where the one-electron integral

$$\xi_{AA} \equiv \left\langle x_A \left| \frac{1}{r_A^3} l^A \right| y_A \right\rangle$$

is equal to $\zeta^3/3$ for a Slater 2p orbital with exponent ζ. For $\mu \approx 1$ and choosing for Z the effective value $2\zeta = 3.25$ we get, with (19),

$$A = 37.9\ \mathrm{cm}^{-1} \tag{23}$$

for the singlet-triplet mixing, which is in good agreement with previous results[42]. This large mixing relative to the two-center case [eq. (21)]—compare the relative sizes of ξ_{AA} and ξ^{π}_{AB}—has led *Basch* and *Chang* to predict[43] that triplet and singlet methylene could equilibrate in 10^{-12} s. However, their calculation depends on a doubtful coincidence of vibronic states[36]; furthermore such rapid mixing seems to be at variance with the fact that singlet and triplet methylene have distinct chemistries[44].

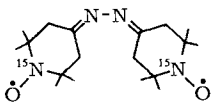
3.5. Other Mechanisms for Intersystem Crossing

In the absence of spin-orbit coupling matrix elements larger than $\approx 0.001\ \mathrm{cm}^{-1}$ (30 MHz)—for instance for extremely weakly coupled electrons of the type studied in Section 1.1—other mechanisms can induce intersystem crossing. The most common mechanism is the hyperfine interaction between the electron spins and nuclear spins, which arises from the Hamiltonian [eq. (24)]. This Hamiltonian describes the scalar product of the spin $\mathbf{I}_i$

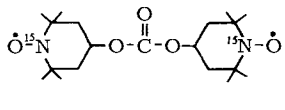
$$H_{hyp} = \sum_{\substack{\text{nuclei} \\ i}} a_i \mathbf{I}_i (\mathbf{S}_1 + \mathbf{S}_2) \tag{24}$$

of nucleus i with the spins $\mathbf{S}_1$ and $\mathbf{S}_2$ of both electrons. The factor a_i is the isotropic electron nuclear hyperfine coupling constant for nucleus i. Its order of magnitude is 30 MHz for carbon or nitrogen. Equation (24) represents the so-called Fermi contact term, which is responsible for nuclear spin-spin coupling as measured by NMR coupling constants and for the hyperfine structure of ESR spectra of radicals. It can also directly induce singlet-triplet mixing. This effect can be observed most simply in electron spin resonance, but also occurs in the now widespread phenomenon of chemically induced dynamic nuclear polarization or CIDNP.

The form of the ESR spectrum of a diradical such as *(21)* or *(22)* depends on the relative magnitude of a_N, the coupling constant for the ^{15}N nucleus, and of the *singlet-triplet energy separation J*. This energy difference J appears in another term of the Hamiltonian[45]:



(21)



(22)

$$H_{exchange} = -J\,\mathbf{S}_1 \cdot \mathbf{S}_2 \tag{25}$$

This term, which accounts for the exchange between the two electrons (*Dirac*'s "vector coupling model") is valid only for weakly coupled electron spins. In the approximation of weak overlap, the singlet-triplet energy difference J is equal to the valence-bond exchange integral[46]. This integral involves both the Coulombic repulsion of the electrons and their attraction for the opposite nuclear center. Now, if J is much larger than a, the ESR spectrum of two odd electrons coupled to a triplet and located on two ^{15}N nuclei shows 3 lines (Figure 13). The spectrum of *(21)* is of this type.

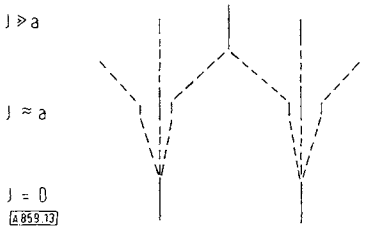


Fig. 13. ESR spectrum of two odd electrons centered on two ^{15}N nuclei [47]. $J \gg a$: triplet state; $J \approx a$: triplet-singlet mixing; $J = 0$: two doublet states.

If the singlet-triplet separation is no larger than a, then the spectrum divides into 6 lines (Figure 13, case $J \approx a$). Such a spectrum is shown by diradical *(22)*, in which the odd electrons are on the average further apart than in *(21)*. One can interpret the additional lines as being due to the admixture of singlet character into the originally pure triplet *via* the hyperfine interaction operator. Ultimately, if the odd electrons are even further apart, one has two totally independent odd electrons (a truly "double" radical); each electron contributes equally to the two ESR lines.

The same hyperfine-induced singlet-triplet mixing is responsible for the *dynamic nuclear spin polarization* (CIDNP) observed in chemical reactions proceeding *via* radical pairs[48]. The main features of CIDNP are:

1. The formation of a radical pair by thermal decomposition or photolysis. This radical pair can be derived either from a triplet state or a singlet state precursor:

$$T_{precursor} \rightarrow [A^{\bullet} \cdots {}^{\bullet}B] \qquad S_{precursor} \rightarrow [A^{\bullet} \cdots {}^{\bullet}B]$$

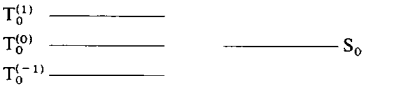
2. An alternative for the radical-pairs, either

a) diffuse with eventual secondary recombination to give products; or

b) collapse in a primary cage-recombination to give products.

While the diffusion process is independent of the nuclear spin states[49][*], the primary collapse process is not: *the intersystem crossing to a singlet electronic configuration, which is necessary to form a bound product occurs more efficiently for certain nuclear states.* NMR transitions involving these states will therefore be enhanced. It can be shown[50][**] that the net polarization observed for collapse of a pair derived from an S precursor is of opposite sign but of similar magnitude to that for a pair derived from a T precursor. Here we will treat the simplest possible case of a caged radical pair produced from a triplet state precursor with both odd electrons coupled to two neighboring protons.

In the presence of the external magnetic field of the NMR spectrometer the three triplet sublevels are largely split (Scheme 9) and one need consider only the (first-order) mixing of S_0, the singlet state, with $T_0^{(0)}$ the $(\alpha_1\beta_2+\beta_1\alpha_2)$ component of the triplet state. The effect of the nuclear spin-electron spin coupling is to induce transitions between the *overall* (electron + nuclear) spin components. If the total



Scheme 9. States of a very loose diradical pair in an external magnetic field.

spin is $\mathbf{R}=\mathbf{S}+\mathbf{I}$, the selection rule is

$$\Delta R_z = 0 \tag{26}$$

for a magnetic field pointing along the z axis. Whence

$$\Delta\left(S_z + \sum_{\text{nuclei}} I_z^i\right) = 0 \tag{27}$$

Since S_z is zero in both states S_0 and $T_0^{(0)}$, $\Delta S_z = 0$ and eq. (27) yields

$$\Delta\left(\sum_i I_z^i\right) = 0 \tag{28}$$

[*] The true picture is actually complicated by the fact that the secondary encounters of radicals ($A^{\bullet}$, $B^{\bullet}$) with uncorrelated electron spins can also yield nuclear-polarized products [49a]. For the experimental discrimination between primary combination of a T pair and the combination from secondary encounters of free radicals, which has the same sign, but which could actually have originated from an S precursor, see [49b].

[**] The state of the diradical pair is a time-dependent singlet-triplet mixture; it is assumed that product formation at time t is proportional to the extent of singlet character at time t—itself a function of the situation at t = 0.

For two nuclei with spins 1/2 the only possibility is

$$\begin{cases} (I_z^1) & 1/2 \rightarrow -1/2 \\ (I_z^2) & -1/2 \rightarrow 1/2 \end{cases} \quad \text{or} \quad \begin{cases} -1/2 \rightarrow 1/2 \\ 1/2 \rightarrow -1/2 \end{cases}$$

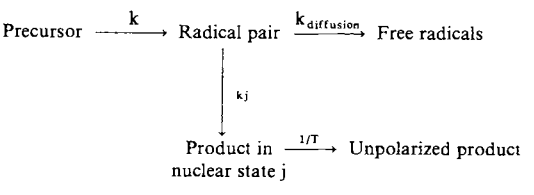
No transition is feasible if I_z^1 and I_z^2 are both equal to 1/2 or both equal to $-1/2$. The net result is a higher rate of formation of nuclear states with

$$I_z^1 + I_z^2 = 0$$

in the final product.

This result alone would not be sufficient to ensure a nuclear polarization. A competitive process which does not depend on the nuclear states is required. If the radical pairs can also separate by diffusion, the following kinetic scheme—in which k_j is the rate of formation of products in the j^{th} nuclear state—shows that the stationary concentration of product in nuclear state j is:

$$[P]_j = \frac{T k_j k [\text{Precursor}]}{k_j + k_d} \tag{29}$$



If k_d were zero, this concentration would clearly be independent of k_j and there would be no nuclear polarization.

Can CIDNP not then occur in an isolated molecular biradical species for which diffusion does not exist? The answer seems to be[51] that in those diradicals where S_0 lies slightly below $T_0^{(0)}$ and is accidentally degenerate with $T_0^{(-1)}$, the selection rule (27) allows a *direct flip of the overall nuclear spins via* the condition

$$\Delta S_z = 1, \qquad \Delta\left(\sum_i I_z^i\right) = -1 \tag{30}$$

Condition (30) can be satisfied if the triplet-singlet mixing in the diradical is accompanied by a $+1/2$ to $-1/2$ nuclear spin flip for only one proton. Thus the product is created with excess $-1/2$ nuclear spins, and NMR emission is observed[51] although there is no competitive kinetic process.

4. Evidence for and against Singlet or Triplet Diradicals as Secondary Minima ("Reaction Intermediates") on Potential Energy Surfaces

The idea that the formation of a diradical by bond breakage is accompanied by electronic rearrangement in the new species, with concomitant energy stabilization, is a common one in Organic Chemistry. Diradicals have been thought to represent small energy minima on the potential energy

surface from the mother-species to the ultimate product. Thermochemical estimates of the heats of formation of diradicals generated by small hydrocarbon ring pyrolysis are consistently smaller than the experimental activation energies for the reactions[52]. The diradical could therefore be a "resting point" which would immediately follow the transition state. The failure to intercept any such diradical by radical scavengers could be accounted for by its short life-time (10^{-10} s) and high local monoradical concentration (10 mol/l)[19].

Kinetic schemes using intermediate diradicals, such as

Ring ⇄ Diradical → Decomposition products
(Structural isomerization)

or

cis-Substituted ring ⇄ Diradical ⇄ *trans*-Substituted ring
(Geometrical isomerization)

give reasonable agreement with experiment[52, 53]. (Such schemes would be meaningless if there were no steady-state concentration of diradicals in the process.) Similarly, for bimolecular reactions, the evidence from reaction order measurements for intermediates accompanied by "dips in the energy profile" is impressive[54][*]. It is therefore tempting to believe that diradicals do lie in secondary minima on the potential energy surfaces which lead to their recombination products, with a "barrier to reclosure" to these products.

The first blow to this well-accepted implication came from the calculations by *Hoffmann et al.* on the tetramethylene diradical[55]. These extended Hückel calculations yield a smooth potential surface with only *one* maximum between cyclobutane and the ethylene decomposition products (Figure 14). No secondary minimum is found on the many-

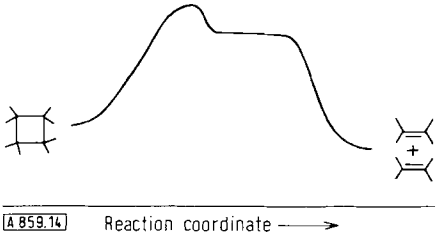
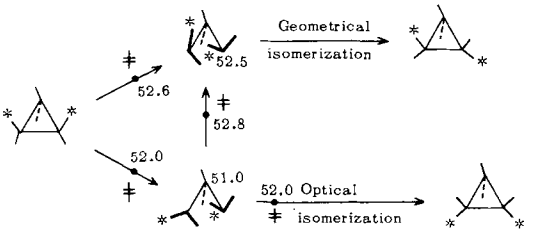


Fig. 14. Energy profile along the reaction coordinate for decomposition of cyclobutane [55].

dimensional potential energy surface. However, the computations do show a very *flat* region in many-dimensional space. This flatness would induce the system in this region—coined "twixtyl"—to spend a relatively long time "exploring" its way out. Such a large, energetically flat region of coordinate space might be "operationally indistinguishable, in its effects on the rate constant, in the possibilities it offers for interception and diversion, from a true minimum"[55]. These results are of course quite startling. However, in view of the approximate nature of the calculations, their failure to discriminate between singlet and triplet, and the low thermochemical estimate (<4 kcal/mol[52]) for the "barrier" to decomposition these novel features awaited confirmation in other cases[**].

Such confirmation now seems to be forthcoming[14][***]. "*A priori*" self consistent field calculations with a minimal basis set of Slater orbitals have been carried out on the potential energy surface for geometrical isomerization of cyclopropane. Both the singlet surface and the triplet surface in the region of the trimethylene diradicals *(15a)* to *(15d)* have been investigated. The reaction path from the closed ring to its geometrical isomer through the region of the resolved transition state climbs monotonically and then goes down again. No energy dip of significance (>0.5 kcal/mol) has been found on the *singlet surface*[14]. Since there is little reason to believe that intersystem crossing occurs in *(15a)* (Section 3.3) or *(15b)* (Section 3.4) which are typical configurations adopted by the molecule along this pathway, it must be concluded that the geometrical isomerization of cyclopropane is a *one-step* reaction.

It is true that structure *(15c)* is found to be in a shallow (≈1 kcal/mol) minimum on the path to optical isomerization, in agreement with *Hoffmann*'s previous calculations[12]. However, the path leading from *(15c)* to *(15b)*—which is required to obtain geometrical isomerization—seems at best just competitive with the direct pathway from cyclopropane to *(15b)*, as shown in Figure 15.



(15c)

Fig. 15. Pathways and energies for geometrical and optical isomerization of cyclopropane [14]. The numbers refer to "*a priori*" calculated energies; ‡ indicates a transition state. The lowest-energy conformations of *(15b)* and *(15c)* have been drawn.

Thus the system does not seem to be required to "stop and rest" in an energy dip. In analyzing these results, however, it is essential to keep in mind that the calculated energies have been obtained in a minimal basis set calculation. Improved "*a priori*" calculations may be seriously at variance with ours, with significant changes in the location and geometry of the extrema.

On the triplet state surface, things seem to be entirely different. The trimethylene diradical in its various conformations corresponds to the region where the triplet state energy is lowest (for a comparison with ethylene, see Figures 3b and 7). It is found[14] that this minimal region lies

[*] *Note that in* [54a] *none of the quoted intermediates is a diradical;* but there are numerous cases of zwitterions, see also [54b].

[**] *R. Hoffmann*, Yale Symposium on Theoretical Analysis of Reaction Pathways (December 1970), was confident that a secondary minimum would be found for trimethylene, in spite of his own results on tetramethylene [55].

[***] *P. J. Hay, W. A. Goddard III*, and *W. J. Hunt*, J. Amer. Chem. Soc., in press, have independently obtained evidence against a secondary minimum in the geometrical isomerization of cyclopropane.

consistently below the singlet surface by 3.5 to 4.5 kcal/mol both for structures *(15b)*, *(15c)* and for intermediate conformations. This is no surprise (Section 2.1, end) since the molecular orbitals of *(15c)* are nearly degenerate[12] while *(15b)* is a heterosymmetric diradical obeying Scheme 6. The overall energy profile along the reaction coordinate for geometrical isomerization can then be described as in Figure 16.

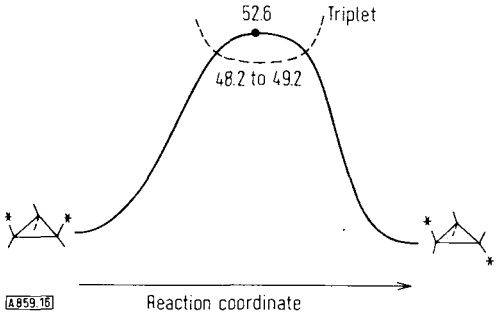


Fig. 16. Energy profile along the reaction coordinate for geometrical isomerization of cyclopropane [14].

If the reactant were to fall onto the triplet surface after reaching the transition state it would certainly become a "reaction intermediate" in the usual sense. But in the absence of favorable intersystem crossing it will simply ignore this lower pathway[*].

In the light of the results for both tetramethylene and trimethylene, what is left of the earlier interpretation of diradicals as reaction intermediates? In our view, the thermochemical estimates of diradical energies and kinetic properties seem to remain valid *only if applied to triplet states*. In trimethylene, for instance, the energy difference of 4.4 kcal/mol between the lowest triplet conformation (48.2 kcal/mol) and the transition state (52.6 kcal/mol) is in not unreasonable agreement with *Benson*'s estimate of 8.2 kcal/mol—which may be somewhat too generous[19]—for the "barrier to reclosure" of the trimethylene intermediate. Thus the thermochemical calculations remain useful if one is careful to keep this spin restriction in mind. Triplet intermediates may actually be quite common in non-concerted reactions of the "anti-Woodward-Hoffmann" type. *Pople* has shown that the lowest energy route through an orbital energy crossing region is *via* the triplet state[56].

Finally, what are the chances of finding a diradical *singlet* in a secondary minimum? We regard these chances as slim[**].

A lowering of energy in the singlet state of a diradical requires that the system be able *to achieve electron pairing without recombination of the radical termini*. In appropriate systems this can occur by acquisition of zwitterionic character[54] *via* electron-pairing on one of the termini. However, the energy minimum is then a zwitterionic state (Scheme 8) or a mixture rather than a true diradical state. In unsubstituted neutral hydrocarbons for which such zwitterionic pairing is costly, the best potential candidates as intermediates should resemble *(15c)*, in which the odd orbitals ϕ_A and ϕ_B are poorly oriented for direct bond closure and in which some ionic character subsists in the ground state (Scheme 4a). However, the energy stabilization of *(15c)* is probably restricted by the fact[12] that the lower of the two molecular orbitals, in which the electrons would tend to pair, is actually antibonding between ϕ_A and ϕ_B. In most cases, therefore, and unless appropriate substituents induce zwitterionic character, one can expect rather flat singlet surfaces without significant minima.

The authors are extremely grateful to the numerous colleagues and friends who did not begrudge them either advice or wisdom: Paul Bartlett, Mustafa El-Sayed, Bill Gelbart, George Hammond, Roald Hoffmann, Martin Karplus, Luitzen Oosterhoff, John Pople, and Stuart Rice. They are also greatly indebted to Dr. H. H. Westen for critical reading of the German and English manuscripts.

Received: June 15, 1971 [A 859 IE]
German version: Angew. Chem. *84*, 86 (1972)

[*] There is some evidence for the cyclopropane surface *that the geometry corresponding to the equilibrium structure of the triplet state is very close to that for the transition state on the singlet surface.* We suspect that this may be generally true for diradicals. Some justification can be given as follows: the transition state and the triplet both belong to a family of structures in which some bond is totally broken. By definition the transition state is the lowest energy member of that family (*i. e.* that structure for which all other energy contributions, such as steric effects, which are not involved in the reaction coordinate, are optimized)—apparently within the singlet manifold; whereas the equilibrium triplet is the lowest energy member of the family in the triplet manifold. Since these other factors should not be very spin-dependent, the two geometries—transition state and equilibrium triplet—should be very similar. The authors are grateful to Dr. *Warren Hehre* for a discussion of this point.

[**] We exclude from this discussion the possible stabilization of the two odd electrons *via* delocalization over adjacent unsaturated bonds.

[1] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[2] a) For the general properties of organic radicals, see *A. R. Forrester, J. M. Hay*, and *R. H. Thomson*: Organic Chemistry of Stable Free Radicals. Academic Press, New York 1968; b) For a study of thermally generated diradicals, see *P. D. Bartlett*, Quart. Rev. Chem. Soc. *24*, 473 (1970); *P. D. Bartlett*, Science *159*, 833 (1968); c) For a study of photochemically generated diradicals, see *P. J. Wagner* and *G. S. Hammond*, Advan. Photochem. *5*, 21 (1968).

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

[4] *A. E. Chichibabin*, Ber. Dtsch. Chem. Ges. *40*, 1810 (1907); *H. M. McConnell*, J. Chem. Phys. *33*, 115 (1960); *H. D. Brauer, H. Stieger, J. S. Hyde, L. D. Kispert*, and *G. R. Luckhurst*, Mol. Phys. *17*, 4571 (1969); *W. J. van der Hart* and *L. J. Oosterhoff, ibid. 18*, 281 (1970); *H. D. Brauer, H. Stieger*, and *H. Hartmann*, Z. Phys. Chem. *63*, 50 (1969).

[5] *R. M. Dupeyre, H. Lemaire*, and *A. Rassat*, J. Amer. Chem. Soc. *87*, 3771 (1965).

[6] *R. Hoffmann, A. Imamura*, and *W. J. Hehre*, J. Amer. Chem. Soc. *90*, 1499 (1968); *D. L. Wilhite* and *J. L. Whitten, ibid. 93*, 2858 (1971). For the stabilization of singlet diradicals by appropriate substitution, see, for instance, *R. Hoffmann*, Chem. Commun. *1969*, 240.

[7] *G. N. Lewis* and *M. Kasha*, J. Amer. Chem. Soc. *66*, 2100 (1944).

[8] *A. J. Merer* and *R. S. Mulliken*, Chem. Rev. *69*, 639 (1969).

[9] *E. Wasserman*, J. Amer. Chem. Soc. *92*, 7491 (1970); *E. Wasserman, V. J. Kuck, R. S. Hutton, E. D. Anderson*, and *W. A. Yager*, J. Chem. Phys. *54*, 4120 (1971).

[10] For *(15a)* see *Y. Jean* and *L. Salem*, Chem. Commun. *1971*, 382.

[11] For *(15b)*, see *L. Salem*, Bull. Soc. Chim. France *1970*, 3161.

[12] For *(15c)* see *R. Hoffmann*, J. Amer. Chem. Soc. *90*, 1475 (1968).

[13] For recent experimental evidence, see the review by *R. G. Bergman* and *W. L. Carter*, J. Amer. Chem. Soc. *91*, 7411 (1969).

[14] *Y. Jean, L. Salem, J. S. Wright, J. A. Horsley, C. Moser*, and *R. M. Stevens*, Pure Appl. Chem. Suppl. (23rd Congress) *1*, 197 (1971); *J. A. Horsley, Y. Jean, C. Moser, L. Salem, R. M. Stevens*, and *J. S. Wright*, J. Amer. Chem. Soc. *94*, 279 (1972).

[15] *R. Hoffmann, S. Swaminathan, G. Odell*, and *R. Gleiter*, J. Amer. Chem. Soc. *92*, 7091 (1970). For recent experimental evidence see a) *J. A. Berson, D. C. Tompkins*, and *G. Jones Jr., ibid. 92*, 5799 (1970); b) *F. D. Lewis* and *T. A. Hilliard, ibid. 92*, 6672 (1970); c) *L. M. Stephenson* and *J. I. Brauman, ibid. 93*, 1988 (1971).

[16] *E. Müller* and *H. Neuhoff*, Ber. Dtsch. Chem. Ges. *72*, 2063 (1939).

[17] *D. Cazes*, Thèse de 3e Cycle, Faculté des Sciences d'Orsay 1971.

[18] *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971).

[19] *G. R. Freeman*, Can. J. Chem. *44*, 245 (1966).

[20] *P. O. Löwdin*, Advan. Chem. Phys. *2*, 207 (1959).

[21] *W. Kołos* and *L. Wolniewicz*, J. Chem. Phys. *43*, 2429 (1965); *45*, 5091 (1966); *50*, 3228 (1969).

[22] *T. H. Dunning, W. J. Hunt*, and *W. A. Goddard*, Chem. Phys. Lett. *4*, 147 (1969).

[23] *C. Herring* in *G. Rado* and *H. Suhl*: Magnetism. Academic Press, New York, 1966, Vol. II B, p. 1.

[24] *M. H. Alexander* and *L. Salem*, J. Chem. Phys. *46*, 430 (1967).

[25] *J. F. Harrison* and *L. C. Allen*, J. Amer. Chem. Soc. *91*, 807 (1969).

[26] For energy patterns similar to Scheme 7 and 8 b, see *J. F. Harrison*, J. Amer. Chem. Soc. *93*, 4112 (1971).

[27] *E. F. Hayes* and *A. K. Q. Siu*, J. Amer. Chem. Soc. *93*, 2090 (1971).

[28] The authors are grateful to *Y. Jean* for the calculation of these curves.

[29] *E. W. Yankee* and *D. J. Cram*, J. Amer. Chem. Soc. *92*, 6331 (1970).

[30] See *C. E. Wulfman* and *S. Kumei*, Science *172*, 1061 (1971).

[31] *W. G. Espersen* and *R. Kreilick*, J. Amer. Chem. Soc. *92*, 3894 (1970).

[32] *F. A. Matsen* and *D. J. Klein*, Advan. Photochem. *7*, 1 (1969).

[33] *W. Kauzmann*, Quantum Chemistry. Academic Press, New York 1957, p. 36.

[34] For this essential factor in radiationless transitions see *J. Jortner, S. A. Rice*, and *R. M. Hochstrasser*, Advan. Photochem. *7*, 149 (1969).

[35] *G. W. Robinson*, J. Chem. Phys. *47*, 1967 (1967); *L. G. Anderson* and *C. S. Parmenter*, J. Chem. Phys. *52*, 466 (1970).

[36] *T. W. Eder* and *R. W. Carr*, J. Chem. Phys. *53*, 2258 (1970).

[37] a) *H. E. Hunziker*, J. Chem. Phys. *50*, 1288 (1969); *D. W. Setser, B. S. Rabinovitch*, and *J. W. Placzek*, J. Amer. Chem. Soc. *85*, 862 (1963); b) *P. J. Kropp, ibid. 91*, 5783 (1970).

[38] *M. Jones*, private communication to the authors (1970).

[39] *S. P. McGlynn, T. Azumi*, and *M. Kinoshita*: Molecular Spectroscopy of the Triplet State. Prentice-Hall, 1969, Chapter 5 and Appendix 1.

[40] *C. A. Coulson*, Proc. Camb. Phil. Soc. *38*, 210 (1942).

[41] *H. F. Hameka* and *L. J. Oosterhoff*, Mol. Phys. *1*, 358 (1958).

[42] *R. F. W. Bader* and *J. I. Generosa*, Can. J. Chem. *43*, 1631 (1965). Their ζ is equal to $Z\xi_{AB}$ here.

[43] *T. Y. Chang* and *H. Basch*, Chem. Phys. Lett. *5*, 147 (1970).

[44] *J. A. Bell*, Progr. in Phys. Org. Chem. *2*, 1 (1964).

[45] *P. A. M. Dirac*: The Principles of Quantum Mechanics. Clarendon Press, Oxford 1958, 4th edit., pp. 222ff.

[46] *C. A. Coulson*: Valence. Oxford University Press, 1961, 2nd edit., p. 120.

[47] *J. R. Briere, R. M. Dupeyre, H. Lemaire, C. Morat*, and *A. Rassat*, Bull. Soc. Chim. France *1965*, 3290.

[48] A far from exhaustive list of references should include *J. Bargon* and *H. Fischer*, Z. Naturforsch. *22a*, 1551, 1556 (1967); *H. R. Ward* and *R. G. Lawler*, J. Amer. Chem. Soc. *89*, 5518 (1967); *G. L. Closs* and *L. E. Closs*, J. Amer. Chem. Soc. *91*, 4549, 4550 (1969); *G. L. Closs, ibid. 91*, 4552 (1969); *G. L. Closs* and *A. D. Trifunac, ibid. 92*, 2183, 2186, 7227 (1970); *G. L. Closs, ibid. 93*, 1546 (1971); *R. Kaptein* and *L. J. Oosterhoff*, Chem. Phys. Lett. *4*, 195 (1969); *R. Kaptein, J. A. den Hollander, D. Antheunis*, and *L. J. Oosterhoff*, Chem. Commun. *1970*, 1687; *M. Tomkiewicz* and *M. Cocivera*, Chem. Phys. Lett. *8*, 595 (1971); *E. Lipmaa, T. Pehk, A. L. Buchachenko*, and *S. V. Rykov*, Chem. Phys. Lett. *5*, 521 (1970); *J. L. Charlton* and *J. Bargon*, Chem. Phys. Lett. *8*, 442 (1971); *F. J. Adrian*, J. Chem. Phys. *54*, 3912 (1971); *H. Fischer*, Topics in Current Chem. *24*, 1 (1972).

[49] a) *G. L. Closs* and *A. D. Trifunac*, J. Amer. Chem. Soc. *92*, 2186 (1970); b) *R. Kaptein, J. A. den Hollander, D. Antheunis*, and *L. J. Oosterhoff*, Chem. Commun. *1970*, 1687.

[50] *G. L. Closs* and *A. D. Trifunac*, J. Amer. Chem. Soc. *91*, 4554 (1969); *92*, 2183 (1970).

[51] *J. F. Garst, R. H. Cox, J. T. Barbas, R. D. Roberts, J. I. Morris*, and *R. C. Morrison*, J. Amer. Chem. Soc. *92*, 5761 (1970).

[52] *S. W. Benson*, J. Chem. Phys. *34*, 521 (1961); *S. W. Benson* and *H. E. O'Neal*, J. Phys. Chem. *72*, 1866 (1968); *S. W. Benson*: Thermochemical Kinetics. Wiley, New York 1968, Section 3.10.

[53] *J. A. Berson* and *J. M. Balquist*, J. Amer. Chem. Soc. *90*, 7343 (1968); *R. G. Bergman* and *W. L. Carter*, J. Amer. Chem. Soc. *91*, 7411 (1969).

[54] a) *R. Huisgen*, Angew. Chem. *82*, 783 (1970); Angew. Chem. internat. Edit. *9*, 751 (1970); b) *H. Hermann, R. Huisgen*, and *H. Mäder*, J. Amer. Chem. Soc. *93*, 1779 (1971).

[55] *R. Hoffmann, S. Swaminathan, B. Odell*, and *R. Gleiter*, J. Amer. Chem. Soc. *92*, 7091 (1970).

[56] *J. A. Pople*, to be published.

Structure of Ion Pair Solvation Complexes[**]

By Johannes Smid[*]

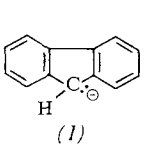
In solvents of low polarity, salts containing a carbanion, e.g. fluorenylsodium, or a radical anion, e.g. coronenesodium, can exist as contact ion pairs or as solvent separated ion pairs. Particular interest attaches to the complexes of ion pairs with the strongly solvating, polydentate polyglycol dimethyl ethers (glymes) and with crown compounds. These systems can be studied by optical spectroscopy, NMR spectroscopy, and other methods.

1. Introduction

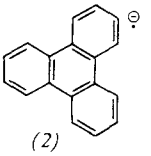
Ionic reactions in media of low dielectric constant often show a complex behavior, largely because of the variety of forms in which the reacting ionic species can exist; *e.g.*, free ions, ion pairs, triple ions, quadrupoles, and higher aggregates. Each of the species may react with its own characteristic rate constant and stereospecificity, and frequently a rapid dynamic equilibrium may exist between two or more ionic species. Such equilibria are often strongly affected, not only by the structure of the reacting ion, but also by the type of counterion, the solvent polarity, the presence of ion-coordinating additives, and the temperature.

Unraveling the complex reactivity behavior of ionic reactions in low polarity media requires, therefore, a knowledge of the structure and solvation state of the existing ionic species. A variety of techniques such as electron spin resonance, nuclear magnetic resonance, electrolytic conductance, ultraviolet, visible, infrared, and Raman spectroscopy and still other methods have been used over the past decade to study the structure of ion pairs and their solvation complexes. The most detailed information has probably been obtained from electron spin resonance studies, particularly as it relates to dynamic phenomena involving the association of ions or solvation of ion pairs. Ultraviolet and visible spectroscopy, on the other hand, is not limited to paramagnetic molecules like the ESR methods, and is also attractive because of its simplicity. Furthermore, high concentrations of reagents are not required, which is often a limiting factor in infrared and nuclear magnetic resonance studies.

In this discussion we shall mainly concern ourselves with the optical and nuclear magnetic resonance spectra of solvation complexes of ion pairs of carbanions and radical anions. It should be pointed out at this stage that a solvent may affect the optical spectrum of a neutral molecule or ionic species in a variety of ways. For example, spectra of pyridinium iodides are very sensitive to a change in solvent polarity, and *Kosower* has shown that the solvent sensitive transition involves a transfer of negative charge from the iodide anion to the pyridinium cation[1,2]. The solvent stabilization of the ground state is therefore lost in the excited state, leading to blue shifts in the more polar solvents. Optical spectra of inorganic and quaternary ammonium iodide salts were studied by *Symons*[3-5] and found to be solvent sensitive. The transition involved appears to result from the transfer of an electron from the iodide anion to the surrounding solvent cage. In another interesting case the optical spectrum of retinylpyrrolidinium perchlorate was shown to be strongly affected by polarizable solvents such as pyridine or dichlorobenzene, but not by a change in polarity of nonpolarizable solvents[6]. The bathochromic shift in the more polarizable solvents was attributed to a stabilization of the greatly delocalized excited state of this conjugated chromophore. The Frank-Condon principle disallows stabilization of the excited state by the much slower solvent-solute reorganization, and polarity itself, therefore, does not affect the transition.



(1)



(2)

The spectra of carbanions and radical ions, when present as free ions, are generally very little affected by a change in solvent polarity. For example, the absorption maxima of the free fluorenyl anion are identical in tetrahydrofuran, pyridine, dimethyl sulfoxide, and hexamethylphosphoramide. However, spectral changes are observed when the radical ions or carbanions are present as ion pairs, due to the perturbation caused by the counterion. The extent of this perturbation depends on the nature of the counterion and its solvation. The observed spectral changes can therefore be utilized to study the interaction of solvents or complexing agents with the counterion and to shed more light on the structure of the ion pair solvation complexes.

The salts of fluorenyl anions are particularly suitable for these types of investigations, as their optical spectra are characterized by sharp absorption bands, and the association with a cation causes a considerable hypsochromic shift, dependent on the cation radius. Moreover, the fluorenyl carbanion not only functions as a convenient optical probe for studying ion pair solvation, it also can be used

[*] Prof. Dr. J. Smid
Chemistry Department, State University of New York,
College of Forestry,
Syracuse, New York 13210 (USA)

[**] The following abbreviations will be used:
DME = dimethoxyethane
DMSO = dimethyl sulfoxide
2-Me-THF = 2-methyltetrahydrofuran
THF = tetrahydrofuran
THP = tetrahydropyran
TMEDA = tetramethylethylenediamine
TMS = tetramethylsilane.

in nuclear magnetic resonance studies. A complexing agent coordinated to the cation will be in the proximity of the aromatic fluorenyl anion, and its protons, therefore, are considerably shifted upfield due to the diamagnetic anistropy. Even more interesting shifts are observed with solvation complexes of certain aromatic radical anion pairs; some of these cases will also be discussed.

In our discussion of ion pair structures we shall frequently use the terms contact and solvent separated ion pairs or tight and loose ion pairs. The latter terminology suggests that more than two kinds of ion pairs may be visualized. For example, the average interionic distance in a contact ion pair may vary depending on the temperature and the type of solvent. Different structures can also be visualized for separated ion pairs, depending on the size and geometry of the complexing molecule. In fact, the distinction between a tight and loose ion pair may depend on the method of investigation.

An interesting example of this was recently found in the behavior of the solutions of triphenylenesodium in 2-methyltetrahydrofuran[7] which contain the radical anion *(2)*. This radical anion pair reveals a sodium coupling in its electron spin resonance spectrum, but the coupling disappears below $-50\,^{\circ}C$, implying a change to a loose ion pair structure. However, the optical spectrum of the ion pair salt remains identical down to $-80\,^{\circ}C$, but changes to that characteristic of the loose ion pair below this temperature. This example points to the necessity of using a variety of methods when studying the structure and properties of ion pairs.

2. Ion Pairing in Fluorenyl Salts

One of the earliest reports on shifts in optical spectra arising from ion pairing concerns a study of the spectra of alkali and alkaline earth salts of ketyls by *Warhurst et al.*[8], who observed bathochromic shifts on increasing the radius of the cation. Similar effects were reported by *Hogen Esch* and *Smid*[9, 10] for fluorenyl and other carbanion salts and by *Zaugg* and *Schaefer*[11] for alkali salts of phenols and enols. Tight ion pairs are involved in all these cases, and the bathochromic shifts can be rationalized by assuming that an enlargement of the cation size causes a greater destabilization of the ground state than of the excited state. A redistribution of charge occurs on excitation, and the cation, while close to the carbon of highest charge density in the ground state, is not allowed to readjust itself on account of the Frank-Condon principle. The transition frequency, therefore, becomes larger as the cation decreases in size. Since the perturbation of the molecular orbital levels of the anion by the cation is largely electrostatic in nature[8], it is not surprising to find that the transition frequencies are roughly proportional to the reciprocal of the cation radius r_c. This is depicted for fluorenyl salts in Figure 1. A similar relationship was observed for enols[11], while for ketyls a linear correlation of the frequency is found with the reciprocal of the function $r_c + 2$, the constant being the contribution of the anion to the interionic distance[8].

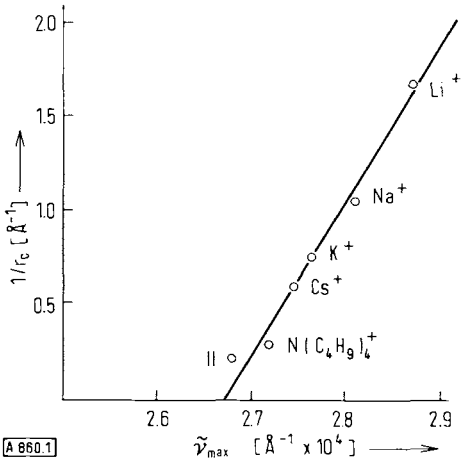


Fig. 1. Correlation between wave number and the inverse of the cationic radius for contact fluorenyl ion pairs in THF at 25 °C. || = solvent separated ion pair.

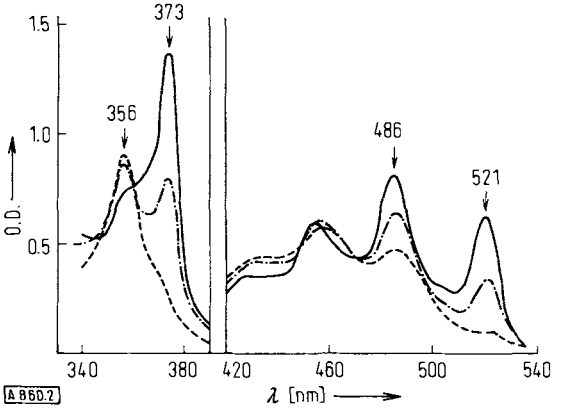


Fig. 2. Optical absorption spectrum of fluorenylsodium in THF at 25 °C (– – –), −30 °C (–·–·–), and −50 °C (——). Cell length 0.0283 cm (left-hand part of spectrum) and 0.208 cm (right-hand part).

Spectrophotometric evidence for the existence of two kinds of ion pairs was first obtained for fluorenyl salts in ethereal solvents. The spectrum of fluorenylsodium in THF at 25 °C (Fig. 2) shows a sharp absorption band at 356 nm, which is replaced at lower temperatures by a new band emerging at 373 nm. Similar changes are observed in the visible region of the spectrum. The change is reversible, and the ratio of the peak heights is independent of the carbanion concentration and is not affected by addition of Na^+ ions. The spectral changes can only be rationalized by postulating a dynamic equilibrium between tight ion pairs (fluorenyl$^-$,M$^+$) and loose ion pairs (fluorenyl$^-$||M$^+$), with the latter being favored at low temperatures[10]:

$$F^-, M^+ + nS \rightleftharpoons \text{fluorenyl}^-\|M^+ \qquad (1)$$

The driving force for the formation of the separated ion pairs is essentially the coordination of solvent molecules, S, with the cation. It makes this ion pair equilibrium a particularly suitable probe for quantitative studies of cation interactions with solvating molecules and their effects on ion pair structures and reactivities.

2.1. Effect of Cation

The ion pair equilibrium (1) is strongly affected by the nature of the cation[10]. Figure 3 shows spectra of fluorenyllithium, -sodium, and -cesium in THF at −30 °C. Solvation of the large Cs^+ ion is weak, and only contact ion pairs are found, even at −70 °C; a similar behavior is observed for the potassium and tetrabutylammonium salts. The sodium salt has approximately equal fractions of the two kinds of ion pairs at −33 °C, while the Li salt is found to exist as a separated ion pair below 0 °C. Usually, the proportion of separated ion pairs decreases along the series Li, Na, K, Cs, but this may change for polydentate solvating species such as polyglycol dimethyl ethers or macrocyclic polyethers.

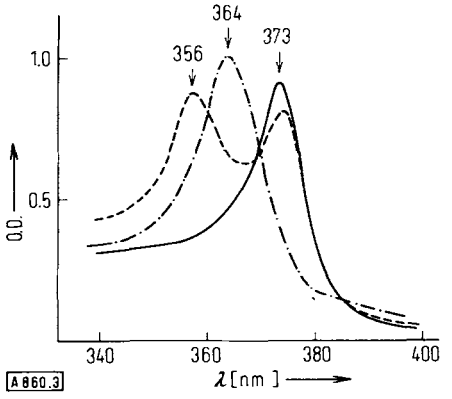


Fig. 3. Absorption spectrum of fluorenyl salts in THF at −30 °C as a function of counterion Li^+ (——), Na^+ (– – –), and Cs^+ (–·–·).

2.2. Effect of Polarity and Structure of Solvent

The equilibrium between tight and loose ion pairs is often drastically affected by the polarity and structure of the solvent[10, 12]. Typical examples are given in Figure 4.

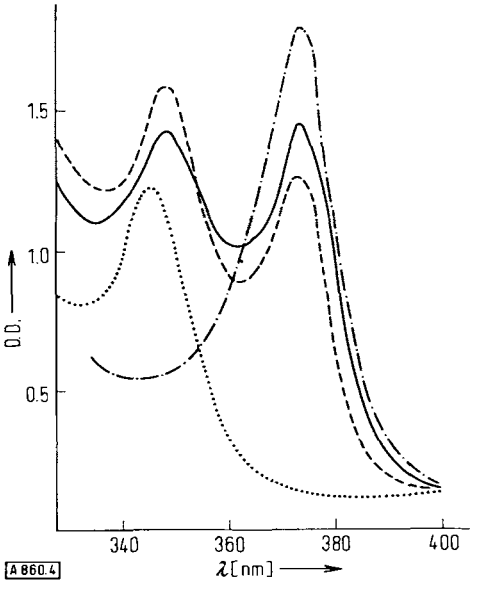
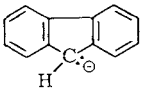


Fig. 4. Optical spectra of contact and separated ion pairs of fluorenyllithium *(1)*Li^+ at 25 °C in 3,4-dihydropyran (·····), 3-methyltetrahydrofuran (– – – –), 2,5-dihydrofuran (——), and hexamethylphosphoramide (–·–·–).

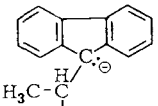
Generally, the separated ion pair maximum at 373 nm is unaffected by a change in solvent polarity. For example, no change is found where tetrahydropyran is replaced by dimethyl sulfoxide or hexamethylphosphoramide. The carbanion transition as such appears, therefore, unaffected by solvent polarity, and the spectral changes can be entirely attributed to the solvent induced separation of the ions. In certain amines[13] changes in the absorption maximum of the separated ion pair have been found, and carbanion solvation may be responsible here[14].

Small bathochromic shifts in the contact ion pair maxima are often noticeable when the solvent polarity is increased, especially with strong complexing agents such as hexamethylphosphoramide or macrocyclic polyethers. External solvation of the contact ion pair is the probable cause of this phenomenon, and it will be discussed in more detail when dealing with the polyethers (Section 4).

The ratio of the concentrations of the two types of fluorenyl ion pairs in a given solvent at a fixed temperature can be calculated from a knowledge of the absorption spectra of the individual ion pairs. This quantity K_i^* provides a measure of the effectiveness of the solvent in complexing the respective cations. Values of K_i^* for a series of unsubstituted cyclic ethers and substituted tetrahydrofurans are given in Tables 1 and 2, respectively. Fluorenyllithium [*(1)*Li^+] and 9-(1-methylpentyl)fluorenyllithium [*(3)*Li^+] were employed as the ion pair salts.



(1)



(3)

For the unsubstituted cyclic ethers the effectiveness of forming separated ion pairs appears to be directly related to the basicity of the respective ring oxygen atom, with the exception of oxepane. The latter compound is reported to be more basic than THF[15] but it appears to be less effective in forming solvent separated ion pairs. When bulky substituents are present close to the coordination site, as in certain substituted tetrahydrofurans, packing in the solvation shell becomes a critical factor. Basicity, as measured by the proton affinity of the ether, is less affected by the structure of the ether since only one solvent molecule is involved. The alkali ion in the solvent separated ion pair, however, is coordinated to several solvent molecules, and steric factors like those observed with substituted tetrahydrofurans become important and are amplified when small cations are used. For example, in 3,3-dimethyloxetane the ratio of separated to contact ion pairs for fluorenyllithium and fluorenylsodium are 1.2 and 0.6 respectively, while in THF the values are much farther apart, *viz.*, 4.6 and 0.05. In oxetane itself both salts exist as loose ion pairs. The lower value in oxepane as compared in THF is also most likely due the larger molar volume of the former solvent.

The behavior of 2-(methoxymethyl)tetrahydrofuran and *o*-dimethoxybenzene exemplifies the importance of chelation. This appears to be most effective when the oxygen atoms are separated by two carbon atoms[16] as in the

Table 1. Solvent separated ion pair formation for fluorenyllithium *(1)*Li^+ and 9-(1-methylpentyl)fluorenyllithium *(3)*Li^+ in unsubstituted cyclic ethers at 25 °C. K_i^* is the ratio of loose to tight ion pairs.

Solvent	K_i^* for *(1)*Li^+	K_i^* for *(3)*Li^+
Oxetane [a]	> 50	—
Tetrahydrofuran	4.6	> 50
Tetrahydropyran	0.45	20
Oxepane	0.24	2.3
2,5-Dihydrofuran	1.1	50
3,4-Dihydropyran	0.01	0.14
Furan	< 0.01	0.02
Dioxolane	0.08	10
Dioxane	0.01	0.3

[a] The lithium salts of fluorenyl anions were not stable in oxetane. The value listed for oxetane represents that of fluorenylsodium which is stable in this solvent.

Table 2. Solvent separated ion pair formation for fluorenyllithium *(1)*Li^+ and 9-(1-methylpentyl)fluorenyllithium *(3)*Li^+ in substituted tetrahydrofurans and some other solvents at 25 °C. K_i^* is the ratio of loose to tight ion pairs.

Solvent	K_i^* for *(1)*Li^+	K_i^* for *(3)*Li^+
Tetrahydrofuran	4.6	> 50
3-Methyltetrahydrofuran	0.85	> 50
2-Methyltetrahydrofuran	0.33	1.50
2,5-Dimethyltetrahydrofuran	0.02	0.07
2,5-Dimethoxytetrahydrofuran	0.04	
2-(Methoxymethyl)tetrahydrofuran	> 50	
3,3-Dimethyloxetane	1.2	> 50
o-Dimethoxybenzene	> 50	
m-Dimethoxybenzene	0.01	
Hexamethylphosphoramide	> 50	

linear polyglycol dimethyl ethers. These solvating agents will be discussed later.

Shatenshtein[17,18] has shown that the formation of biphenyllithium from biphenyl and lithium in a series of ethers decreases in the order DME ≈ THF > THP > dioxolane > dioxane. The order of decreased formation of the sodium salt of biphenyl or naphthalene is DME > THF > dioxolane > 2-MeTHF ≈ THP > dioxane. In the method developed by *Shatenshtein* the solvation involves both tight and loose ion pairs. On the other hand, the method involving the ion pair equilibrium of fluorenyl salts measures the difference in solvation state between the two kinds of ion pairs. Steric factors may affect the solvation state of the two ion pairs in a different way, and one anticipates that different approaches of measuring the solvating power of organometallic reagents will not always give identical results.

The higher basicity of the amines as compared to that of ethers facilitates ion pair separation in the former solvents and certain amines can therefore be classified as powerful alkali metal complexing agents. Small quantities of ethylenediamine can convert fluorenyllithium and -sodium contact ion pairs into amine separated pairs[13]. In pyridine both salts exist as loose ion pairs at room temperature[10], and the same is observed for the lithium salt in cyclohexylamine[19]. Tetramethylethylenediamine (TMEDA), known as an excellent complexing agent for organolithium reagents in hydrocarbon solvents[20,21], turns out to be a poor solvent separating agent[13]. Apparently it easily complexes externally to the contact ion pair, as indicated by the much higher solubility of fluorenyllithium in TMEDA as compared to hydrocarbon solvents. But the bulky methyl groups hinder the ion pair separation, which probably requires two TMEDA molecules.

2.3. Effect of Temperature and Pressure

The formation of separated ion pairs of carbanions or radical anions from the contact ion pairs is usually exothermic[10,22]. An example of this is found in Figure 5, showing the transformation of 9-(1-methylpentyl)fluorenyllithium *(3)*Li^+ in 2,5-dimethyltetrahydrofuran from a predominantly contact ion pair structure at −20 °C to that of a loose structure at −40 °C. Although there appears to be an isosbestic point, it is usually not expected for temperature dependent ion pair transformations, because on lowering the temperature the extinction coefficients of the absorption maxima of the two kinds of ion pairs often increase in a different way while simultaneously the two spectral bands are narrowed. Calculation of the ion pair fractions as a function of temperature must take these changes into account.

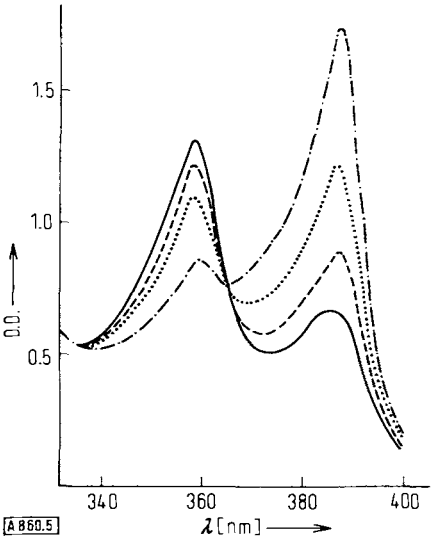


Fig. 5. Temperature dependence of the equilibrium between contact and solvent separated ion pairs of 9-(1-methylpentyl)fluorenyllithium in 2,5-dimethyltetrahydrofuran at −20 °C (——), −26 °C (– – –), −31 °C (···), and −41 °C (–·–·).

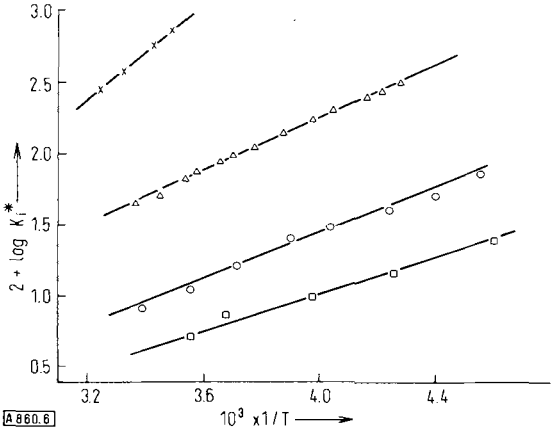


Fig. 6. Plots of log K_i^* *versus* $1/T$ for fluorenyllithium *(1)*Li^+ in tetrahydrofuran (×–×), tetrahydropyran (□–□), 1,3-dioxolane (○–○), and 2,5-dimethoxytetrahydrofuran (□–□).

The enthalpy change ΔH_i for a number of solvents (as calculated from the respective slopes of plots of $\log K_i^*$ *versus* $1/T$, some of which are shown in Fig. 6) are collected in Table 3[40]. In the absence of specific ion-solvent interactions the enthalpy change for the separation of two ions is given by

$$\Delta H = Ne^2(1 + d\ln D/d\ln T)/aD$$

a being the ion pair distance before separation and D denoting the macroscopic dielectric constant[23]. The ion pair separation is expected to be exothermic for a negative value of $(1+d\ln D/d\ln T)$. This is the case in THF, DME, and 2-Me-THF, the respective $d\ln D/d\ln T$ values being -1.16, -1.28, and -1.12[24, 25]. But the calculated exothermicities would amount to only a few kcal/mol, even at a comparatively short interionic distance. Moreover, the separation in THP is expected to be essentially thermoneutral, as $d\ln D/d\ln T = -0.97$[22]. The observed ΔH_i values imply, therefore, that specific ion pair solvation must be the major contributing factor to the exothermicity of the ion pair separation equilibrium. Once the ion pair is in the solvent separated state, further dissociation into free ions is usually described reasonably well by the above Denison-Ramsey relationship[24, 26]. For example, the dissociation of the macrocyclic polyether separated ion pair of fluorenylsodium in THF is found to be thermoneutral[27].

Table 3. Enthalpy and entropy changes for solvent separated ion pair formation from the contact ion pairs, considered for fluorenyllithium *(1)*Li^+ and 9-(1-methylpentyl)fluorenyllithium *(3)*Li^+.

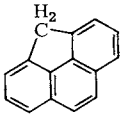
Solvent	*(1)*Li^+		*(3)*Li^+	
	$-\Delta H_i$ (kcal/mol)	$-\Delta S_i$ (e. u.)	$-\Delta H_i$ (kcal/mol)	$-\Delta S_i$ (e. u.)
2,5-Dimethoxy-tetrahydrofuran	2.9	16	—	—
2,5-Dimethyl-tetrahydrofuran	2.0	14	10.0	50
Dioxolane	3.5	17	—	—
3,4-Dihydropyran	3.0	16	8.2	33
Tetrahydropyran	6.6	28		
Tetrahydrofuran	7.5	22		
2-Methyl-tetrahydrofuran	7.5	27	9.8	32
Dioxane-tetrahydrofuran (50%)	3.6	14		
Dioxane-tetrahydrofuran (28%)	—	—	11.0	36
Oxepane	4.3	16		

No simple relationship between ΔH_i and solvent structure is to be expected. The total enthalpy change is determined by the coulombic interactions between the two ions in both the tight and loose ion pair, and by physical and specific solvation of the two ion pair species. The extent of specific solvation is closely related to the structure of the solvent molecules, and the latter may affect the solvation of the two ion pairs in a different way (*e.g.*, the solvation of fluorenyllithium by tetramethylethylenediamine). Also, dielectric saturation must be taken into account in calculating coulombic interactions. Generally, tighter contact ion pairs are expected in less polar solvents, resulting in lower exothermicities. Steric hindrance in the contact ion pair would also lead to small enthalpy values. It is therefore surprising to find such high negative ΔH_i values for the 9-alkylfluorenyllithium *(3)*Li^+. The corresponding sodium salt gives—ΔH_i values which are less than those of fluorenylsodium. An explanation for the peculiar behavior of the lithium salts may be the possible existence of higher aggregates for the planar fluorenyllithium ion pairs in ethereal solutions[12, 28].

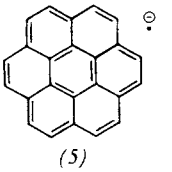
Increased pressure was found to shift the ion pair equilibrium to the separated pair[29, 30]. The observed volume contraction, -16.4 ml/mol for fluorenyllithium in THF and -24.2 ml/mol for fluorenylsodium, results from a tight binding of solvent molecules around the cations in the loose ion pairs. The smaller value for the lithium salt was interpreted to indicate a higher degree of solvation for the tight lithium ion pair as compared to that of the sodium salt[30].

2.4. Effect of Anion Structure

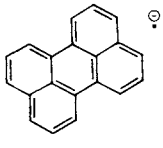
The simultaneous existence of tight and loose ion pairs has been observed spectrophotometrically for many carbanions and radical anions. In some cases, as with salts of the triphenylmethyl anion, only an absorption shift rather than distinctly separated absorption bands are observed. Such shifts cannot always be taken as evidence for the existence of chemically distinct ion pairs. *Szwarc et al.*[31] have pointed out that the fluctuating environment of the solvating molecules affects the vibrational motion of the ions in the ion pair. A broad potential energy well may be visualized with the two ions vibrating between the two extreme interionic distances characterizing the tight and loose ion pair. The potential energy as function of the interionic ion pair distance is temperature dependent, and while tight ion pairs may exist at high temperature, more favorable solvation at lower temperature can gradually increase the interionic distance. Physical properties of the ion pairs depending on this distance, such as the optical spectra, will then undergo a gradual change with temperature, and do not result from the superposition of the properties of two distinct species. This type of ion pair behavior may often be encountered in systems with large counterions, with steric hindrance in the contact ion pair, or in low polarity solvents, *i.e.*, in cases where the potential energy barrier separating the tight and loose ion pair is expected to be low.



(4)



(5)



(6)

Charge delocalization facilitates ion pair separation, and this accounts for the higher fraction of separated ion pairs found for the benzofluorenylsodium salts (derived, *e.g.* from benzo[*b*]- and benzo[*c*]fluorene) as compared to fluorenylsodium[10]. The same is observed with 4,5-methano-

phenanthrene (≡ benzo[*def*]fluorene) *(4)*. Studies carried out on salts containing the anion of this fluorene derivative[32] show effects of solvent, counterion, and temperature which closely parallel those obtained for the fluorenyl salts. Other examples of the effect of charge delocalization on ion pair separation can be found in the behavior of the aromatic radical anion salts. Both optical and conductance data clearly reveal a strong increase in the fraction of separated ion pairs as the hydrocarbon structure allows more charge delocalization in the radical anion. Salts such as triphenylenesodium *(2)* Na^+[7, 22, 33], coronenesodium *(5)* Na^+[34], and perylenesodium *(6)* Na^+[22] are separated ion pairs in THF at 25 °C, while the salts of naphthalene and biphenyl are contact ion pairs[10, 35].

Large substituents on the anion lower the stability of the contact ion pair. A typical example can be found in the behavior of the sodium salt of the monoradical anion of tetraphenylethylene[36–38] where the four phenyl groups are twisted out of the plane of the double bond, preventing a close approach of the Na^+ ion. The optical spectra and conductance behavior of this salt in THF demonstrate that separated ion pairs exist between 25 and −70 °C. The structure of the dianion of this hydrocarbon, however, permits a close contact between positive and negative ion, as free rotation around the single bond puts the two $C(C_6H_5)_2$ groups in two mutually perpendicular planes. The dianion is a tight ion pair in THF at 25 °C, with the proportion of loose ion pairs increasing rapidly at lower temperature. Its behavior resembles that of the dianion of 1,1,4,4-tetraphenylethylene[10] and that of the diphenylhexyl anion[39]. Steric hindrance in the triphenylmethyl anion contact ion pair results in higher fractions of separated ion pairs than found with salts of the diphenylmethyl anion[40].

Tight ion pairs are expected to be stable in ethereal solutions of alkoxides, even in solvents such as dimethoxyethane. Solvents of high dielectric constant would favor free ion formation more than that of separated ion pairs, as the latter process is less dependent on dielectric constant. Cation complexing reagents such as macrocyclic ethers or DMSO could possibly induce formation of loose ion pairs in solvents such as THF. However, the tendency of alkoxides to aggregate[60] complicates the study of these systems.

3. Complexation of Polyglycol Dimethyl Ethers to Ion Pairs

In solvents such as ethylenediamine, hexamethylphosphoramide, or polyglycol dimethyl ethers, most fluorenyl salts form only separated ion pairs. The complexation of these powerful solvating agents to ion pairs can be studied by adding small quantities of the complexing agent to a solution of the fluorenyl ion pair in a solvent in which the salt predominantly exists as a contact ion pair.

Because of their polydentate structure, polyglycol dimethyl ethers or glymes of the general formula $CH_3O(CH_2CH_2O)_xCH_3$ are of special interest as coordinating agents of ion pairs[35, 41–43]. Their ability to complex with alkali metal ions depends on the number of available

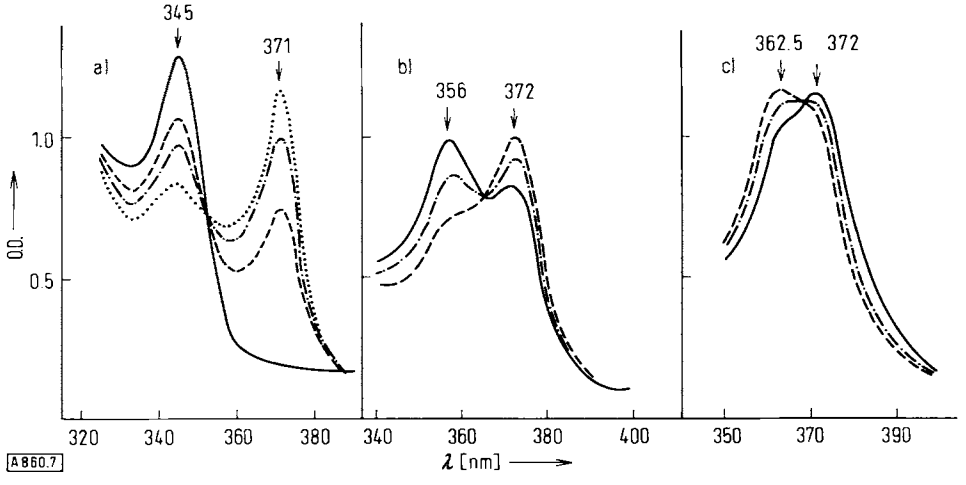


Fig. 7. Spectral changes on addition a) of glyme-4 to fluorenyllithium (≈ 1.5×10^{-3} M in dioxane), b) of glyme-6 to fluorenylsodium (≈ 2×10^{-3} M in THF), and c) of glyme-7 to fluorenylpotassium (5×10^{-4} M in THF).
$[glyme\text{-}4]_0 = 0.0$ (——), 6.46×10^{-3} (– – –), 11.3×10^{-3} (–·–·–), and 24.3×10^{-3} mol/l (·····)
$[glyme\text{-}6]_0 = 1.34 \times 10^{-3}$ (——), 2.64×10^{-3} (–·–·–), and 4.32×10^{-3} mol/l (– – –)
$[glyme\text{-}7]_0 = 1.02 \times 10^{-3}$ (– – –), 2.78×10^{-3} (–·–·–), and 4.8×10^{-3} mol/l (——).

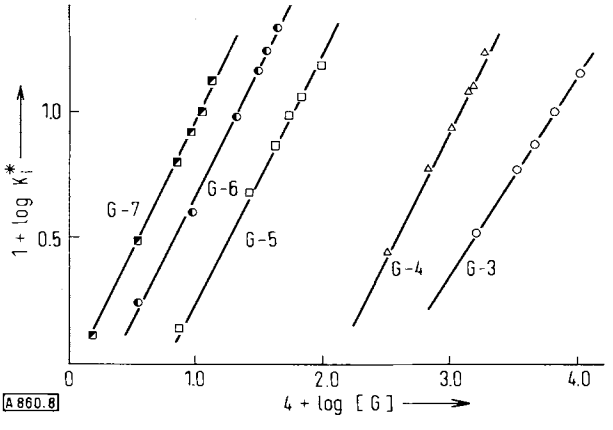


Fig. 8. Glyme separated ion pair formation of fluorenylsodium in THF at 25 °C with glyme-3 (G-3) to glyme-7 (G-7).

coordination sites. The spectral changes which one observes on addition of small amounts of glymes to a dioxane solution of fluorenyllithium or to a THF solution of fluorenylsodium or -potassium are shown in Figure 7. The glyme separated ion pair has an absorption maximum identical with that of the solvent separated ion pair. Plots of log K_i^* (K_i^* being the ratio of separated over contact ion pairs) *versus* log [G] ([G] being the concentration of glyme) for fluorenylsodium are shown in Figure 8, the slopes being equal or close to unity. The same linear relationships are observed with fluorenyllithium, and both results point to a simple complexation mechanism:

$$\text{fluorenyl}^-,M^+ + G \rightleftharpoons \text{fluorenyl}^-,G,M^+ \quad (K_i)$$

However, when the measurements are carried out under conditions such that the concentration of glyme is much greater than that of the fluorenyl ion pair (this is the case for the systems fluorenyl$^-$,Na$^+$-glyme-3, fluorenyl$^-$,Na$^+$-glyme-4, and fluorenyl$^-$,Li$^+$-glyme-3)[*], one cannot exclude the possibility that the contact ion pair is already coordinated to a glyme molecule, *i.e.*, fluorenyl$^-$,M$^+$,G. We will return to this point when discussing the results for fluorenylpotassium.

with combinations of five consecutive oxygen atoms linked by ethylene bridges[16], one expects an increase in the K_i for fluorenyl$^-$,Na$^+$ by a factor of 3 when glyme-7 is used instead of glyme-5[42,43]. The observed increase by a factor of 4.5 is slightly higher, and appears to accelerate for glymes of longer chain length such as glyme-9 and glyme-22 (average molecular weight 1000). There may be certain preferred conformations in the longer glymes which are favorable for cation complexation. Moreover, it is likely that combinations of coordination sites other than those involving consecutive oxygen atoms can form stable complexes with fluorenylsodium. It is also interesting to note that on addition of a tenfold excess of fluorenylsodium to glyme-22 the ratio of fluorenyl$^-$,G,Na$^+$ ion pairs to glyme-22 does not exceed the value two, indicating a maximum of two such pairs per chain[44].

The dielectric constant of the solvent usually does not affect K_i to any great extent, probably because dielectric saturation makes the effective dielectric constant considerably less than the macroscopic one. Also, while a less polar solvent yields a tighter contact ion pair, the removal of solvent molecules by the glyme will cost more energy in a polar solvent, and the two effects apparently largely compensate one another. On the other hand, the glyme

Table 4. Equilibrium constants for glyme-separated ion pair formation in solutions of fluorenylalkali metal salts at 25 °C. $K_i = [\text{fluorenyl}^-,G,M^+]/[\text{fluorenyl}^-,M^+]\,[G]$

Glyme	x	K_i [a] for fluorenyllithium [b]	K_i [a] for fluorenyllithium [b]
DME	1	0.055 ($n=2.4$)	[c]
2-(Methoxymethyl)-THF		0.25 ($n=2$)	[d]
Glyme-3	2	3.1	1.2
Glyme-4	3	130	9.0
Glyme-5	4	240	170
Glyme-6	5		450
Glyme-7	6		800
Glyme-9	8		4800 [44]
Glyme-22	21, average		~25000 [44]

[a] All K_i values were calculated by taking $n=1$, except for DME ($n=2.4$) and 2-(methoxymethyl)tetrahydrofuran ($n=2$).
[b] Dioxane was used as solvent for the lithium salt, THF for the sodium salt.
[c] No titration carried out; proportion of solvent separated ion pairs at 25 °C is about 90% in pure DME.
[d] At room temperature only solvent separated ion pairs in the pure solvent.

The complexation constants for fluorenyllithium and -sodium are given in Table 4. For the lithium salt, the constant K_i strongly increases with the number of oxygen atoms in the glyme up to glyme-4, and then appears to level off. This may indicate that a maximum of four oxygen atoms coordinate with one lithium ion. The K_i for the sodium salt levels off above glyme-5. Apparently, the weaker interaction with the larger Na$^+$ ion requires at least five oxygen atoms to give a complexation constant comparable with that found for the system fluorenyl$^-$,Li$^+$, glyme-4.

As the chain length increases beyond glyme-5, the complexation constant is expected to further increase for purely statistical reasons. Assuming that coordination only occurs

complexation constants may be entirely different in solvents where the ion pairs wholly or partially exist as loose ion pairs. An example can be found by comparing the complexation constants of glyme-4 with the following salts (all referring to THF as solvent, except fluorenyllithium, which was measured in dioxane):

fluorenyl$^-$,Li$^+$ + G-4 $\rightleftharpoons$ fluorenyl$^-$,G-4,Li$^+$	K =	130 l/mol
fluorenyl$^-$,Na$^+$ + G-4 $\rightleftharpoons$ fluorenyl$^-$,G-4,Na$^+$	K =	9 l/mol
coronene$^-$‖Li$^+$ + G-4 $\rightleftharpoons$ coronene$^-$,G-4,Li$^+$	K =	1 l/mol
coronene$^-$‖Na$^+$ + G-4 $\rightleftharpoons$ coronene$^-$,G-4,Na$^+$	K =	$>10^4$ l/mol

Both the lithium and sodium salt of the coronene radical anion exist as separated ion pairs in THF (the complexation constants in these cases were obtained from NMR measurements[34]). This leads to a high complexation constant for the sodium salt (as in sodium tetraphenylborate), whereas the removal of THF from the lithium ion requires a considerable amount of energy.

[*] The number behind each glyme refers to the number of oxygen atoms present in the molecule $CH_3O(CH_2CH_2O)_xCH_3$. This notation particularly emphasizes the analogy between the glymes and the crown compounds (Section 4). Names such as di- and triglyme, in which the multiplying prefix refers to x, are more commonly used.

The enthalpy change of glyme separated ion pair formation amounts to between -5 and -9 kcal/mol, and does not differ much from that found in THF, *i.e.*, -7.6 kcal/mol[42]. The effectiveness of glymes in solvating cations is clearly a result of a more favorable entropy change. In pure THF the change is about -30 e.u.[10], while only -14 to -18 e.u. for the glymes.

Complexation of glymes to fluorenylpotassium appears to be more involved. Plots of $\log K_i^*$ *versus* $\log[G]$ are strongly curved[42]. For glyme-6 and -7 the ratio $K_i^* = [\text{fluorenyl}^-,G,K^+]/[\text{fluorenyl}^-,K^+]$ reaches a constant value at higher glyme concentration. This behavior can be rationalized by postulating two competitive modes of complexation (also observed with mixtures of certain radical anion salts and glymes, see ref. [35]) producing glymated contact ion pairs and glyme separated ion pairs, respectively[42]:

$$\begin{array}{lll} \text{fluorenyl}^-,K^+ + G \rightleftharpoons \text{fluorenyl}^-,K^+,G & K_1 \\ \text{fluorenyl}^-,K^+ + G \rightleftharpoons \text{fluorenyl}^-,G,K^+ & K_i \\ \text{fluorenyl}^-,K^+,G \rightleftharpoons \text{fluorenyl}^-,G,K^+ & K_2 \end{array}$$

The experimental quantity $K_i^* = [\text{fluorenyl}^-,G,K^+]/[\text{fluorenyl}^-,K^+ + \text{fluorenyl}^-,K^+,G]$ is now given by

$$\frac{1}{K_i^*} = \frac{1}{K_2} + \frac{1}{K_1 K_2 [G]}$$

Plots of $1/K_i^*$ *versus* $1/[G]$ for the systems fluorenyl$^-$,K$^+$ with glyme-6 and glyme-7 are indeed linear, as shown for glyme-6 in Figure 9, their slopes and intercepts yielding the complexation constants K_1 and K_2.

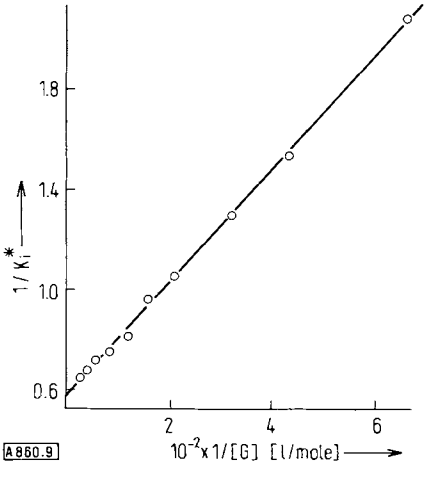


Fig. 9. Plots of $1/K_i^*$ *vs* $1/[\text{glyme}]$ for fluorenylpotassium in THF with glyme-6.

Similar plots for glyme-4 and glyme-5 are curved and extrapolate to the origin, *i.e.* $K_i^* \rightarrow \infty$ for sufficiently large glyme concentration. (This must also be true for glyme-6 and -7, as in the pure glymes only separated ion pairs are found.) This behavior can be explained by postulating a third complexation step in which the glymated contact ion pairs are converted to glyme-separated ion pairs by addition of a second glyme molecule:

$$\text{fluorenyl}^-,K^+,G + G \rightleftharpoons \text{fluorenyl}^-,G,K^+,G \quad (K_3)$$

The quantity K_i^* is now given by

$$K_i^* = \frac{K_2 + K_3[G]}{1 + 1/K_1[G]}$$

which reduces for $K_1[G] \gg 1$ to

$$K_i^* = K_2 + K_3[G]$$

Plots of K_i^* *versus* $[G]$ are indeed linear for glyme-4 and -5 in both THF and THP (see Fig. 10). This also means that in the concentration range of glyme needed to form glyme-separated ion pairs all fluorenylpotassium ion pairs are already externally coordinated with glyme-4 or glyme-5 (*i.e.*, $K_1[G] \gg 1$).

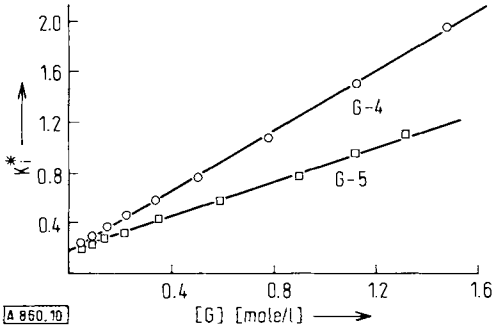


Fig. 10. Plots of K_i^* *vs* [glyme] for fluorenylpotassium in THF at 25 °C with glyme-4 and glyme-5 (G-4 and G-5) respectively.

Values of the various complexation constants K_1, K_2, K_3 of fluorenylpotassium with four glymes are collected in Table 5. Although only a lower limit for the K_1 values can be obtained for glyme-4 and glyme-5, it is probable that they are close to those observed for glyme-6 and glyme-7. Four or five oxygen atoms may be the maximum number that can be coordinated with a K$^+$ ion which is shielded on one side by a fluorenyl anion, and K_1 will only increase by a statistical factor on changing to glyme-6 or glyme-7.

Table 5. Equilibrium constants for glyme-coordinated ion pair formation of fluorenylpotassium in THF and THP at 25 °C. The concentration of fluorenylpotassium lies between 1×10^{-4} and 5×10^{-4} mol/l.

Glyme	Medium	K_1 (l/mol)	K_2	K_3 (l/mol)
Glyme-3	THF	—	0	0.21
Glyme-4	THF	>50	0.24	2.27
	THF [a]	>50	0.30	2.2
	THP	>50	0.18	1.2
Glyme-5	THF	>50	0.35	1.07
	THF [a]	>50	0.28	0.92
	THP	>50	0.18	0.69
Glyme-6	THF	250	1.75	—
Glyme-7	THF	530	2.5	—
	THP	1700	2.7	—

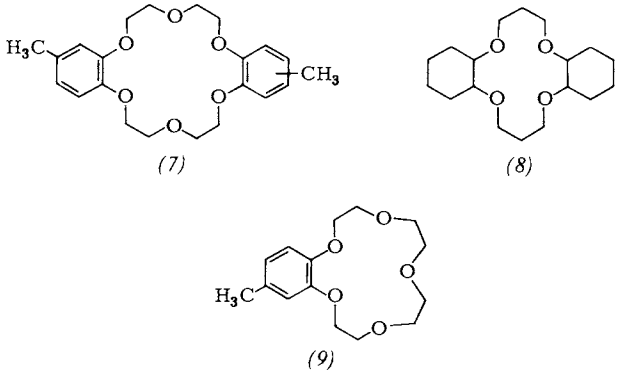
[a] Concentration of fluorenylpotassium $\approx 6 \times 10^{-3}$ mol/l.

The constant K_2 describing the equilibrium between glymated fluorenylpotassium contact ion pairs and glyme-separated ion pairs is small for glyme-4 and glyme-5 but sharply increases for higher glymes. Apparently, at least six oxygen atoms are needed to accomplish separation with the weakly interacting K$^+$ ion, and with glyme-4 and

glyme-5 this can be accomplished when two molecules are coordinated with the potassium ion. It is likely that at high glyme-6 or glyme-7 concentrations the fluorenylpotassium ion pair also contains two glyme molecules, as the ratio K_i^* does eventually increase to ∞. No values for the complexation constant K_3 were determined in these cases, but they may be even lower than the value found for glyme-5 if steric repulsion between the two complexed glyme molecules becomes an important factor.

4. Ion Pair Interactions with Macrocyclic Polyethers

Macrocyclic polyethers or crown compounds are much more effective in binding cations than the linear glymes due to their cyclic structure. A large number of crown compounds of different structure have recently been synthesized by *Pedersen*[45, 46] and some of them are shown below, *i.e.* dimethyldibenzo[18]crown-6 *(7)*, perhydrodibenzo[14]crown-4 *(8)*, and 4-methylbenzo[15]crown-5 *(9)*[*].



Crown compounds considerably improve the solubility of inorganic salts in low polarity solvents[45] and are known to affect the rate and stereochemistry of organometallic reactions[47]. They also are used as model compounds for ion carriers across biological membranes[48].

The stability of cation-crown complexes depends on the diameter of the cation relative to that of the polyether hole, the charge of the ion, the number of ring oxygen atoms, their basicity, coplanarity and symmetrical placement, steric hindrance in the polyether ring, and the nature of the solvent[45]. In most studies, methanol and water have been used as solvents[45, 48, 49] and the cations are not associated with the anions. With fluorenyl salts in ethereal solvents, the addition of crown compounds changes the ion pair structure, and generally the interaction follows the mechanism outlined for polyglycol dimethyl ethers (glymes)[50].

Ion pairs separated by crown compounds ($\lambda = 373$ nm) are formed on mixing of equimolar quantities of fluorenylsodium with dimethyldibenzo[18]crown-6, perhydrodibenzo[18]crown-6, and 4-methylbenzo[18]crown-6 in THF or THP[50]. The complexation constants are all higher than 5×10^6 l/mol, compared with a value of only 450 l/mol for the linear glyme-6. With 4-methylbenzo[15]crown-5 *(9)*[51], both separated fluorenyl$^-$,*(9)*,Na$^+$ ion pairs and contact ion pairs are formed (the latter species have their absorption maximum at 359 nm as compared to 354 nm for fluorenylsodium in THP). The ratio

$$K_i^* = [\text{fluorenyl}^-,(9),\text{Na}^+]/[\text{fluorenyl}^-,\text{Na}^+,(9)]$$

increases only slowly on addition of more *(9)*. This behavior is similar to that observed with fluorenylpotassium and glyme-6 or glyme-7, and is again indicative of two competing modes of complexation. Plots of K_i^* *versus* [C] (concentration of the crown compound) are shown in Figure 11, the intercept giving the complexation constant K_2 of the transformation

$$\text{fluorenyl}^-,\text{M}^+,\text{C} \rightleftharpoons \text{fluorenyl}^-,\text{C},\text{M}^+$$

The two isomers A and B of perhydrodibenzo[18]crown-6[49] also give a K_i^* value with fluorenylpotassium which is nearly independent of the crown concentration[51]. The

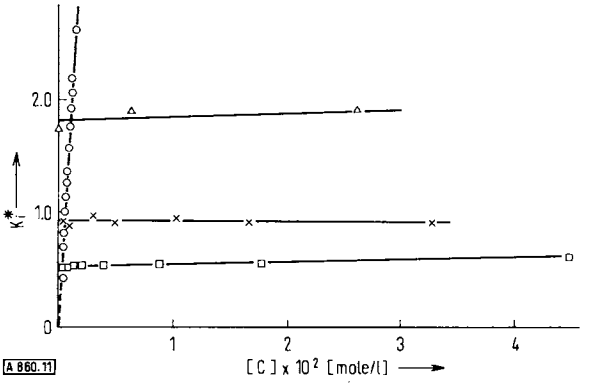


Fig. 11. Plots of K_i^* *vs* [crown] for the systems 4-methylbenzo[15]crown-5 *(9)*-fluorenylsodium in THF (△–△) and THP (□ – □), *(9)*-fluorenylpotassium in THF (○–○), and dimethyldibenzo[18]crown-6 *(7)*-fluorenylpotassium in THF (×–×); fluorenyl salt concentration $\approx 6 \times 10^{-4}$ mol/l.

system fluorenylpotassium-*(9)* deviates significantly from all other systems, and the strong rise in K_i^* with increasing concentration of *(9)* is evidence that a second molecule of *(9)* is complexed to fluorenyl$^-$,K$^+$,*(9)* forming the separated [fluorenyl$^-$,*(9)*,K$^+$,*(9)*] ion pair, similar to that observed with glyme-4 and glyme-5.

The respective complexation constants derived from plots of $1/K_i^*$ *versus* $1/[C]$ and plots of K_i^* *versus* [C] (for the pertinent equations see Section 3) are collected in Table 6. The solvent dependency of K_2, also found with glymes, can largely be attributed to solvent participation in the equilibrium

$$\text{fluorenyl}^-,\text{K}^+,\text{C} + n\text{S} \rightleftharpoons \text{fluorenyl}^-,\text{C},\text{K}^+,\text{S}_n$$

where S denotes a solvent molecule. Due to its planar conformation, complexation of a crown with fluorenyl$^-$,M$^+$

[*] The number preceding the word crown refers to the total number of atoms in the polyether ring, and the second number corresponds to the number of oxygen atoms—*(8)* is often incorrectly termed dicyclohexyl-14-crown-4.

ion pair does not necessitate removal of the entire solvation shell if the interaction leads to a separated ion pair (*i.e.*, if the cation occupies the center of the polyether hole). Hence, more polar solvents will shift the above equilibrium to the separated ion pair.

A smaller polyether ring favors formation of externally complexed contact ion pairs, particularly when the cation barely fits the hole of the crown. For example, with fluorenylsodium and the [15]crown-5 derivative *(9)*, the Na^+ ion may slightly protrude from the plane of the ring, with the oxygen atoms most probably in a nearly planar conformation such that an electron rich environment exists just above the ring. Such a structure would resemble that of the solid complex between perhydrodibenzo[18]crown-6 and rubidium thiocyanate[52, 53].

The existence of 2:1 complexes of [15]crown-5 compounds with fluorenylpotassium is in agreement with potentiometric measurements by *Frensdorff* who found 1:1 and 2:1 complexes of perhydrobenzo[15]crown-5 with free K^+ ions in methanol[49]. Moreover, this compound was shown to form a solid 2:1 complex with potassium iodide[54].

5. Competitive Complexation in Ion Pair Mixtures

When ion pair complexation constants are too high to measure spectrophotometrically (such as those of fluorenylpotassium and fluorenylsodium with dibenzo[18]crown-6), the use of ion pair mixtures can still yield information on the cation selectivity of the complexing agent. For example, when fluorenylsodium ($\lambda_m = 356$ nm) in THF is mixed with an equimolar quantity of the complex formed from fluorenylpotassium and dimethyldibenzo[18]crown-6 ($\lambda_m = 373$ nm), the polyether is immediately transferred to the fluorenylsodium ion pair as evidenced by the appearance of the fluorenyl$^-$,K^+ contact ion pair maximum at 362 nm:

fluorenyl$^-$,C,K^+	+ fluorenyl$^-$,Na^+	⇌ fluorenyl$^-$,C,Na^+	+ fluorenyl$^-$,K^+
λ_m = 373 nm	356 nm	373 nm	362 nm

The selectivity order of dimethyldibenzo[18]crown-6 as measured from this type of experiment was found to be $Na^+ > K^+ > Cs^+ > Li^+$[50]. A different order was found by *Pedersen*[45] and others[48, 49] in methanol and water for perhydrodibenzo[18]crown-6, *viz.* $K^+ > Cs^+ > Na^+ > Li^+$. Clearly, the selectivity order is solvent dependent, as can be shown by repeating the above experiment in oxetane, which is more basic than tetrahydrofuran. In oxetane, fluorenylsodium is a solvent separated ion pair ($\lambda_m = 373$ nm), and addition of fluorenyl$^-$,C,K^+ (C being dimethyldibenzo[18]crown-6) does not lead to a transfer of the polyether to the fluorenylsodium[50]. It apparently costs too much energy to remove the oxetane solvation shell around the Na^+ ion.

Table 6. Complexation constants [a] of macrocyclic polyethers with fluorenyl ion pairs in ethereal solvents at 25 °C.

Ion pair	Crown Compound	Solvent	K_1 $\times 10^{-3}$ (l/mol)	K_2	K_3 (l/mol)	K_i $\times 10^{-3}$ (l/mol)
Fluorenyl$^-$ Na^+	4-methylbenzo-[15]crown-5 *(9)*	THF	9.2	1.8	3.5	16.5
		THP	>20	.52	2.8	>10
	dimethyldibenzo-[18]crown-6 *(7)*	THF				>20000
		THP				>40000
	perhydrodibenzo-[18]crown-6	THP				>40000
Fluorenyl$^-$ K^+	4-methylbenzo-[15]crown-5 *(9)*	THF	≈ 5	≈0.2	1840	≈1
	dimethyldibenzo-[18]crown-6 *(7)*	THF	>10	0.93		>9
		THP	>10	0.55		>5.5
	perhydrodibenzo-[18]crown-6 A	THF	>30	1.80		>54
	perhydrodibenzo-[18]crown-6 B	THF	>40	0.80		>32

[a] Complexation constants refer to the following equilibria:

fluorenyl$^-$,M^+ + C ⇌ fluorenyl$^-$,M^+,C (K_1)
fluorenyl$^-$,M^+ + C ⇌ fluorenyl$^-$,C,M^+ (K_i)
fluorenyl$^-$,M^+,C ⇌ fluorenyl$^-$,C,M^+ (K_2)
fluorenyl$^-$,M^+,C + C ⇌ fluorenyl$^-$,C,M^+,C (K_3)

Recent studies[55] on the cation binding properties of polymers containing crown-5 groups demonstrated a pronounced increase in the efficiency of complexing large cations such as K^+ and Cs^+, compared to that of monomeric methylbenzo[15]crown-5. Cooperative effects between neighboring crown-5 groups enhance the formation of 2:1 complexes with the cations. It was also shown that the maximum number of fluorenylpotassium ion pairs that can be bound to the polymer is close to half that of the total number of available crown-5 units, whereas with fluorenylsodium each crown-5 unit can bind an ion pair[56].

The selectivity could also reverse on changing the temperature. For example, fluorenylsodium changes in THF from a contact ion pair at 25 °C to a separated ion pair at −70 °C, while the fluorenylpotassium ion pair remains a tight ion pair over this temperature range. Hence, the observed selectivity of the dibenzo[18]crown-6 with respect to the two fluorenyl salts (*i.e.*, $Na^+ \gg K^+$) may be reversed at low temperature.

It should also be realized that optical spectra may not always give correct information regarding the selectivity behavior of complexing agents. One can visualize reactions of the type

$$\text{fluorenyl}^-,C,M^+ + \text{fluorenyl}^-,M'^+ \rightleftharpoons \text{fluorenyl}^-\|M^+ + \text{fluorenyl}^-,M'^+,C$$

in which the complexing agent C is transferred to fluorenyl$^-$,M'^+ by external complexation while the fluorenyl$^-$,M^+ ion pair remains separated by acquiring a solvation shell of solvent molecules. No change in optical spectrum would be observed, except when fluorenyl$^-$,M'^+ and fluorenyl$^-$,M'^+,C have different absorption maxima.

Where ion pair solvation does not lead to changes in the optical spectra (*e.g.*, the tight and loose ion pair may have almost identical spectra) competition experiments are often useful. For example, information on complexation of glymes or crown compounds with salts such as sodium tetraphenylborate can be obtained by adding the salt to the glyme- or crown-separated ion pair of a fluorenyl salt:

$$\text{fluorenyl}^-,C,Na^+ + Na^+\|B(C_6H_5)^- \rightleftharpoons \text{fluorenyl},Na^+ + Na^+,C,B(C_6H_5)_4^-$$

when C is dimethyldibenzo[18]crown-6, one observes a change in the optical absorption maximum from 373 nm to 356 nm[50], the latter one being characteristic of the fluorenylsodium ion pair. Sodium tetraphenylborate is a separated ion pair in THF[58], and the crown compound, by removing (at least partially) the solvation shell of the Na^+ ion, now becomes associated with the $NaB(C_6H_5)_4$. The equilibrium constant for this reaction was found to be 2. The same experiment would fail in oxetane, since fluorenylsodium is a separated ion pair in this solvent. Hence, even if transfer of the crown to sodium tetraphenylborate took place, there would be no change in optical spectrum. In such cases, changes in the NMR spectrum of the bound complexing agent can give the desired information (see Section 7).

Other inorganic salts show similar effects, *e.g.*, addition of sodium perchlorate to the fluorenyl$^-$,C,Na^+ complex produces the fluorenyl$^-$,Na^+ ion pair. However, the equilibrium constant is only 0.04. Sodium perchlorate is a tight ion pair in THF (its conductance in THF is very low as compared to that of sodium tetraphenylborate[57, 58], and an efficient binding with the crown compound may require a considerable increase in the interionic distance in the ion pair.

6. Ion Pair Solvation of Fluorenyl Salts of Divalent Cations

The fluorenyl anion again provides us with a convenient system to study solvation and complexation to ion pairs of divalent cations. The salts can be prepared in liquid ammonia[14], but are also directly obtainable in THF (at least difluorenylbarium and -strontium) by reaction of a mixture of 1,1-diphenylethylene and fluorene in THF with a clean metal mirror under vacuum[59]. A THF solution of the barium salt shows a sharp absorption maximum at 347 nm (see Fig. 12) and even at −70 °C the proportion of

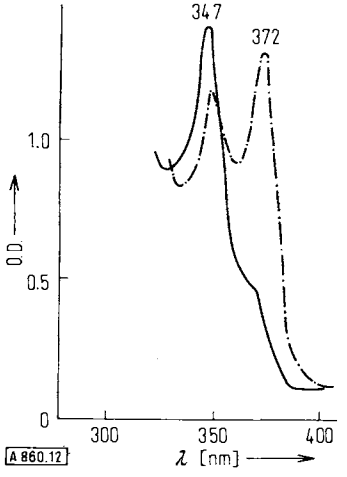


Fig. 12. Optical absorption spectrum of difluorenylbarium (——) and its 1:1 complex with dimethyldibenzo[18]crown-6 (–·–·) in THF at 25 °C.

loose ion pairs appears to be less than 10%. Since in the divalent salt the positive ion is probably sandwiched in between the two fluorenyl rings, the solvation of the cation is hindered, especially the external solvation of the contact ion pair. This is also reflected in the low dissociation constant for the equilibrium

$$Ba^{2+},(\text{fluorenyl}^-)_2 \rightleftharpoons (Ba, \text{fluorenyl})^+ + \text{fluorenyl}^-$$

the value in THF being 3×10^{-9} mol/l at 25 °C[59], compared to 6.2×10^{-7} mol/l and 1.6×10^{-7} mol/l, respectively, for the sodium and potassium salt[26]. The difluorenylbarium ion pair is probably a tighter ion pair than those of the alkali salts, and dissociation produces again a tight $(Ba^{2+},\text{fluorenyl}^-)^+$ ion pair which is only solvated on one side of the barium ion.

Higher fractions of separated ion pairs in THF are obtained with difluorenylstrontium. At −25 °C two absorption maxima of approximately equal height are observed at 344 nm and 373 nm[61]. The results show that the following equilibrium is established:

$$\text{fluorenyl}^-,Sr^{2+},\text{fluorenyl}^- \rightleftharpoons \text{fluorenyl}^-\|Sr^{2+},\text{fluorenyl}^-$$

the ΔH being about −12 kcal/mol. The free ion dissociation constant changes from 1.8×10^{-7} mol/l at 20 °C to 2×10^{-6} mol/l at −20 °C, the ΔH_d at 25 °C being close to −13 kcal/mol. The second ion pair solvation step, *i.e.*

fluorenyl$^-$||Sr^{2+},fluorenyl$^-$ ⇌ fluorenyl$^-$||Sr^{2+}||fluorenyl$^-$

probably occurs at a considerably lower temperature.

Ion pair separation can also be accomplished by adding complexing agents such as glymes or macrocyclic polyethers. The addition of dimethyldibenzo[18]crown-6 to difluorenylbarium in a 1:1 ratio in THF at 25 °C produces an optical spectrum of equal fractions of separated and contact ion pairs (see Fig. 12), and no change in this spectrum occurs on addition of more crown compound. A similar behavior is observed with glyme-6. Apparently the solvation with the crown compound or glyme is asymmetric, leading to species of the type fluorenyl$^-$,Ba^{2+},C,fluorenyl$^-$. It is also possible that the Ba^{2+} rapidly vibrates through the hole of the polyether ring as shown in Figure 13, with the ring conformation changing accordingly during the motion.

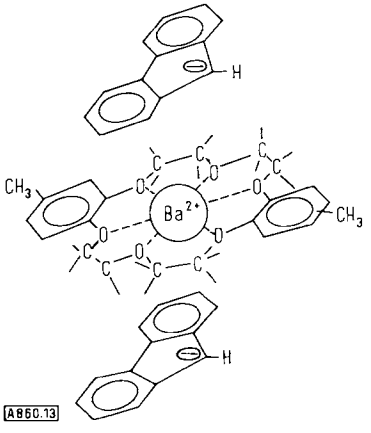
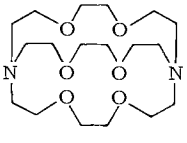


Fig. 13. Possible structure of the difluorenylbarium-dimethyldibenzo-[18]crown-6 complex in THF or pyridine.

Stable 1:1 complexes with difluorenylbarium and -strontium are formed on addition of the bicyclic amino polyether *(10)*, a powerful cation binding reagent, which has been synthesized recently by *Lehn et al.*[62,63].

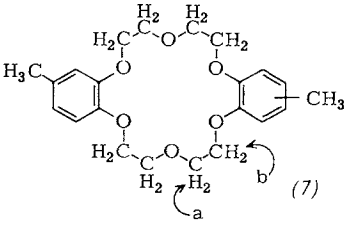


(10)

The spectra of these complexes in THF show only one absorption peak at 373 nm. This is not surprising since the cation is symmetrically surrounded by the amino polyether. Similar separated ion pair spectra of difluorenylbarium are found on addition of ethylenediamine or hexamethylphosphoramide, but it is not known whether a multistep solvation mechanism is involved.

7. NMR Studies of Ion Pair Complexation

Interactions of solvent molecules or complexing agents with ion pairs can also be studied by nuclear magnetic resonance. Only a few selected examples will be discussed, particularly those that provide supporting evidence for the spectrophotometric studies discussed in the previous sections. Ion pairs of fluorenyl salts and certain salts of aromatic radical anions are convenient systems for NMR investigations, since the complexing agents are brought into the close proximity of ions that will strongly affect their proton chemical shift. The use of NMR is particularly helpful in cases where complexation to the ion pair does not lead to changes in optical spectra, as in the complexation of glymes to ion pairs of coronenesodium in THF (see Section 3).



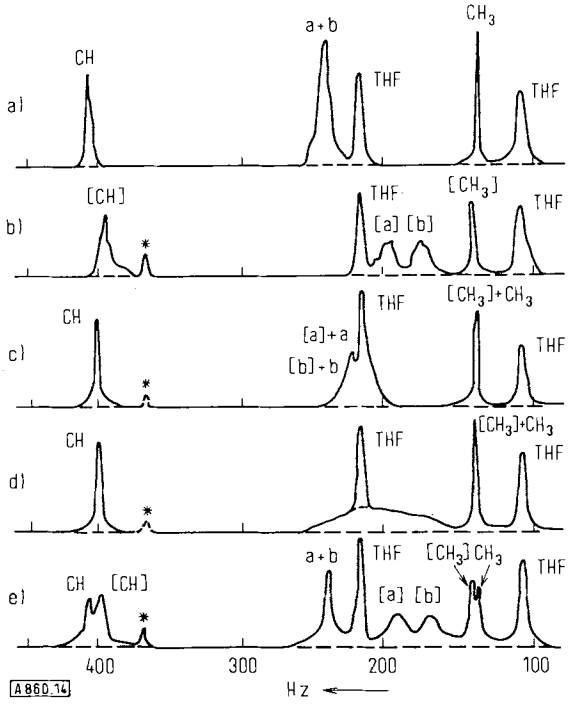


Fig. 14. NMR spectrum of the methyl derivative of dibenzo[18]crown-6 and its complex with fluorenylsodium in perdeuterated THF. The [ ] symbol signifies that the proton peaks belong to complexed *(7)*; * denotes fluorenyl protons. a) *(7)* at 40 °C; b) complex with *(7)* at 40 °C, *(7)*: fluorenylsodium ≈1; c) complex at 40 °C, *(7)*: fluorenylsodium ≈2; d) complex at 2 °C, *(7)*: fluorenylsodium ≈2; e) complex with *(7)* at −40 °C, *(7)*: fluorenylnatrium ≈2.

Strong upfield shifts of the protons of THF and of DME molecules complexed to fluorenyllithium dissolved in deuterated benzene were found by *Dixon et al.*[64]. For a 1:1 fluorenyllithium-DME mixture the CH_2 protons are shifted upfield by 1.22 pm and the CH_3 protons by 0.76 ppm. Similar shifts are found on complexation of glymes or macrocyclic polyethers to fluorenyl ion pairs[42,50]. An example is shown in Figure 14, which depicts the NMR spectrum of dimethyldibenzo[18]crown-6 and its 1:1 and 2:1 mixtures with fluorenylsodium, all recorded in deuterated THF. The complexation of the crown compound leads to a splitting of the polyether ring protons into two

peaks of equal intensity, the upfield shifts being 1.1 ppm and 0.75 ppm, respectively (selective deuteration showed the inner "a" CH_2 protons to undergo the largest shift). The upfield direction is due to the diamagnetic anisotropy exerted by the aromatic fluorenyl ring. This is partially compensated by a downfield shift that is expected on coordination of the crown to the Na^+ ion, as observed in ethereal solutions of certain alkali metal salts[65]. The aromatic protons of the crown are shifted upfield by 0.2 ppm, but the CH_3 protons show a downfield shift of 0.07 ppm, probably because they are located on the periphery of the fluorenyl ring.

A rapid exchange spectrum is observed with 2:1 mixtures of the crown compound and fluorenylsodium (Fig. 14c), but a slow exchange spectrum is obtained at low temperatures. The coalescence temperature for the polyether ring protons was found to be 2 °C (Fig. 14d). The concentrations of complexed and free crown being equal, one may calculate the rate constant of the reaction

$$\text{fluorenyl}^-, C, Na^+ + C^* \rightarrow \text{fluorenyl}^-, C^*, Na^+ + C$$

(C and C* representing the same crown compound) at the coalescence temperature from the equation

$$k = 1/2\tau[C]_{free}$$

with the relaxation time[66]

$$\tau = \sqrt{2}/2\pi(\gamma_A^0 - \gamma_B^0)$$

This expression can be applied at the respective coalescence temperatures of the polyether ring protons ($t_C = 2$ °C, $\Delta\gamma = 56$ Hz), the aromatic CH protons ($t_C \approx -18$ °C, $\Delta\gamma = 10$ Hz), and the CH_3 protons ($t_C \approx -27$ °C, $\Delta\gamma = 4$ Hz). The rate constants thus calculated are 3200 (2 °C), 550 (−18 °C), and 220 l mol^{-1} s^{-1} (−27 °C), giving an activation energy for the exchange process of 12.5 kcal/mol. The actual exchange process may be more complex, and could conceivably involve the free ions, with the rate determining step being the dissociation of the complex into the free cyclic ether and the contact ion pair fluorenyl$^-$, Na^+, followed by a rapid association step leading to the exchange.

The exchange rate is considerably faster with fluorenylpotassium, and even down to −60 °C a 2:1 mixture of dibenzo[18]crown-6 and fluorenylpotassium gives a rapid exchange spectrum. This confirms the results obtained by optical spectroscopy, namely, that this crown ether is more strongly bound to Na^+ than to K^+, at least in THF.

Upfield shifts are also observed for the fluorenylsodium-crown complex in other solvents such as pyridine. In this solvent fluorenylsodium is a separated ion pair, but addition of the dibenzo[18]crown-6 replaces the pyridine molecules around the Na^+ ion. The large proton shifts observed for the complexed crown compound also imply that the fraction of free ions at 0.1 mol/l salt concentration in pyridine ($D = 14.0$) must be small. Dissociation should remove the Na^+-crown complex from the fluorenyl moiety, and a downfield, rather than an upfield shift is then anticipated.

Sandwiched in between two fluorenyl rings, the crown complex of difluorenylbarium (see Fig. 13) shows an even stronger upfield shift for the polyether ring protons (0.5 and 1.4 ppm). The rate of the exchange reaction

$$\text{fluorenyl}^-, Ba^{2+}, C, \text{fluorenyl} + C^* \rightarrow \text{fluorenyl}^-, Ba^{2+}, C^*, \text{fluorenyl}^- + C$$

in pyridine at 60 °C (the solubility of the complex in THF is only $\approx 10^{-2}$ mol/l) is of the order of 500 l mol^{-1} s^{-1}. The (extrapolated) value of this rate constant at 60 °C for the fluorenylsodium-crown complex in THF is close to 10^5 l mol^{-1} s^{-1}. The exchange reaction involving the barium complex is probably sterically hindered. Also, the barium ion is more tightly bound to the crown compound than Na^+, as evidenced by the fact that on addition of difluorenylbarium to the fluorenylsodium-crown complex the crown compound is completely transferred to the barium salt.

Interesting NMR patterns are observed on complexation of glymes to certain paramagnetic ion pairs. It has frequently been observed that the NMR solvent shift for solutions of aromatic hydrocarbon radical anions is considerably less than the value predicted theoretically for solutions of paramagnetic species[67, 68]. Apparently, those solvent molecules which are bound to the radical anion pairs acquire spin density, due to their close proximity to the unpaired electron. This produces a downfield shift of the solvent protons, and partially balances the upfield paramagnetic bulk susceptibility shift[33].

A striking example of this effect is observed for 1:1 complexes of coronenesodium and glymes[34]. In the absence of glyme a 0.1 M solution of coronene$^-$, Na^+ in THF shows a solvent shift of only 0.05 to 0.07 ppm upfield with respect to pure THF. However, addition of an equivalent amount of glyme-5 causes both the α and β protons of THF to acquire their theoretically predicted solvent shift value of 0.25 ppm at 33 °C for a 0.1 M solution of paramagnetic species of spin ½. Apparently the glyme-5 has replaced the THF solvation shell around the Na^+ ion by forming the separated ion pair coronene$^-$, G-5, Na^+.

The high complexation constant ($> 10^4$ l/mol) excludes the presence of any free glyme. The change in the solvation shell is most clearly demonstrated by the NMR spectrum of the complexed glyme. At 120 °C, four absorption peaks can be observed at $\delta = 9.5$, 8.8, 7.5, and 5.5 ppm downfield from the α-THF peak with intensity ratios of 8:4:4:6 (a total of 22 protons). For a solution of glyme-5 in THF, only two glyme peaks are observed, 0.08 and 0.35 ppm upfield from the THF peak.

A similar downfield shift is found for the glyme protons of the 1:1 coronene$^-$, Na^+, glyme-4 complex (18 protons) at 33 °C. The NMR spectrum of this complex is depicted in Figure 15, and shows four well resolved peaks with intensity ratios 4:4:4:6. In this complex, the THF solvent protons still do not give their theoretically predicted solvent shift values, indicating that a few solvent molecules remain bound to the Na^+ ion.

Addition of two glyme-4 molecules per coronenesodium ion pair results in a shift of the glyme protons which is considerably larger than that calculated on the basis of a rapid exchange process for a 1:1 complex. Apparently, a second glyme-4 is coordinated to the coronenesodium ion

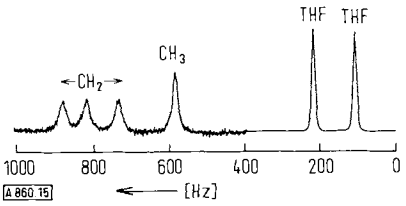


Fig. 15. ^{1}H-NMR spectrum (60 MHz) of the 1:1 complex of coronene-sodium with glyme-4 in tetrahydrofuran at 33 °C. The four signals on the left-hand side are due to glyme protons.

pair, a conclusion which is supported by the NMR data obtained for glyme-4 complexes of fluorenylsodium[42].

A concentration dependent shift of the glyme protons is observed in a 0.1 M mixture of glyme-4 and coronenelithium in THF at 33 °C[34]. The glyme-4 is only partially bound to coronenelithium under these conditions, the equilibrium constant for

$$\text{coronene}^-, \text{Li}^+ + \text{G-4} \rightleftharpoons \text{coronene}^-, \text{G-4}, \text{Li}^+$$

being approximately 1.0 l/mol (see Section 3).

The glyme proton shifts most probably result from a Fermi contact interaction between the glyme protons and the unpaired electron. The g factor for radical anion pairs is nearly isotropic, which makes it unlikely that dipolar interactions between the unpaired electron and glyme protons are causing the downfield shift. The contact shifts are actually larger than the observed downfield shift, since they are partially balanced by an upfield shift of approximately 0.8 ppm caused by the diamagnetic anisotropy of the aromatic ring, similar to that observed for the fluorenyl-sodium-crown complexes (see Fig. 14).

The protons showing the smallest downfield shift are the CH_3 protons. Using a partially deuterated glyme-5[69] it was found that at least in this glyme the eight protons of the two ethylene groups adjacent to the center oxygen atom undergo the largest chemical shift. The difference in chemical shift for the various CH_2 protons of the complexed glyme indicates that the glyme-coordinated Na^+ ion does not rotate indiscriminately above the plane of the coronene molecule, as this would produce the same average shift for all CH_2 protons.

The contact shifts are small for glyme complexes of the radical anion salts of naphthalene, triphenylbenzene, and anthracene, but with triphenylenesodium the CH_2 glyme protons are shifted by about 3.3 ppm[33]. Apparently, an effective overlap between electron orbital and glyme protons only occurs when the spin density is high at the periphery of a comparatively large aromatic molecule. The glyme complex may have a structure in which the glyme is bound to Na^+ in a ring type conformation parallel to the aromatic ring. This provides for a maximum coulombic attraction between the two oppositely charged ions, and should bring the glyme protons close to those coronene atoms which possess the higher spin density.

The large proton shifts for the glyme complexes of coronene radical anion pairs are reminiscent of those often observed for diamagnetic cations in the presence of paramagnetic anionic transition metal complexes. The latter shifts have frequently been utilized to detect ion pairing and to measure equilibrium constants for ion pair formation. For example, *LaMar*[70] observed strong upfield shifts for the protons of the tetrabutylammonium cation in the paramagnetic complex $[(C_4H_9)_4N]^+[(C_6H_5)_3PCoI_3]^-$, and large downfield shifts for the same protons in the corresponding nickel complex. Other systems for which large shifts are observed include tetraalkylammonium ion pairs of tris(2,4-pentanedionato)cobalt(II) and -nickel(II) complexes[71] and ion pairs of tetrahalometalates[72]. Also mixed cations like butyltriphenylphosphonium have been used[73]. The above shifts are usually interpreted in terms of a "pseudo contact" mechanism, *i.e.*, a direct dipolar interaction between the unpaired electron and the protons of the cation. Such an interpretation is plausible since the g factor is often anisotropic for these transition metal complexes.

Other approaches have been used to study ion pairing by nuclear magnetic resonance. While finding no effect of the cation on the coupling constants of the fluorenyl carbanion protons in THF, *Cox*[74] observed downfield shifts with increasing radius of the cation, the lithium salt being an exception. For example, the respective chemical shifts for H-9 in fluorenyllithium, sodium, potassium, and rubidium are 7.21, 7.37, 7.27, and 7.25 ppm downfield from TMS. The downfield trend is caused by a change in charge distribution in the contact ion pair. The deviation shown by the fluorenyllithium is to be expected, since this ion pair is predominantly a separated ion pair in THF at 25 °C[10], hence the cation should have little effect on the chemical shift. Similar studies were carried out by *Chan*[40] who arrived at the same conclusions. Since the effects are small, quantitative data on ion pairing may not be very reliable, particularly since some of the observed changes in chemical shifts could be caused by ion pair aggregation at the high salt concentrations employed.

Interactions between solvent and ion pair can be conveniently studied in the alkali metal tetraalkylaluminates. $NaAl(C_4H_9)_4$ is soluble in most hydrocarbon solvents, which means that ion solvent interactions with coordinating species such as ethers can be studied with a minimum of interference by the medium itself. *Schaschel* and *Day*[75] measured the proton shifts of tetrahydrofuran in cyclohexane in the presence of sodium tetrabutylaluminate as a function of the THF: $NaAl(C_4H_9)_4$ ratio. Up to a ratio of 1:1, the shift relative to the unperturbed THF in cyclohexane is nearly constant at 0.22 ppm, indicating formation of a complex THF/$NaAl(C_4H_9)_4$. Whether this constitutes a THF-separated ion pair or an externally solvated contact ion pair cannot easily be decided, although the authors favor a separated ion pair because of observed shifts in the $Al\cdots CH_3$ proton signal. As more THF is added, the shift difference with respect to unperturbed THF decreases, with a distinct break noticeable at THF: $NaAl(C_4H_9)_4 = 4:1$. This was interpreted as evidence for the presence of $NaAl(C_4H_9)_4 \cdot 4$ THF species. A similar study by *Wuepper* and *Popov*[76] for the system $NaAl(C_4H_9)_4$ and DMSO in dioxane showed a probable solvation number of six for the DMSO-solvated Na^+ ion, but no conclusions can be drawn about possible structures of the ion pair solvation complexes.

Ion pair equilibria may also be studied from the NMR line shapes. An interesting application was reported by *Gore* and *Gutowsky*[77], who studied the NMR spectra of lithium- and sodium tetramethylaluminate in ether, THF, and DME. In the solvent separated ion pair the electric field gradient at the ^{27}Al nucleus is small because of a nearly tetrahedral symmetry of the electric field. The spin lattice relaxation rate of the ^{27}Al is therefore small enough to cause indirect spin-spin splitting by the Al nucleus ($I=\frac{5}{2}$), and the CH_3 group appears as a sharp sextuplet. On the other hand, the electric field gradient at the Al nucleus is large for an intimate ion pair and the resulting high rate of relaxation causes the CH_3 sextuplet to collapse into a singlet. In DME only separated ion pairs were observed for both the Li and Na salts, while in diethyl ether only contact ion pairs were found. However, mixtures of the two ion pairs were found in THF. The thermodynamic parameters for the equilibrium

$$Li^+Al(CH_3)_4^- \rightleftharpoons Li^+\|Al(CH_3)_4^-$$

were calculated to be $\Delta H = -6.5$ kcal/mol and $\Delta S = -11$ e. u. at 40 °C. The ΔH value is close to that found by *Hogen Esch* and *Smid* for fluorenyllithium in THF[10]. The equilibrium constant for the sodium ion pair at 40 °C is about ten times less than for the lithium salt, which is at least qualitatively in agreement with that observed for fluorenyl salts.

Extensive proton and alkali metal NMR measurements on ion pairs of radical anions of biphenyl and naphthalene were reported by *de Boer et al.*[78, 79]. However, a thorough discussion of their interesting work falls outside the scope of this review. There is little doubt that alkali metal NMR measurements can provide very useful information on interactions of complexing agents with alkali metal ions. An example is found in recent work of *de Boer, Grotens,* and *Smid*[80] which shows that the ^{23}Na-NMR line width strongly increases when the THF solvation shell around Na^+ in $NaB(C_6H_5)_4$ is replaced by glyme-7 or dimethyldibenzo[18]crown-6, largely because of an increase in the field gradient at the ^{23}Na nucleus. Solvents will also affect the chemical shift of the ^{23}Na-NMR line[81] and this can often be correlated with the solvating ability of the solvent.

Part of the work described in this review was carried out at the Chemistry Department, College of Forestry, Syracuse, New York, and the author gratefully acknowledges the financial support of the National Institutes of Health (Grant GM 15965) and the Petroleum Research Fund, administered by the American Chemical Society. He is grateful to his many co-workers, in particular Dr. T. E. Hogen Esch, who has pioneered much of the work on fluorenyl ion pairs, and also for many stimulating discussions with Dr. M. Szwarc and Dr. E. de Boer.

Received: April 13, 1971 [A 860 IE]
German version: Angew. Chem. *84*, 127 (1972)

[1] *E. M. Kosower*, J. Amer. Chem. Soc. *80*, 3253, 3261, 3267 (1958).
[2] *E. M. Kosower:* An introduction to Physical Organic Chemistry. Wiley, New York 1968.
[3] *T. R. Griffiths* and *M. C. R. Symons*, Mol. Phys. *3*, 90 (1960).
[4] *M. Smith* and *M. C. R. Symons*, Trans. Faraday Soc. *54*, 338, 347 (1957).
[5] *M. J. Blandamer, T. E. Gough*, and *M. C. R. Symons*, Trans. Faraday Soc. *62*, 301 (1966).
[6] *C. S. Irving, G. W. Byers*, and *P. A. Leermakers*, J. Amer. Chem. Soc. *91*, 2141 (1966).
[7] *J. A. M. van Broekhoven*, Ph. D. Thesis, University of Nijmegen 1970, p. 68.
[8] *H. V. Carter, B. J. McClelland*, and *E. Warhurst*, Trans. Faraday Soc. *56*, 455 (1960).
[9] *T. E. Hogen Esch* and *J. Smid*, J. Amer. Chem. Soc. *87*, 669 (1965).
[10] *T. E. Hogen Esch* and *J. Smid*, J. Amer. Chem. Soc. *88*, 307 (1966).
[11] *H. E. Zaugg* and *A. D. Schaefer*, J. Amer. Chem. Soc. *87*, 1857 (1965).
[12] *L. L. Chan* and *J. Smid*, J. Amer. Chem. Soc. *90*, 4654 (1968).
[13] *R. Smyk*, M. Sc. Thesis, College of Forestry, Syracuse, New York 1968.
[14] *J. P. Pascault*, Thesis, l'Université de Lyon 1970.
[15] *E. M. Arnett* and *C. Y. Wu*, J. Amer. Chem. Soc. *84*, 1684 (1962).
[16] *A. I. Shatenshtein, E. S. Petrov, M. I. Belousova, K. G. Yanova*, and *E. A. Yakovleva*, Dokl. Akad. Nauk. SSSR *151*, 353 (1963).
[17] *A. I. Shatenshtein, E. S. Petrov*, and *E. A. Yakovleva*, J. Polymer Sci. *C 16*, 1729 (1967).
[18] *A. I. Shatenshtein* and *E. S. Petrov*, Usp. Khim. *36*, 269 (1967).
[19] *A. Streitwieser, Jr., J. H. Hammons, E. Ciuffarin*, and *J. I. Brauman*, J. Amer. Chem. Soc. *89*, 59 (1967).
[20] *G. G. Eberhardt* and *W. A. Butte*, J. Org. Chem. *29*, 2928 (1964).
[21] *A. W. Langer*, Trans. New York Acad. Sci., Ser II, *27*, 741 (1965).
[22] *M. Szwarc:* Carbanions, Living Polymers and Electron Transfer Processes. Interscience, New York 1968.
[23] *J. T. Denison* and *J. B. Ramsey*, J. Amer. Chem. Soc. *77*, 2615 (1955).
[24] *T. E. Hogen Esch* and *J. Smid*, J. Amer. Chem. Soc. *88*, 318 (1966).
[25] *D. Nicholls, C. A. Sutphen*, and *M. Szwarc*, J. Phys. Chem. *72*, 1021 (1968).
[26] *T. Ellingsen* and *J. Smid*, J. Phys. Chem. *73*, 2712 (1969).
[27] *T. E. Hogen Esch* and *J. Smid*, to be published.
[28] *T. E. Hogen Esch* and *J. Smid*, J. Amer. Chem. Soc. *89*, 2764 (1967).
[29] *W. J. Le Noble* and *A. R. Das*, J. Phys. Chem. *74*, 3429 (1970).
[30] *S. Claesson, B. Lundgren*, and *M. Szwarc*, Trans. Faraday Soc. *66*, 3053 (1970).
[31] *P. Chang, R. V. Slates*, and *M. Szwarc*, J. Phys. Chem. *70*, 3180 (1966).
[32] *D. Casson* and *B. J. Tabner*, J. Chem. Soc. *B 1969*, 572.
[33] *E. de Boer, A. M. Grotens*, and *J. Smid*, J. Amer. Chem. Soc. *92*, 4742 (1970).
[34] *E. de Boer, A. M. Grotens*, and *J. Smid*, Chem. Commun. *1970*, 1035.
[35] *R. V. Slates* and *M. Szwarc*, J. Amer. Chem. Soc. *89*, 6043 (1967).
[36] *J. F. Garst, E. R. Zabolotny*, and *R. S. Cole*, J. Amer. Chem. Soc. *86*, 2257 (1964).
[37] *R. C. Roberts* and *M. Szwarc*, J. Amer. Chem. Soc. *87*, 5542 (1965).
[38] *J. F. Garst* and *E. R. Zabolotny*, J. Amer. Chem. Soc. *87*, 495 (1965).
[39] *R. Waack, M. A. Doran*, and *P. E. Stevenson*, J. Amer. Chem. Soc. *88*, 2109 (1966).
[40] *L. L. Chan*, Ph. D. Thesis, College of Forestry, Syracuse, New York 1970.
[41] *L. L. Chan* and *J. Smid*, J. Amer. Chem. Soc. *89*, 4547 (1967).
[42] *L. L. Chan, K. H. Wong*, and *J. Smid*, J. Amer. Chem. Soc. *92*, 1955 (1970).
[43] *J. Ugelstad* and *O. A. Rokstad*, Acta Chem. Scand. *18*, 474 (1964).
[44] *Z. Machacek, T. E. Hogen Esch*, and *J. Smid*, to be published.
[45] *C. J. Pedersen*, J. Amer. Chem. Soc. *89*, 7017 (1967).
[46] *C. J. Pedersen*, J. Amer. Chem. Soc. *92*, 391 (1970).
[47] *J. Almy, D. C. Garwood*, and *D. J. Cram*, J. Amer. Chem. Soc. *92*, 4321 (1970).
[48] *G. Eiseman, S. Ciani*, and *G. Szabo*, J. Membrane Biol. *1*, 294 (1969).
[49] *H. K. Frensdorff*, J. Amer. Chem. Soc. *93*, 600 (1971).
[50] *K. H. Wong, G. Konizer*, and *J. Smid*, J. Amer. Chem. Soc. *92*, 666 (1970).
[51] *U. Takaki, T. E. Hogen Esch*, and *J. Smid*, J. Amer. Chem. Soc. *93*, 6760 (1971).
[52] *D. Bright* and *M. R. Truter*, Nature *225*, 177 (1970).
[53] *D. Bright* and *M. R. Truter*, J. Chem. Soc. *B 1970*, 1544.

[54] *M. R. Truter*, personal communication.

[55] *S. Kopolow, T. E. Hogen Esch*, and *J. Smid*, Macromolecules *4*, 359 (1971).

[56] *Z. Machacek* and *J. Smid*, to be published.

[57] *D. N. Bhattacharyya, C. L. Lee, J. Smid*, and *M. Szwarc*, J. Phys. Chem. *69*, 612 (1965).

[58] *C. Carvajal, K. J. Tölle, J. Smid*, and *M. Szwarc*, J. Amer. Chem. Soc. *87*, 5548 (1965).

[59] *T. E. Hogen Esch* and *J. Smid*, J. Amer. Chem. Soc. *91*, 4580 (1969).

[60] *J. F. Garst, R. A. Klein, D. Walmsley*, and *E. R. Zabolotny*, J. Amer. Chem. Soc. *86*, 2257 (1964).

[61] *T. E. Hogen Esch* and *J. Smid*, to be published.

[62] *B. Dietrich, J. M. Lehn*, and *J. P. Sauvage*, Tetrahedron Lett. *1969*, 2885.

[63] *J. M. Lehn, J. P. Sauvage*, and *B. Dietrich*, J. Amer. Chem. Soc. *92*, 2916 (1970).

[64] *J. A. Dixon, P. A. Gwinner*, and *D. C. Lini*, J. Amer. Chem. Soc. *87*, 1379 (1965).

[65] *D. Nicholls* and *M. Szwarc*, J. Phys. Chem. *71*, 2727 (1967).

[66] *J. A. Pople, W. G. Schneider*, and *H. J. Bernstein*: High Resolution Nuclear Magnetic Resonance. McGraw-Hill, New York 1959.

[67] *E. de Boer* and *C. MacLean*, J. Chem. Phys. *44*, 1334 (1966).

[68] *E. de Boer* and *H. V. Willigen*, Progt. Nucl. Magn. Resonance Spectrosc. *2*, 157 (1967).

[69] *A. M. Grotens* and *J. Smid*, unpublished results from this laboratory.

[70] *G. N. LaMar*, J. Chem. Phys. *41*, 2992 (1964).

[71] *W. D. Horrocks, Jr., R. M. Fischer, J. R. Hutchinson*, and *G. N. LaMar*, J. Amer. Chem. Soc. *88*, 2436 (1966).

[72] *T. M. Walker* and *R. S. Drago*, J. Amer. Chem. Soc. *90*, 6951 (1968).

[73] *R. M. Fischer* and *W. D. Horrocks, Jr.*, Inorg. Chem. *7*, 2659 (1968).

[74] *R. H. Cox*, J. Phys. Chem. *73*, 2649 (1969).

[75] *E. Schaschel* and *M. C. Day*, J. Amer. Chem. Soc. *90*, 503 (1968).

[76] *J. L. Wuepper* and *A. I. Popov*, J. Amer. Chem. Soc. *92*, 1493 (1970).

[77] *E. S. Gore* and *H. S. Gutowsky*, J. Phys. Chem. *73*, 2515 (1969).

[78] *G. W. Canters, E. de Boer, B. M. Hendricks*, and *H. van Willigen*, Chem. Phys. Lett. *1*, 627 (1968).

[79] *G. W. Canters, E. de Boer, B. M. P. Hendriks*, and *A. A. K. Klaassen*, Colloque Ampire XV. North Holland, Amsterdam 1969, p. 242.

[80] *E. de Boer, A. M. Grotens*, and *J. Smid*, Chem. Commun. *1971*, 759.

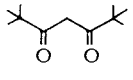
[81] *R. H. Erlich, E. Roach*, and *A. I. Popov*, J. Amer. Chem. Soc. *92*, 4989 (1970).

COMMUNICATIONS

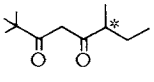
Synthesis of the Lithium Enolate of (*S*)-(+)-*sec*-Butyl Methyl Ketone and Formation of Chiral 1,3-Diketones by Acylation

By *Dieter Seebach* and *Volker Ehrig*[*]

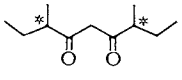
In connection with our studies on lanthanoid complexes of chiral 1,3-diketones suitable for determining the purity of enantiomers[1] we were confronted with the problem of synthesizing dipivaloylmethane-(DPM-)like ligands such as *(1)* and *(2)*.



DPM



(1)

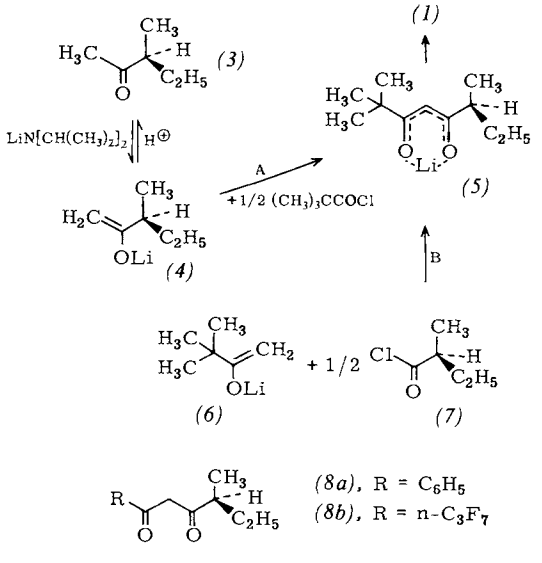


(2)

For a synthesis of *(1)*, the enolate *(4)* of the optically active 3-methylpentanone *(3)*[2] has to be *C*-acylated. Amine-free solutions of (*S*)-*(4)* in toluene/THF could be prepared by modification of the procedures given by *Schlosser*[3] and *House*[4] for preparation of lithium enolates. "Neutralization" with the calculated amount of acid regenerates the ketone *(3)* with less than 5% loss of optical activity; addition of one half equivalent of pivaloyl chloride at −80 °C proceeds according to reaction A to give the lithium salt *(5)* from which 2,2,6-trimethyl-3,5-octanedione *(1)* is liberated.

[*] Prof. Dr. D. Seebach and Dipl.-Chem. V. Ehrig
Institut für Organische Chemie der Universität Karlsruhe
Present address:
Institut für Organische Chemie der Universität
63 Giessen, Ludwigstrasse 21 (Germany)

Neither the NMR spectrum nor the gas chromatogram of the diketone *(1)* isolated in 83% yield by molecular distillation gives any indication of contamination by *O*- or α′-*C*-acylated product. Compound *(1)* was also prepared by acylation of the lithium enolate *(6)* of pinacolone with optically active α-methylbutyryl chloride *(7)* (route B).



The ketone *(3)* used for route A had $[\alpha]_D^{25} = +17.8°$ (neat), was at most[2,5] 60% optically pure, and gave diketone *(1)* of $\alpha_D^{25} = +19.0°$ (1 dm, neat); the (*S*)-(+)-acid chloride *(7)* used for route B was at least[6] 89% optically pure and afforded compound *(1)* having $\alpha_D^{25} = +27.5°$; a value of +31° for optically pure diketone was calculated from both experiments.

The diketone *(2)* having two centers of asymmetry and the compounds *(8)* were obtained similarly (see Table); accord-

Table. Starting materials for synthesis and physical data of the diketones *(1)*, *(2)*, and *(8)*; physical data of the diketone complexes CuL_2 and EuL_3. The acylation yields lie between 70 and 90%, based on starting acid chloride.

Li enolate + $^1/_2$ acid chloride	diketone	b.p. (°C/torr)	n_D^{20}	$[\alpha]_D^{25}$ (°) [a] (1 dm, neat)
(4) + $(CH_3)_3C$—COCl	(*S*)-*(1)*	95/15	1.4610	+31
(6) + *(7)*				+31
(4) + C_6H_5—COCl	(*S*)-*(8a)*	80/0.3	1.5672	+47
$C_6H_5(LiO)C{=}CH_2$ + *(7)*				+38
(4) + *(7)*	(*S,S*)-*(2)*	90/7	1.4608	+53
(4) + *n*-C_3F_7—COCl	(*S*)-*(8b)*	74/19	1.3832	+30

L	complex	m.p. (°C)	$[\alpha]_D^{25}$ [a] (*c*, in pentane)
(*S*)-*(1)*	CuL_2	110–111	
(*S*)-*(1)*	EuL_3	209–210	+30 (9.6)
(*S*)-*(8a)*	CuL_2	113–115	
(*S*)-*(8a)*	EuL_3	206–210 (decomp.)	−170 (5.7)
(*S,S*)-*(2)*	EuL_3		+67 (10)

[a] Based on sample of *(3)* having the highest extrapolatable rotation ($[\alpha]_D = +30°$ (neat)) [5] and optically pure *(7)* ($[\alpha]_D = +17.8°$ (neat)) [6].

ing to their NMR spectra (CCl_4) they all exist to the extent of >90% in the enol form.

The above experiments show that under suitable conditions open-chain ketones that are asymmetric, enolizable, and therefore subject to racemization in the α position relative to the carbonyl group, can be "enolatized" at the less substituted α′-carbon and acylated in high yields without extensive racemization[7].

Received: September 6, 1971 [Z 526 IE]
German version: Angew. Chem. *84*, 107 (1972)

[1] *G. M. Whitesides* and *D. W. Lewis*, J. Amer. Chem. Soc. *92*, 6979 (1970).

[2] *D. Seebach* and *D. Steinmüller*, Angew. Chem. *80*, 617 (1968); Angew. Chem. internat. Edit. *7*, 619 (1968); and literature cited therein.

[3] *M. Schlosser* and *G. Heinz*, Chem. Ber, *102*, 1944 (1969).

[4] *H. O. House et al.*, J. Org. Chem. *34*, 2324 (1969).

[5] *P. D. Bartlett* and *C. H. Stauffer*, J. Amer. Chem. Soc. *57*, 2583 (1935).

[6] *K. Freudenberg* and *W. Cowowski*, Liebigs Ann. Chem. *594*, 76 (1955); *F. L. Weisenborn* and *J. W. Bolger*, J. Amer. Chem. Soc. *76*, 1793 (1954).

[7] On formation of the enolate and subsequent trimethylsilylation of 2-butanone, 2-heptanone, and 2-methyl-3-pentanone, *House et al.* [4] observed less regiospecificity and up to 40% aldol formation from the ketone.

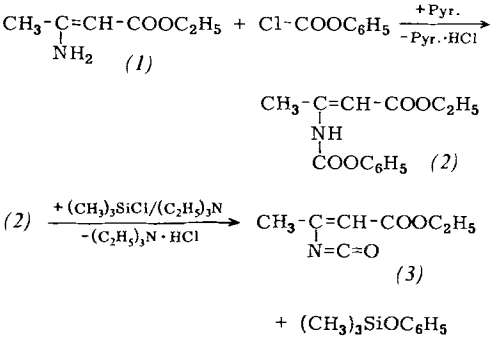
Reversible Isomerization in β-Isocyanatocrotonic Esters

By *Hans R. Kricheldorf* [*]

Ethyl β-isocyanatocrotonate *(3)* could be synthesized by conversion of ethyl β-aminocrotonate *(1)* into the *N*-phenoxycarbonyl derivative *(2)*, which on treatment with trimethylchlorosilane is cleaved into *(3)* and phenoxytrimethylsilane (cf. Ref. [1, 2]).

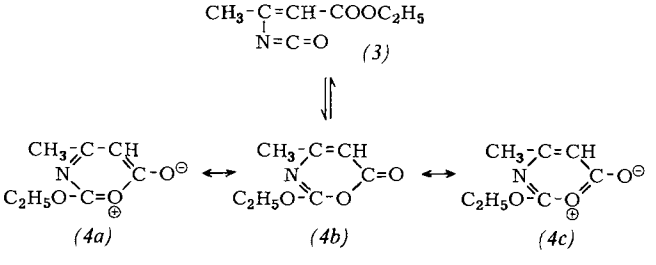
[*] Dr. H.-R. Kricheldorf
Institut für makromolekulare Chemie der Universität
78 Freiburg, Stefan-Meier-Strasse 31 (Germany)

The isocyanate *(3)* boils at 82—83 °C/12 torr; it is a colorless liquid with a penetrating, lacrimatory odor. It undergoes rapid reaction with aniline at 0 °C to give the same urea that is formed in the reaction of *(1)* with phenyl isocyanate.



The IR spectrum contains bands for the isocyanate group (2270 cm^{-1}), the ester carbonyl group (1695 cm^{-1}), and the CC double bond (1610 cm^{-1}). The NMR spectrum shows signals for the ethyl groups at τ = 8.72 (t) and 5.82 (q), for the methyl group at 8.09 (s), and for the C—H group at 4.44 (s) (3:2:3:1).

At temperatures below 30 °C an isomer having m.p. 68 to 70 °C crystallizes from pure *(3)*; on the basis of previous investigations this isomer was assigned the structure of a 2-ethoxy-4-methyl-1,3-oxazin-6-one *(4)*. *(4)* can be isolated and stored at 0 °C, but in solution regeneration of *(3)* takes place; in carbon tetrachloride at 20 °C equilibrium is established within 4 days, the ratio of *(3)*:*(4)* being 1:1. The proportion of *(3)* increases on increasing the temperature (at 70 °C in CCl_4 *(3)*:*(4)* = 3:1).



The IR spectrum of *(4)* contains a carbonyl band at 1770 cm^{-1} as well as the band at 1610 cm^{-1} which also occurs in the spectrum of *(3)* and which can be due to a CC or CN double bond. The NMR spectrum of *(4)* shows the same signals as that of *(3)*, but with a larger paramagnetic shift throughout: τ = 8.59 (t), 7.89 (d), 5.57 (q), and 4.38 (d), (3:3:2:1). The signals of the C—H and CH_3 groups occur as doublets (J = 1 Hz), as is to be expected for an allyl *cis* conformation. In accord with the presence of three conjugated double bonds, the UV spectrum of *(4)* shows an intense absorption at 274 nm.—*(4)* does not react with aniline at 0 °C if *(3)* is not present.

Ethyl β-isocyanatocrotonate (3)

Phenyl chloroformate (157 g, 1 mol) is added dropwise to a mixture of *(1)* (127 g) and pyridine (79 g, 1 mol) in ethyl acetate (1 l). The resulting solution is heated to boiling for 30 minutes, then cooled, washed with dilute hydrochloric acid, and finally dried with Na_2SO_4. On evaporation under

vacuum, *(2)* crystallizes out (m. p. 70—72 °C after recrystallization from ethyl acetate/petroleum ether); yield *ca.* 95%.

A mixture of *(2)* (249 g, 1 mol), trimethylchlorosilane (108 g, 1 mol), and triethylamine (101 g, 1 mol) in toluene (1.2 l) is heated to boiling for 2 h, allowed to cool and then filtered. *(3)* is isolated from the filtrate by fractional distillation in a 20 cm packed column; yield 30—50%. For isolation of *(4)*, *(3)* is allowed to stand for 2 weeks at 0 °C and the crystals which separate are filtered off, thoroughly washed with petroleum ether, and finally dried under vacuum; yield 70—85%.

Received: September 28, 1971 [Z 534 IE]
German version: Angew. Chem. *84*, 107 (1972)

[1] *G. Greber* and *H. R. Kricheldorf*, Angew. Chem. *80*, 1028 (1968); Angew. Chem. internat. Edit. *7*, 941 (1968).

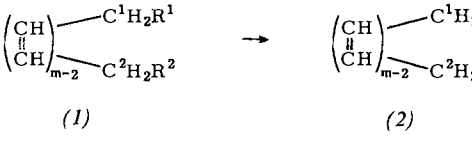
[2] *H. R. Kricheldorf*, Synthesis *1970*, 649.

Dyotropic Rearrangements, a New Class of Orbital-Symmetry Controlled Reactions. Type I

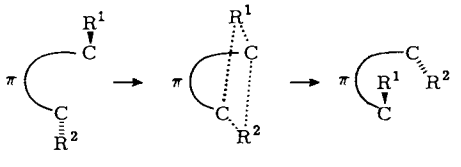
By *Manfred T. Reetz*[*]

A *dyotropic*[1] reaction can be defined as an uncatalyzed process in which two σ-bonds simultaneously migrate intramolecularly. Reactions in which the two σ-bonds interchange their positions are of Type I. In Type II processes no direct positional interchange occurs. This communication treats only Type I reactions[2].

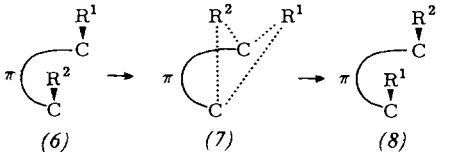
A dyotropic reaction in a conjugated polyene with $m-2$ ($m=2,3,4$) double bonds *(1)*→*(2)* has the order[3] [*m*,*m*] and can proceed out of two distinct conformations, *anti (3)* and *syn (6)*.



(1) *(2)*



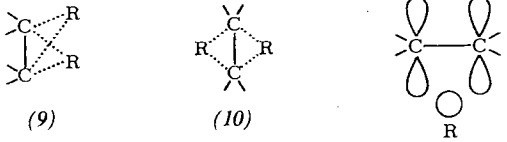
(3) *(4)* *(5)*



(6) *(7)* *(8)*

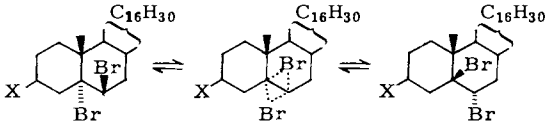
If both substituents remain on their initial side of the π-system during the reaction, *(supra, supra)*, two transition states result: *anti (4)* and *syn (7)*. The *anti* rearrangement necessarily leads to inversion of configuration of both *stationary* terminal atoms, whereas the *syn* reaction results in double retention. Four additional transition states not shown here are conceivable: *anti(supra, antara)*, *anti(antara, antara)*, *syn(supra, antara)*, *syn(antara, antara)*.

The principle aspects of this reaction type can be illustrated by considering rearrangements of the order [2,2] in which both groups migrate suprafacially. Assuming retention of configuration at the *migrating* groups, application of the formal orbital-symmetry rules[4] leads to the following prediction: The *syn (9)* as well as the sterically more favorable *anti* rearrangement *(10)* are $[_\sigma 2_s + _\sigma 2_s]$ processes and are therefore thermally forbidden. If one of the R groups has a p-orbital available, it can migrate with inversion *(11)*, whereby the reaction would become a thermally allowed $[_\sigma 2_s + _\sigma 2_s]$ process[5].



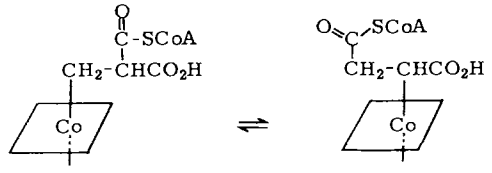
(9) *(10)* *(11)*

Several reactions in which two σ-bonds interchange positions have already been reported[6]; however, few stereochemical studies have been carried out. The long known mutarotation of dibromocholestane *(12)*⇌*(14)*[7] may be a [2,2] dyotropic shift in which one of the bromine atoms utilizes a p-orbital according to *(11)*. In a mechanistic study *Grob* and *Winstein*[8] showed that the reaction rate is unaffected by addition of radical initiators or inhibitors, and that in non-ionizing solvents (such as heptane) a four-membered transition state *(13)* best explains the stereochemical and kinetic data.



(12) *(13)* *(14)*

A similar exchange of substituents has been postulated for a number of coenzyme B_{12} mediated isomerizations[9]. Thus, the equilibrium *(15)*⇌*(16)* in the isomerization of methylmalonyl-CoA to succinyl-CoA[9] represents a formal dyotropic [2,2] rearrangement in which —COSCoA and cobalt participate as migrating groups.



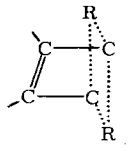
(15) *(16)*

It has been suggested that in this step of the isomerization the —COSCoA group migrates intramolecularly and that the cobalt moiety does not become detached from the substrate[9]. In case of a dyotropic rearrangement, d-orbitals of cobalt would necessarily have to participate.

In dyotropic reactions of higher order, for example a [4,4] shift, the two stationary terminal atoms are connected by one or more π-systems. In the transition state *(17)* of the

[*] Dr. M. T. Reetz
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

[4,4] reaction, a four-membered cyclic orbital array prevails in which the added double bond is not directly involved. This as well as any additional π-system must be treated as a perturbation. As a first approximation, shifts of order [m,m] should behave much like the [2,2] case. Whether a π-system will stabilize the four-membered orbital array, will depend on its symmetry properties and can be analyzed from case to case using the frontier-orbital method[10, 11].



(17)

Three additional points deserve attention:

1. The selection rules are reversed for photochemical reactions.
2. Application of the Dewar-Zimmerman method[4] leads to the same results[10].
3. Since two σ-bonds are being broken simultaneously, the activation energy of dyotropic reactions could be high. A given system may thus choose alternative reaction paths.

Received: December 27, 1971 [Z 548a IE]
German version: Angew. Chem. 84, 161 (1972)

[1] From the Greek *dyo*, meaning two.

[2] Type II see: *M. T. Reetz*, Angew. Chem. *84*, 163 (1972); Angew. Chem. internat. Edit. *11*, 130 (1972).

[3] The order designation is analogous to that of sigmatropic reactions [4].

[4] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969); see also: *K. Fukui*, Accounts Chem. Res. *4*, 57 (1971); *H. E. Zimmerman*, J. Amer. Chem. Soc. *88*, 1563, 1566 (1966); *M. J. S. Dewar*, Tetrahedron, Suppl. *8*, 75 (1966).

[5] If one (or both) of the migrating groups constitutes a π-system itself, this entire system may be incorporated into the reaction. For example, an allyl group can migrate in a type of Cope rearrangement with inversion.

[6] See for example: *U. Wannagat*, Inorg. Nucl. Chem. Lett. *1*, 13 (1965); *C. A. Grob, H. P. Fischer, W. Raudenbusch*, and *J. Zergenyi*, Helv. Chim. Acta *47*, 1003 (1964); *D. B. Denney*, J. Amer. Chem. Soc. *77*, 1706 (1955); *D. B. Denney* and *B. Goldstein, ibid. 79*, 4948 (1957); *F. T. Smith*, J. Chem. Phys. *29*, 235 (1958).

[7] *J. Mauthner*, Monatsh. Chem. *27*, 421 (1906).

[8] *C. A. Grob* and *S. Winstein*, Helv. Chim. Acta *99*, 782 (1952).

[9] *W. W. Miller* and *J. H. Richards*, J. Amer. Chem. Soc. *91*, 1498 (1969) and references therein.

[10] *M. T. Reetz*, unpublished.

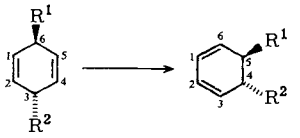
[11] *Roald Hoffmann* (Cornell University) describes a similar phenomenon in a study of the stabilization of bridged ethane structures. I would like to thank Prof. *Hoffmann* for discussions and for sending me his manuscript prior to publication in Helv. Chim. Acta.

Dyotropic Rearrangements, a New Class of Orbital-Symmetry Controlled Reactions. Type II

By *Manfred T. Reetz*[*]

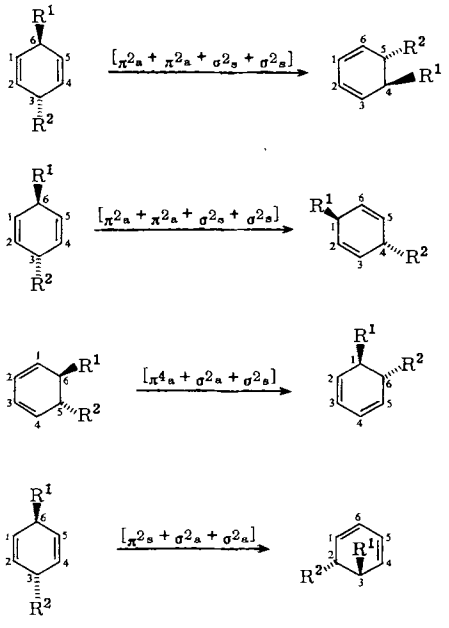
A dyotropic reaction of Type II was defined[1] as an intramolecular process in which two σ-bonds migrate in such a way as not to interchange positions. In this paper it is proposed that a wide variety of structurally different molecules may undergo such reactions and that for a given system several dyotropic reaction paths are conceivable.

Substituted cyclohexadienes serve as illustrative models. The migration of both R groups with retention of configuration as in (1) represents a dyotropic rearrangement of Type II.



(1)

The analysis of this reaction with the aid of a correlation diagram using a two-fold axis of symmetry shows that orbital symmetry[2] is not conserved in a thermal process. Four additional[3] dyotropic reaction modes are shown in (2), (3), (4), and (5). Application of the orbital symmetry rules[2] leads to the prediction that (2), (3), and (4) are thermally forbidden[4], unless one of the R groups migrates with inversion. In (5) one of the double bonds is not directly involved in the reaction, so that the rearrangement is already thermally allowed. In photochemical rearrangements the predictions are reversed.



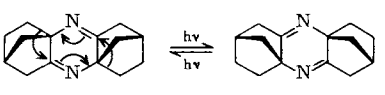
(2)

(3)

(4)

(5)

Dyotropic reactions have not yet been reported for cyclohexadiene itself. However, *Farnum* and *Carlson*[5] have studied a system analogous to (3). In order to explain the photochemically induced racemization of the dihydropyrazine shown below, they postulate a rearrangement (6) in which, like (3), two σ-bonds migrate simultaneously.

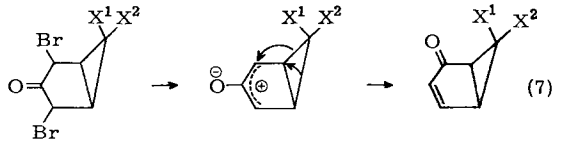


(6)

A reaction analogous to (4) in which one σ-bond migrates to a new position while the second one follows synchronously in its "tracks" has been recently described: In order to account for the stereochemistry of the Favorski reaction of bicyclo[3.1.0]hexanone derivatives, *Zimmerman*[6] invokes a sigmatropic [1,4] rearrangement with inversion of configuration. In the same publication *Zimmerman* proposes

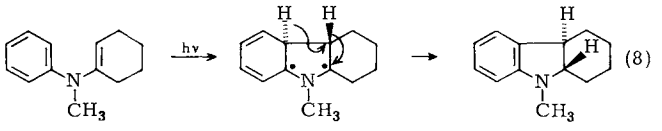
[*] Dr. M. T. Reetz
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

an alternative view in which both σ-bonds of the cyclopropane ring "slither" simultaneously along the C_5 framework (see arrows). This represents a thermally allowed $[{}_{\pi}2_s + {}_{\sigma}2_s + {}_{\sigma}2_s]$ dyotropic reaction.



(7)

Chapman[7] has recently considered, *inter alia*, a double hydrogen shift according to (8) in the photocyclization of *N*-aryl enamines; this corresponds to a photochemically allowed $[{}_{\pi}4_s + {}_{\sigma}2_a + {}_{\sigma}2_a]$ dyotropic rearrangement.



(8)

These few examples show that dyotropic rearrangements should be considered principally as possible reaction modes. However, since the simultaneous breakage of two σ-bonds generally requires high activation energies, it is difficult to predict the generality of dyotropic reactions.

Received: December 27, 1971 [Z 548b IE]
German version: Angew. Chem. *84*, 163 (1972)

[1] *M. T. Reetz*, Angew. Chem. *84*, 161 (1972); Angew. Chem. internat. Edit. *11*, 129 (1972).

[2] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[3] *Syn* reaction paths are not illustrated here. As far as orbital symmetry is concerned, they behave qualitatively just like the above discussed *anti* rearrangements. Two "simultaneous" sigmatropic [1,3] reactions have also not been considered.

[4] Besides the possibility of a dyotropic reaction, (2) also represents a sequence of two sigmatropic shifts, [1,3] and [1,5].

[5] *D. G. Farnum* and *G. R. Carlson*, J. Amer. Chem. Soc. *92*, 6700 (1970).

[6] *H. E. Zimmerman* and *D. S. Crumrine*, J. Amer. Chem. Soc. *90*, 5612 (1968); see also *T. M. Brennan* and *R. K. Hill*, *ibid.* *90*, 5614 (1968).

[7] *O. L. Chapman*, *G. L. Eian*, *A. Bloom*, and *J. Clardy*, J. Amer. Chem. Soc. *93*, 2918 (1971).

Vinylogous Heptafulvenes from Vinylogous Fulvenes[1][**]

By *Horst Prinzbach*, *Hans-Jürgen Herr*, and *Walter Regel*[*]

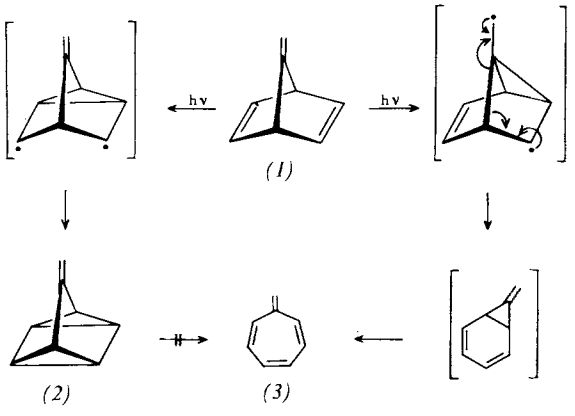
According to an undoubtedly naive working hypothesis, selective photoexcitation of the endo- and exocyclic partial chromophores in the methylenenorbornadiene system *(1)*, which are only formally independent[2], leads selectively to quadricyclane *(2)* and heptafulvene derivatives *(3)*[3] respectively.

[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. H.-J. Herr
Lehrstuhl für Organische Chemie der Universität
78 Freiburg, Albertstrasse 21 (Germany)
Dr. W. Regel
Institut für Makromolekulare Chemie der Universität
78 Freiburg, Stephan-Meier-Strasse 31 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

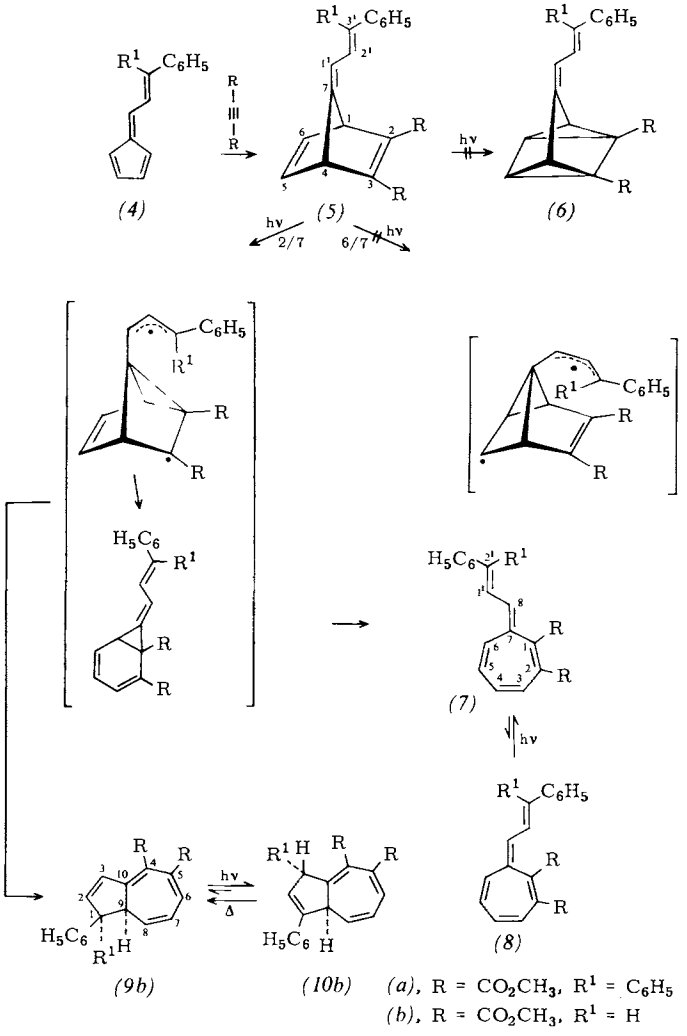
It is therefore to be expected that vinylogous heptafulvenes *(7)*[4] should be accessible by excitation of the butadiene chromophore in propenylidenenorbornadienes *(5)*.

Irradiation of a solution of *(5a)* (2.0 g), prepared from *(4a)*[5] [10 g *(4a)*; 5.6 g dimethyl acetylenedicarboxylate;



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

60 ml chloroform; 50°C; 2 d; 70%], in acetone (2 l) until conversion is complete [−20°C; *ca.* 2.5 h; Pyrex filter, Hanau TQ 2024 2000-W lamp] affords *(7a)* (70%, blue-black prisms having metallic luster) and *(8a)* (4%); the photoequilibrium[6] lies largely on the side of



(4) *(5)* *(6)* *(7)* *(8)* *(9b)* *(10b)*

(a), R = CO_2CH_3, R^1 = C_6H_5
(b), R = CO_2CH_3, R^1 = H

Table. Properties of the new compounds.

Cpd. m.p. (°C) yield	UV [a] λ_{max} (nm; ε)	NMR (τ) [b] H^1	H^3	H^4 (H^2)	H^5 (H^7)	H^6	H^8	H^9	$H^{1'}$	$H^{2'}$	$H^{3'}$	C_6H_5	$-OCH_3$	J (Hz)
(5a) 159–160 70%	295 (29500) 227 (21100)	5.93 (M)		5.35 (M)	3.0 (M)	3.0 (M)			4.93 (D)	3.47 (D)		2.60 to 2.93	6.26 6.31	$J_{1',2'}=11.5$
(5b) 85%	310 (S, 18600) 290 (34000) 282 (S, 29800) 234 (14200) 227 (17600) 221 (17000)	5.82 (M)		5.38 (M)	3.0 (M)	3.0 (M)			4.90 (D)	3.37 (dD)	3.71 (D)	2.57 to 2.94	6.20 6.20	$J_{1',2'}=10.0$ $J_{2',3'}=15.0$
(7a) 183 70% [c]	369 (27500) 286 (10100) 242 (16400)		3.54 (D)	3.86 (dD)	4.07 (dD)	3.70 (D)	4.18 (D)		3.24 (D)			2.58 to 3.14	6.39 6.50	$J_{3,4}=12.0$ $J_{4,5}=6.0$ $J_{5,6}=11.0$ $J_{8,1'}=11.2$
(7b) 108 25% [c]	358 (28800) 286 (15700) 234 (12500)		3.35 (D)	4.05 (dD)	4.28 (dD)	3.88 (D)	3.62 (D)		2.91 (dD)	3.68 (D)		2.68 to 3.14	6.43 6.68	$J_{3,4}=12.0$; $J_{4,5}=6.0$ $J_{5,6}=11.0$ $J_{8,1'}=12.0$ $J_{1',2'}=15.0$
(8a) 4%	349 (16200) 290 (S, 6000) 240 (12800)		3.52 (M)	3.68 (M)	4.10 (M)	3.91 (M)	4.15 (dD)		3.20 (D)			2.55 to 3.12	6.28 6.35	$J_{3,4}=11.5$; $J_{3,5}=1.5$ $J_{3,6}=1.0$; $J_{4,5}=6.5$ $J_{4,6}=1.0$; $J_{5,6}=10.5$ $J_{6,8}=1.5$; $J_{8,1'}=11.8$
(8b) 4%	343 (7300) 272 (4800) 234 (7000)		3.47 (M)	3.93 (M)	4.28 (M)	3.95 (M)	4.12 (M)		under phenyl (dD)	3.66 (D)		2.50 to 3.12	6.52 6.58	$J_{3,4}=11,5$; $J_{3,5}=1.0$ $J_{4,5}=6.0$; $J_{4,6}=1.0$ $J_{5,6}=10.8$; $J_{8,1'}=12.0$ $J_{1',2'}=15.2$
(9b) 7% [c]	306 (3400) 254 (18200)	6.26 (M)	2.74 (dD)	3.84 (dD)	4.17 (M)	2.60 (dD)	4.52 (dD)	7.16 (M)				2.87 to 3.16	6.33 6.53	$J_{1,2}=2.9$; $J_{1,9}=3.0$ $J_{1,3}=2.0$; $J_{2,3}=5.5$ $J_{6,7}=5.0$; $J_{6,8}=1.4$ $J_{7,8}=9.8$; $J_{7,9}=2.0$ $J_{8,9}=4.0$
(10b) 14% [c]	240 (8400)		6.32 (M) 6.44 (M)	4.24 (M)	4.08 (M)	3.97 (M)	4.08 (M)	6.72 (M)				2.58 to 2.85	6.18 6.18	
(11a) 166–168 10%	380 (39700) 253 (S, 12800)	5.18 (D)			4.97 (D)		3.94 (dD)	3.68 (dD)	3.34 (D)	2.48 (D)		2.51 to 3.00	6.61 6.71	$J_{1,8}=6.5$; $J_{5,9}=7.0$ $J_{8,9}=7.0$; $J_{1',2'}=11.5$
(11b) 196–197 21%	361 (28800) 269 (10400)	5.23 (D)			5.02 (D)		4.00 (dD)	3.72 (dD)	3.33 (D)	2.51 (dD)	3.43 (D)	2.64 to 3.06	6.39 6.61 6.65 6.77	$J_{1,8}=6.5$; $J_{5,9}=6.5$ $J_{8,9}=6.5$ $J_{1',2'}=11.5$ $J_{2',3'}=15.0$
(12a) 124–127 (dec.) 100%	330 (S, 1700) 261 (17300) [d]		2.82 (D)	4.27 (dD)	4.19 (dD)	4.02 (D)	5.28 (D)		3.71 (D)			2.73 to 3.19	6.60 6.81	$J_{3,4}=7.5$; $J_{4,5}=11.0$ $J_{5,6}=7.0$; $J_{8,1'}=10.5$
(12b) 141–143 (dec.) 100%	330 (4300) 293 (4700) 285 (S, 6500) 256 (19500) [d]		2.50 (D)	3.37–3.60 multiplets			5.36 (D)		3.70 (dD)	3.21 (D)		2.54 to 2.70	6.09 6.22	$J_{3,4}=7.8$; $J_{8,1'}=9.0$ $J_{1',2'}=15.5$

[a] In acetonitrile. [c] Acetone-sensitized. [d] Possibly partly dissociated.
[b] *(5a)* in $CDCl_3$, 60 MHz; *(5b)* in CCl_4, 60 MHz; *(7a)* and *(10b)* in CCl_4, 220 MHz; *(7b)*, *(11a)*, *(11b)*, *(12a)* in C_6D_6, 220 MHz; *(8a)* in CCl_4, 100 MHz; *(8b)* in C_6D_6, 100 MHz; *(9b)* in C_6D_6, 60 MHz; *(12b)* in $CDCl_3$, 220 MHz. – The coupling constants in the 220 MHz spectra are ±0.5 Hz.

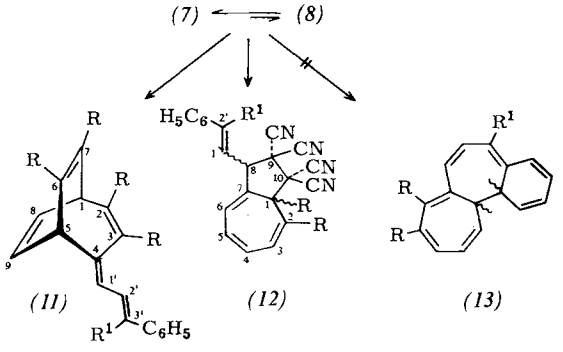
(7a) [90% *(7a)*, 10% *(8a)*]. The quadricyclane *(6a)* cannot be detected[7].

Under the same conditions compound *(5b)* gives only 25% of *(7b)* (amethyst prismatic crystals) and 4% *(8b)*, the photoequilibrium mixture[6] contains 87% *(7b)* and 13% *(8b)*. Chromatography with benzene on SiO_2 also gave 20% of a mixture of the dihydroazulenes *(9b)* and *(10b)* (1:2), *(10b)* actually being formed from *(9b)*: on heating, *(9b)* is quantitatively regenerated. Control experiments show that *(9b)* is not formed from *(7b)* or *(8b)*; it is not yet clear when ring closure takes place[9].

Direct irradiation of *(5a)* and *(5b)* (CH_3CN; otherwise identical conditions) yields only the products *(7a)* and *(8a)* and *(7b)* and *(8b)* respectively with slightly varying relative proportions of components[11]. In this case too

no isomers of *(7)* and *(9)*, *i.e.* reaction products of the diradical formed by 6/7 bridging in *(5)*, could be detected.

The structures *(5)*, *(7)*, *(8)*, *(9)*, and *(10)* are characterized by elemental analysis and by mostly typical spectral data (Table); they were further confirmed by addition reactions or oxidation to the corresponding azulenes[10]. Reaction of *(7a)* and *(7b)* with dimethyl acetylenedicarboxylate only occurs in a temperature range in which their thermal rearrangement[10] is already very fast; the adducts which were consequently isolated in only small yields were shown by spectroscopy to have the structures *(11a)* and *(11b)* resulting from a [4+2]-addition. Tetracyanoethylene adds rapidly and almost quantitatively at 20°C to give the [8+2]-adducts *(12a)* and *(12b)*[12]. $[{}_{\pi}2_s+{}_{\pi}10_a]$-addition to the *s-cis* conformations, which appears sterically reasonable and would give heptalene derivatives, does not occur. A further expectation based on the synthesis of the vinylogous heptafulvenes was not fulfilled either: no photochemical cyclization to give fused heptalene derivatives [*e.g. (13)*] could be achieved under a variety of conditions.



Received: November 5, 1971 [Z 540a IE]
German version: Angew. Chem. *84*, 113 (1972)

[1] Photochemical transformations, Part 46.— Part 45: *W. Eberbach, M. Perroud-Argüelles, H. Achenbach, E. Druckrey,* and *H. Prinzbach,* Helv. Chim. Acta, *54*, 2579 (1971).

[2] *H. D. Martin* and *D. Forster,* Angew. Chem. *84*, 65 (1972); Angew. Chem. internat. Edit. *11*, 54 (1972).

[3] *H. Prinzbach* and *J. Rivier,* Helv. Chim. Acta *53*, 2201 (1970); *H. Prinzbach* and *M. Thyes,* Chem. Ber. *104*, 2489 (1971); *G. Kaupp,* Angew. Chem. *83*, 361 (1971); Angew. Chem. internat. Edit. *10*, 340 (1971).

[4] *D. J. Bertelli, C. Golino,* and *D. L. Dreyer,* J. Amer. Chem. Soc. *86*, 3329 (1964).

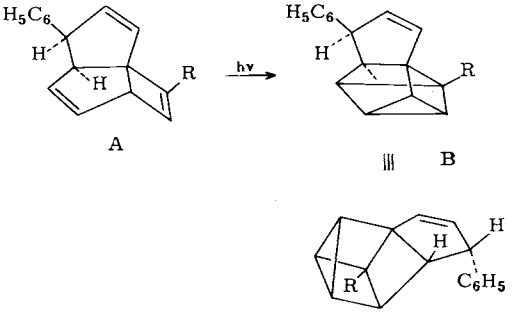
[5] *J. Thiele* and *H. Balhorn,* Liebigs Ann. Chem. *348*, 9 (1906).

[6] Hanovia 450-W Hg high-pressure lamp, CH_3CN, Pyrex filter.

[7] Quantitative isomerization of *(6a)* to *(5a)* [8] and/or *(7a)* is rather unlikely.

[8] *G. Kaupp* and *H. Prinzbach,* Liebigs Ann. Chem. *725*, 52 (1969).

[9] Intermediates of structure A can be ruled out. We have synthesized A (R = CO_2CH_3) by another route [10]; it gives a fairly uniform yield of the homoprismane derivative B on direct and on sensitized irradiation.



[10] *H. Prinzbach* and *H.-J. Herr,* Angew. Chem. *84*, 117 (1972); Angew. Chem. internat. Edit. *11*, 135 (1972).

[11] Compare the different result obtained in the case of the fused methylenenorbornadiene: *W. Eberbach, P. Würsch,* and *H. Prinzbach,* Helv. Chim. Acta *53*, 1235 (1970). Very recent studies show the isomerization to proceed exclusively *via* primary bond formation in the norbornadiene system *(W. Mehnert,* Staatsarbeit, Universität Freiburg 1971).

[12] *W. v. E. Doering* and *D. W. Wiley,* Tetrahedron *11*, 183 (1960); *M. Oda* and *Y. Kitahara,* Bull. Chem. Soc. Jap. *213*; 1920 (1970).

Sesquifulvalenes from Dihydrofulvalenes[1][**]

By *Horst Prinzbach* and *Hubert Sauter*[*]

Suitably substituted sesquifulvalenes have become of preparative significance as polyene reactants in the synthesis of σ-bridged annulenes[2]. We have now opened up a new route to this class of compounds in the preparation of 1,2-bis(methoxycarbonyl)-8,9-diphenylsesquifulvalene *(8)* by a method developed on the basis of the photoisomerization of vinylogous methylenenorbornadienes to vinylogous heptafulvenes[3].

Condensation of hydroxydiphenylcyclopentenone *(3)*[4] with cyclopentadiene under standard conditions[5] affords the dihydrofulvalene *(4)* in 70% yield. Mild dehydration over Al_2O_3 yields 2,3-diphenylfulvalene *(1)* pure in solution[6]; however, owing to the rapid dimerization of the fulvalene[7] and the formation of 1:2 adducts addition of dimethyl acetylenedicarboxylate to *(1)* gives an insufficient yield of cyclopentadienylidenenorbornadiene *(2)*. In contrast, *(4)* reacts with dimethyl acetylenedicarboxylate to give at least 90% of a mixture (*ca.* 1:1) of the adducts *(5)* and *(6)*; the latter can be separated by chromatography [Al_2O_3, basic, deactivated with 10% H_2O (Woelm), benzene/CH_2Cl_2 (1:1)]. Acid-catalyzed dehydration to *(2)*, which is isolated as yellow crystals, proceeds in 60 to 70% yield.

Previous studies have shown that the electronically excited polyene *(2)* avoids substantial conversion into *(8)* by undergoing side reactions. While *direct* irradiation (ether, Pyrex filter, Hanau Q 81 high-pressure mercury arc lamp) furnishes only traces of *(8)* alongside products of high molecular weight, the *sensitized* reaction (acetone) affords about 10% of *(8)*. Rearrangement of *(5)* and *(6)*, individually or together, proceeds almost quantitatively on irradiation in acetone (Hanovia 2000-W high-pressure mercury arc lamp, Pyrex filter); a 3:1 mixture (photoequilibrium) of the isomeric dihydrosesquifulvalenes *(9)* and *(10)* is formed in each case. On treatment with acid *(9)* and *(10)* lose water to yield the sesquifulvalene *(8)* which crystallizes as violet needles from ether. At 20°C, *(8)* rapidly adds one equivalent of tetracyanoethylene in positions 7/10; however, the resulting adduct is not stable but slowly rearranges *via* the product of α,ω-([12+2])-addition[6,8] to *(7)*.

Correct elemental analyses were obtained for all new compounds. The characteristic spectral data are presented in the Table. Assignment of the isomeric pairs *(5)/(6)* and *(9)/(10)* is not yet definite.

[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. H. Sauter
Lehrstuhl für Organische Chemie der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

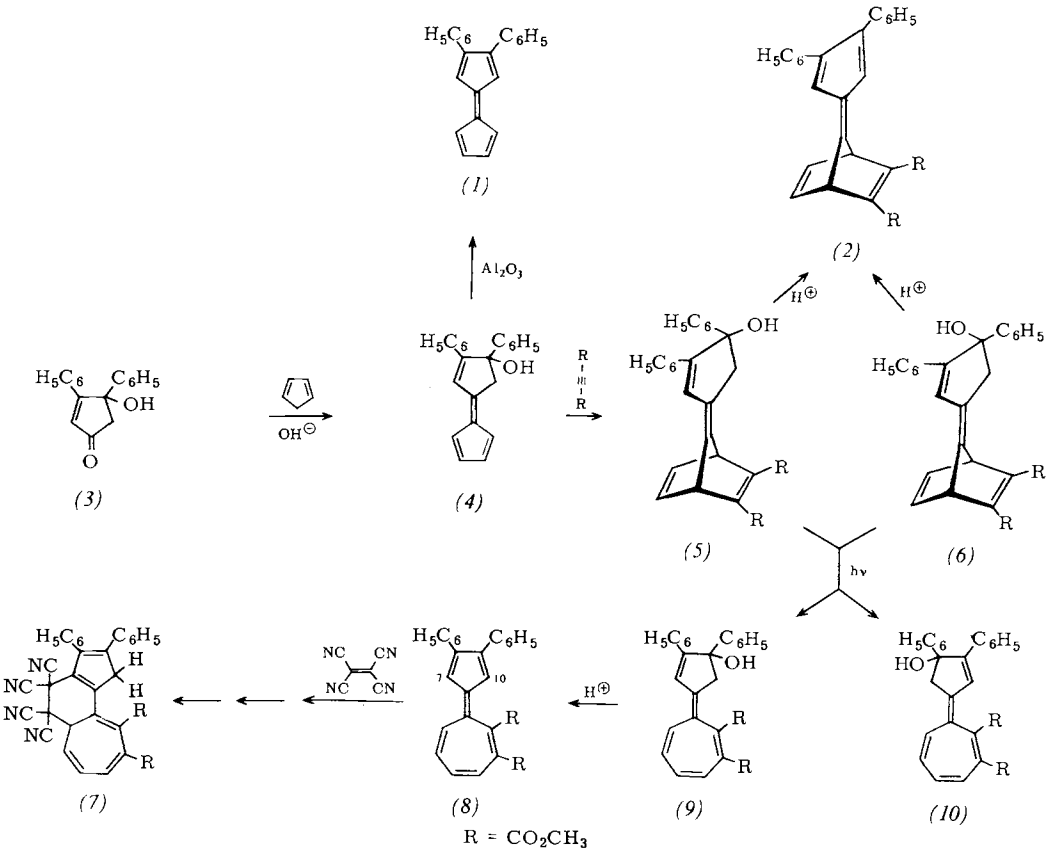


Table. Properties of the new compounds.

Cpd. m.p. (°C)	UV [a] λ_{max} (nm; ε)	NMR (τ)		
(1)	361	2.6–2.9	(10 H/M)	[b]
		3.26	(2 H/S)	
		3.40	(4 H/br. "S", AA'BB')	
(2)	380 (S, 1000)	2.5–3.1	(10 H/M)	[c]
170	311 (23000)	3.24	(2 H/M)	
	250 (24000)	3.54	(2 H/S)	
		3.38	(2 H/M)	
		6.53	(6 H/S)	
(4)	355 (36000)	2.4–3.1	(11 H/M)	[d]
134–136	258 (S, 7700)	3.2–3.9	(4 H/M)	
	252 (8100)	6.72	(2 H/AB, J^{AB} = 18.9 Hz)	
		7.9	(1 H/br. S)	
(5)	322 (S, 16000)	2.4–3.3	(12 H/M)	[c]
	307 (S, 27000)	3.36	(1 H/S)	
	296 (28000)	5.35	(1 H/M)	
	238 (S, 17000)	5.82	(1 H/M)	
	230 (21000)	6.49	(3 H/S)	
		6.54	(3 H/S)	
		7.27	(2 H/AB, J^{AB} = 16.8 Hz)	
		7.9	(1 H/br. S)	
(6)	322 (S, 16000)	2.4–3.3	(12 H/M)	[c]
147–148	307 (S, 27000)	3.35	(1 H/S)	
	296 (28000)	5.35	(1 H/M)	
	238 (S, 17000)	5.83	(1 H/M)	
	230 (21000)	6.49	(3 H/S)	
		6.50	(3 H/S)	
		7.31	(2 H/br. "S", AB)	
		7.9	(1 H/br. S)	

Cpd. m.p. (°C)	UV [a] λ_{max} (nm; ε)	NMR (τ)		
(8)	385 (24000)	2.6–3.1	(10 H/M)	[e]
141	257 (26000)	3.24	(1 H/D, J = 2.5 Hz)	
		3.39	(2 H/2 superimposed D, $J' = J'' \approx 11$ Hz)	
		3.47	(1 H/D, $J \approx 2.5$ Hz)	
		3.91	(1 H/dD, $J' \approx 11, J''' \approx 6.5$ Hz)	
		4.16	(1 H/dD, $J'' \approx 11, J''' \approx 6.5$ Hz)	
		6.56	(3 H/S)	
		6.65	(3 H/S)	
(9)	347 (20000)	2.3–3.2	(11 H/M)	[e]
	270 (S, 12500)	3.42	(1 H/D, $J \approx 11$ Hz)	
	240 (18000)	3.91	(1 H/dD, $J \approx 11, J'' \approx 6$ Hz)	
		4.21	(1 H/D, $J' \approx 10.5$ Hz)	
		4.30	(1 H/dD, $J' \approx 10.5, J'' \approx 6$ Hz)	
		6.56	(6 H/S)	
		7.14	(2 H/AB, $J^{AB} \approx 17$ Hz)	
		7.3	(1 H/br. S)	
(10)	342 (23000)	2.2–3.2	(11 H/M)	[e]
149–150	287 (14000)	3.39	(1 H/D, $J \approx 11$ Hz)	
	233 (S, 13500)	3.61	(1 H/D, $J' \approx 10.5$ Hz)	
		3.80	(1 H/dD, $J \approx 11, J'' \approx 6$ Hz)	
		4.08	(1 H/dD, $J' \approx 10.5, J'' \approx 6$ Hz)	
		6.60	(3 H/S)	
		6.74	(3 H/S)	
		7.08	(2 H/AB, $J^{AB} \approx 17$ Hz)	
		7.4	(1 H/br. S)	

[a] In ethanol, except for *(1)* (pentane).
[b] In CCl_4 (−15 °C; 60 MHz).
[c] In C_6D_6 (60 MHz).
[d] In $CDCl_3/C_6D_6$ (1:1) (60 MHz).
[e] In C_6D_6 (220 MHz).

1,2-Bis(methoxycarbonyl)-8,9-diphenylsesquifulvalene (8)

(4) (14.9 g, 50 mmol) is refluxed with dimethyl acetylenedicarboxylate (7.8 g, 55 mmol) in anhydrous benzene (100 ml) for 4 h. After removal of the benzene the residue [*(5)*/*(6)*] is dissolved in acetone (1.7 liter) and irradiated in a Pyrex vessel (0 °C) with the light from a Hanau TQ 2024 2000-W lamp until reaction is complete (6 h, NMR monitoring). The acetone is distilled off and conc. HCl (20 ml) is added to a solution of the residue in CH_2Cl_2 (2 liter). After 15 min the reaction mixture is neutralized by addition of sodium hydrogencarbonate solution, and the organic phase is dried and chromatographed with benzene on Al_2O_3 [basic, deactivated with 6% H_2O (Woelm)]. The deep red zone that is first eluted gives 8.2 g of *(8)* [39% based on *(4)*] on recrystallization from ether.

Received: November 5, 1971 [Z 540b IE]
German version: Angew. Chem. *84*, 115 (1972)

[1] Photochemical transformations, Part 47. — Part 46, see ref. [3].

[2] For a review, see *H. Prinzbach*, Pure Appl. Chem. *28*, 281 (1971).

[3] *H. Prinzbach, H.-J. Herr*, and *W. Regel*, Angew. Chem. *84*, 113 (1972); Angew. Chem. internat. Edit. *11*, 131 (1972).

[4] *F. R. Japp* and *J. Knox*, J. Chem. Soc. *87*, 673 (1905).

[5] *P. Yates*, Advan. Alicycl. Chem. *2*, 60 (1968).

[6] *H. Prinzbach* and *H. Sauter*, to be published.

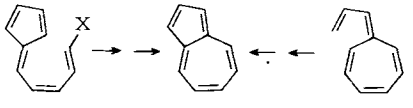
[7] *W. v. E. Doering* in Theoretical Organic Chemistry. Butterworths, London 1959, p. 35.

[8] *H. Prinzbach, H. Knöfel* and *E. Woischnik* in: Aromaticity, Pseudo-Aromaticity, Anti-Aromaticity. The Jerusalem Academy of Sciences and Humanities, Jerusalem 1971, p. 269; *H. Prinzbach* and *H. Knöfel*, Angew. Chem. *81*, 900 (1969); Angew. Chem. internat. Edit. *8*, 881 (1969).

New Routes to the Azulene System[1][**]

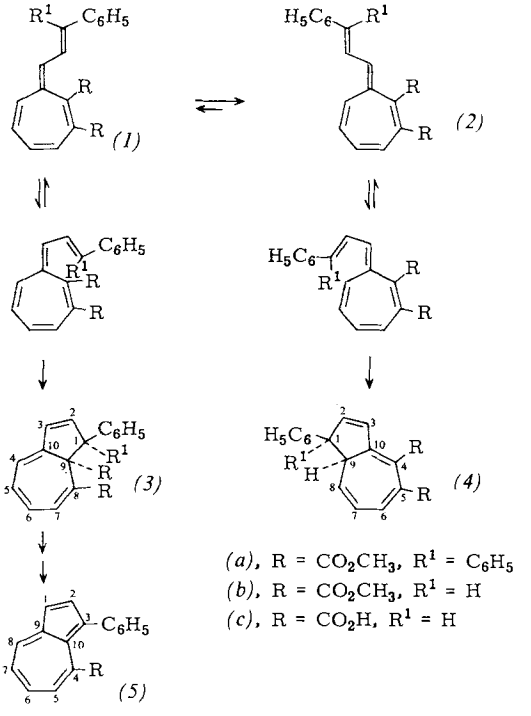
By *Horst Prinzbach* and *Hans-Jürgen Herr*[*]

The most important synthesis of azulenes, which has repeatedly been modified[2], involves cyclization of doubly vinylogous fulvenes to form seven-membered rings. We have now found that the azulene system is also accessible by formation of the five-membered ring from vinylogous heptafulvenes.



If a solution of *(1a)* or *(2a)*, or *(1b)* or *(2b)*[3], (1.5 mmol) in pure perchlorobutadiene (5 ml) is heated to 170 °C the *cis/trans* equilibrium *(1a)*⇌*(2a)* or *(1b)*⇌*(2b)* (*ca.* 1:9 in each case) is rapidly established (*ca.* 5 min). NMR and UV spectroscopy show that *(4a)* is formed selectively in the slower electrocyclic reaction of *(1a)*⇌*(2a)* (*ca.* 60 min, 80% colorless needles), while *(1b)*⇌*(2b)* yields *(3b)* (90% yellow prisms).

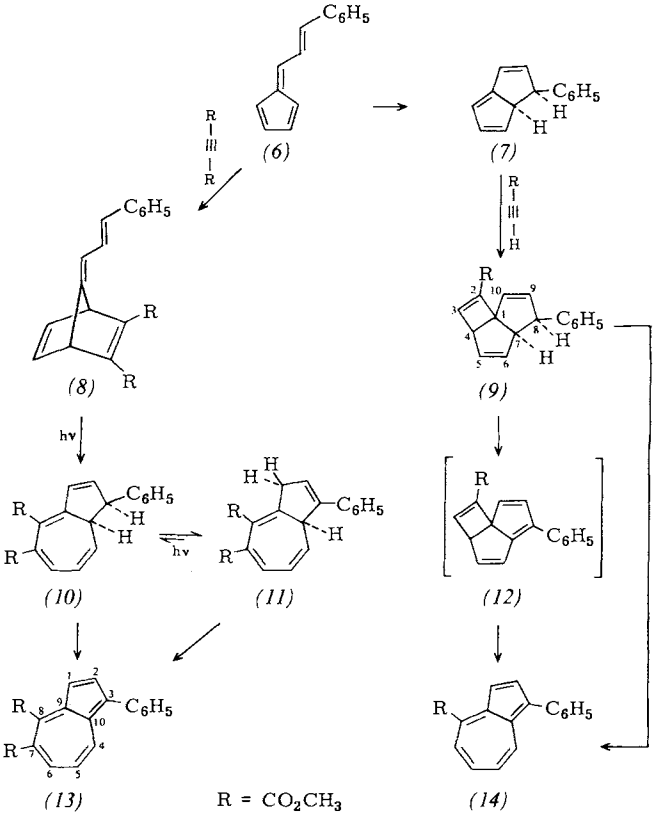
Treatment of *(3b)* (2.5 mmol) with dilute caustic potash (10 mmol of KOH in 40 ml of H_2O; 100 °C) gives the



(a), R = CO_2CH_3, R^1 = C_6H_5
(b), R = CO_2CH_3, R^1 = H
(c), R = CO_2H, R^1 = H

azulenecarboxylic acid *(5c)* by way of hydrolysis, decarboxylation, and oxidation; *(5c)* reacts almost quantitatively with diazomethane to give methyl 3-phenylazulene-4-carboxylate *(5b)*.

It is most improbable that the dihydroazulene *(10)*, formed in photoequilibrium with *(11)* from the vinylogous methylenenorbornadiene *(8)* on acetone-sensitized irradiation[3], arises *via (1b)* or *(2b)*. *(10)* and *(11)* are readily oxidized by 2,3-dichloro-5,6-dicyanoquinone (in benzene or CCl_4) at 20 °C to blue-black crystals of dimethyl 3-phenylazulene-7,8-dicarboxylate *(13)*[4].



R = CO_2CH_3

[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. H.-J. Herr
Lehrstuhl für Organische Chemie der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Table. Properties of the new compounds.

Cpd. m.p. (°C) yield	UV λ_{max} (nm; ε)	NMR (τ) [c] H^1	H^2	H^3	H^4	H^5	H^6	H^7	H^8	H^9	H^{10}	C_6H_5	$-OCH_3$	J (Hz)
(3b) 157 90%	399 (2800) [a] 273 (S, 4300) 266 (S, 5700) 237 (21700)	4.72 (D)	3.95 (dD)	4.07 (D)	4.07 (D)	4.16 (dD)	4.32 (dD)	3.27 (D)				2.59 to 3.08	6.55 6.94	$J_{1,2}=2.5$; $J_{2,3}=5.5$ $J_{4,5}=7.0$; $J_{5,6}=9.0$ $J_{6,7}=8.0$
(4a) 155.5 80%	308 (8400) [a] 248 (18800)		2.30 (D)	3.41 (D)			3.66 (D)	4.00 (dD)	4.20 (dD)	5.46 (D)		2.71 to 3.02	6.57 6.84	$J_{2,3}=6.0$; $J_{6,7}=6.5$ $J_{7,8}=9.5$; $J_{8,9}=8.5$
(5b) 113 50–60%	710 (S, 260) [b] 662 (310) 625 (S, 260) 375 (S, 2300) 358 (5700) 300 (49000) 240 (23000) 224 (17000)	1.98 (D)	1.84 (D)			1.59	2.00 under H^1 (dD)	under C_6H_5 (dD)	1.36 (D)			2.30 to 2.68	6.05	$J_{1,2}=3.8$; $J_{5,6}=10.0$ $J_{7,8}=10.5$
(9) 20–25%	268 (2500) [a] 259 (2600) 253 (2900) 233 (2900)			2.68 (dD)	6.66 (M)	3.48 (dD)	3.07 (D)	7.18 (D)	6.53 (M)	3.20 (M)	4.24 (dD)	2.73 to 2.94	6.53	$J_{3,4}=3.0$; $J_{3,7}=1.0$ $J_{4,5}=3.0$; $J_{4,7}=1.0$ $J_{4,9}=1.0$; $J_{5,6}=5.2$ $J_{7,8}=9.0$; $J_{8,9}=2.8$ $J_{8,10}=1.7$; $J_{9,10}=5.9$
(13) 120 60–65%	717 (S, 81) [b] 642 (S, 230) 600 (280) 560 (S, 230) 400 (13500) 301 (38800) 243 (S, 17400) 224 (22400)	2.40 (D)	1.97 (D)		1.49 (D)	2.93 (dD)	1.62 (D)					2.46 to 2.73	5.93 6.08	$J_{1,2}=3.8$; $J_{4,5}=9.6$ $J_{5,6}=10.8$
(14) 60%	635 (430) [b] 361 (7000) 300 (47500) 238 (32200)	1.98 (D)	1.87 (D)		1.57 (D)	3.34 (dD)	2.89 (dD)	2.64 (D)				2.42 to 3.05	6.43	$J_{1,2}=3.8$; $J_{4,5}=9.7$ $J_{5,6}=9.7$; $J_{6,7}=10.1$

[a] In acetonitrile. [b] In ethanol.

[c] *(3b)*, *(4a)*, and *(14)* in C_6D_6, 220 MHz; *(5b)* in $CDCl_3$, 220 MHz; *(9)* in C_6D_6, 60 MHz; *(13)* in $CDCl_3$, 60 MHz. – The coupling constants in the 220-MHz spectra are ±0.5 Hz.

The synthesis of methyl 3-phenylazulene-8-carboxylate *(14)* also follows a rather unusual route that is not yet clear in all details. Reaction of the vinylogous fulvene *(6)* with methyl propiolate (1:3, toluene, 110°C) yields, in addition to the norbornadiene derivative analogous to *(8)*, an isomeric 1:1 adduct (20–25%) that is not the product of an [8+2]addition[5] but, according to monitoring experiments, results from the dihydropentalene *(7)*[6]. The tricyclic compound, which is stable up to at least 80°C, is oxidized by dichlorodicyanoquinone in boiling benzene to *(14)* in 60% yield. Mainly for this reason we tentatively assign structure *(9)* in preference to the alternative structure from a [4+2] addition to *(7)*. There is evidence for the occurrence of an intermediate, possibly *(12)*, which is unstable under the reaction conditions.

The spectral data collected in the Table for the new compounds prepared[7] need no further explanation. It should be mentioned that the electronic spectrum of *(4a)* closely resembles that of the analogous monophenyl compound[3] and that the absorption maxima of the azulenes *(5)*, *(13)*, and *(14)* are as expected[8]. The positions of the substituents are also established unequivocally by the NMR data.

Received: November 5, 1971 [Z 540c IE]
German version: Angew. Chem. *84*, 117 (1972)

[1] Cyclic cross-conjugated bond systems, Part 24.—Part 23: *H. Prinzbach*, Pure Appl. Chem. *28*, 281 (1971).

[2] *K. Hafner*, Angew. Chem. *67*, 301 (1955); *W. Keller-Schierlein* and *E. Heilbronner* in *D. Ginsburg*: Non-Benzenoid Aromatic Compounds. Interscience, New York 1959, p. 277.

[3] *H. Prinzbach*, *H.-J. Herr*, and *W. Regel*, Angew. Chem. *84*, 113 (1972); Angew. Chem. internat. Edit. *11*, 131 (1972).

[4] We are currently determining the scope of this process by variation of the substituents in *(8)*.

[5] Cf. *R. W. Alder* and *G. Whittaker*, Chem. Commun. *1971*, 776.

[6] *R. Kaiser* and *K. Hafner*, Angew. Chem. *82*, 877 (1970); Angew. Chem. internat. Edit. *9*, 892 (1970); *K. Hafner*, Pure Appl. Chem. (1971), in press; cf. *J. J. Gajewski* and *C. J. Cavender*, Tetrahedron Lett. *1971*, 1057.

[7] Satisfactory elemental analyses were obtained.

[8] *E. Heilbronner* in *D. Ginsburg*: Non-Benzenoid Aromatic Compounds. Intersience, New York 1959, p. 171.

Reaction of a $L_2Ni(0)$ System with Allenes

By *M. Englert*[**], *P. W. Jolly*, and *Günther Wilke*[*]

Nickel(0) complexes having phosphane or phosphite ligands (Ni:P = 1:1) catalyze the dimerization of butadiene to 1,5-cyclooctadiene[1]. Allene undergoes oligomerization

[*] Prof. Dr. G. Wilke, Dr. M. Englert, and Dr. P. W. Jolly
Max-Planck-Institut für Kohlenforschung
433 Mülheim-Ruhr, Lembkestrasse 5 (Germany)

[**] Part of Doctoral Dissertation, Universität Bochum 1971.

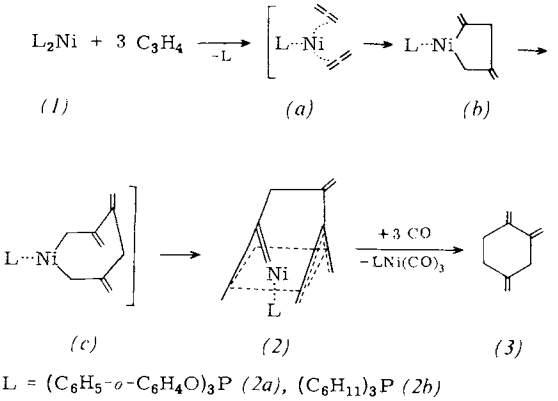
giving dimers to pentamers in the presence of similar Ni(0) complexes[2–4]. An intermediate with a ligand system consisting of three allene molecules was recently described[5]. In the present communication we report findings that led eventually to a complete structure analysis of such an intermediate by three-dimensional X-ray methods.

Our studies on bis(tri-2-biphenylylphosphite)nickel *(1)*[6] have shown that this complex containing coordinately unsaturated nickel(0) can be used to trap intermediates in the oligomerization of allene.

Allene reacts with *(1)* (3:1) in toluene at 20 °C to give an orange crystalline product *(2a)* of composition $C_9H_{12}NiL$ [$L=(C_6H_5\text{-}o\text{-}C_6H_4O)_3P$], which reacts quantitatively with triphenylphosphane or carbon monoxide to yield 1,2,4-trimethylenecyclohexane *(3)*. The ^{1}H-NMR spectrum of *(2a)*, which resembles that of the analogous Pd complex[7], indicates the presence of a free C=C bond and of a *cis*-bis(π-allyl)nickel system: τ = 5.3 (1H), 5.6 (1H), 7.40 (2H), 7.56 (2H), 7.63 (2H) [8.60d (2H); J = 10.4 Hz], [8.68d (2H); J = 9.7 Hz].

A completely analogous preparation yields the corresponding compound *(2b)*, containing tricyclohexylphosphane as additional ligand, whose structure was proved by the ^{1}H-NMR spectrum—τ = 4.84 (1H), 5.26 (1H), 6.90 (2H), 7.05 (4H), [8.13d (2H); J = 10 Hz], [8.21d (2H); J = 9 Hz] and by X-ray structure analysis[8].

We assume that *(2)* is formed in a multi-step reaction proceeding *via* the following intermediates:

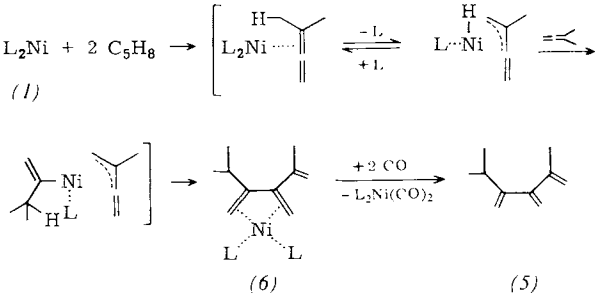


(1) *(a)* *(b)* *(c)* *(2)* *(3)*

L = $(C_6H_5\text{-}o\text{-}C_6H_4O)_3P$ *(2a)*, $(C_6H_{11})_3P$ *(2b)*

Intermediate *(a)* corresponds to a LNi-bis(olefin) complex in which two allene molecules are bonded, as in an analogous bis(ethylene) system[9], through one C=C double bond to the LNi group in such a manner that the four carbon atoms and the L·Ni group are practically coplanar. Carbon-carbon coupling leads to *(b)* containing two C—Ni bonds of which the metal-vinyl bond again adds to allene furnishing *(c)*. The ligand in *(c)* then inverts to give a *cis*-bis(π-allyl)nickel system containing formally five-coordinated nickel. At elevated temperatures or in the presence of donors the allyl groups in *(2)* couple and 1,2,4-trimethylenecyclohexane *(3)* is liberated. *(2)* contains asymmetric allyl groups[8]; and in particular that lying opposite the "*exo*" methylene group should be written as having a C=C bond and a C—C bond.

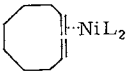
Reaction of *(1)* with 1,1-dimethylallene (1:2) in toluene follows a different course to yield, at 20 °C, a pale yellow, sparingly soluble substance *(4)* having the composition $C_{10}H_{16}NiL_2$ [$L=(C_6H_5\text{-}o\text{-}C_6H_4O)_3P$], which reacts with carbon monoxide at −78 °C or with triphenylphosphane at 80 °C to give 2,5-dimethyl-3,4-dimethylene-1-hexene *(5)* in 90—95% yield. At 60 °C this triene is formed catalytically on the $L_2Ni(0)$ system. It is not possible to decide whether the allene molecules are already joined in (4) or whether such linkage actually happens on displacement. A complex of *(5)* corresponding to *(6)* is probably present which is possibly formed *via* a π-allyl intermediate that is produced in an equilibrium similar to that found for a propylene·NiL complex[10]:



(1) *(6)* *(5)*

(6) corresponds to the complex formed from *(1)* and butadiene[6].

The simplest intermediate was found in the reaction of *(1)* with 1,2-cyclononadiene (1:1) in which a cyclononadiene·NiL_2 complex *(7)* is formed.



(7)

1,2-Cyclononadiene is displaced unchanged from *(7)* by triphenylphosphane. At 60 °C, however, catalytic oligomerization with *(1)* occurs; mass spectrometry shows the product to contain trimers to hexamers.

Received: September 15, 1971 [Z 542a IE]
German version: Angew. Chem. *84*, 120 (1972)

[1] *W. Brenner, P. Heimbach, H. J. Hey, E. W. Müller*, and *G. Wilke*, Liebigs Ann. Chem. *727*, 161 (1969).

[2] *R. E. Benson* and *R. V. Lindsey*, J. Amer. Chem. Soc. *81*, 4247 (1959).

[3] *F. W. Hoover* and *R. V. Lindsey*, J. Org. Chem. *34*, 3057 (1969).

[4] *S. Otsuka, A. Nakamura, K. Tani*, and *S. Ueda*, Tetrahedron Lett. *1969*, 297.

[5] *S. Otsuka, A. Nakamura, S. Ueda*, and *K. Tani*, Chem. Commun. *1971*, 863.

[6] *M. Englert, P. W. Jolly*, and *G. Wilke*, Angew. Chem. *83*, 84 (1971); Angew. Chem. internat. Edit. *10*, 77 (1971).

[7] *T. Okamoto, Y. Sakakitara*, and *S. Kunchika*, Bull. Chem. Soc. Jap. *43*, 2658 (1970).

[8] *B. L. Barnett, C. Krüger*, and *Y.-H. Tsay*, Angew. Chem. *84*, 120 (1972); Angew. Chem. internat. Edit. *11*, 137 (1972).

[9] *C. Krüger* and *Y.-H. Tsay*, J. Organometal. Chem., in press.

[10] *H. Bönnemann*, Angew. Chem. *82*, 699 (1970); Angew. Chem. internat. Edit. *9*, 736 (1970).

Molecular Structure of a Bridged *cis*-Bis(π-allyl)nickel System

By *Bobby L. Barnett, Carl Krüger*, and *Yi-Hung Tsay*[*]

Although the presence of *cis*-bis(π-allyl)nickel in equilibrium with *trans*-bis(π-allyl)nickel has been established by spec-

[*] Dr. C. Krüger, Dr. B. L. Barnett, and Dr. Y.-H. Tsay
Max-Planck-Institut für Kohlenforschung
433 Mülheim-Ruhr, Lembkestrasse 5 (Germany)

troscopy, the former has defied all attempts at isolation and characterization[1]. The complex of nickel(0) with tricyclohexylphosphane and a trimerization product of allene as ligands described in the preceding communication[2] forms triclinic crystals (unit cell: $a=14.443(9)$, $b=11.406(5)$, $c=13.151(9)$ Å; $\alpha=95.97\pm0.04$, $\beta=135.65\pm0.04$, $\gamma=100.32\pm0.03°$; space group $P\bar{1}$; $Z=2$; $d_{calc}=1.195$ g cm^{-3}) and thus allows a three-dimensional X-ray structural analysis to be performed.

The structure was solved by the heavy atom method with 4533 diffractometer data collected in the space group $B\bar{1}$ ($\lambda=1.5418$)[3]. It was found that one molecule of solvent (toluene) is disordered about a center of symmetry in the crystal lattice. Anisotropic least-squares refinement including isotropic hydrogen atoms and a disordered toluene with partial occupancy factors gave a final $R=8.9\%$. Anomalous scattering of the heavy atoms was used in these calculations[4].

The structure of the complex is illustrated in Figure 1; the geometry of the ligands of interest is shown in Figure 2 (distances in Å, angles in °).

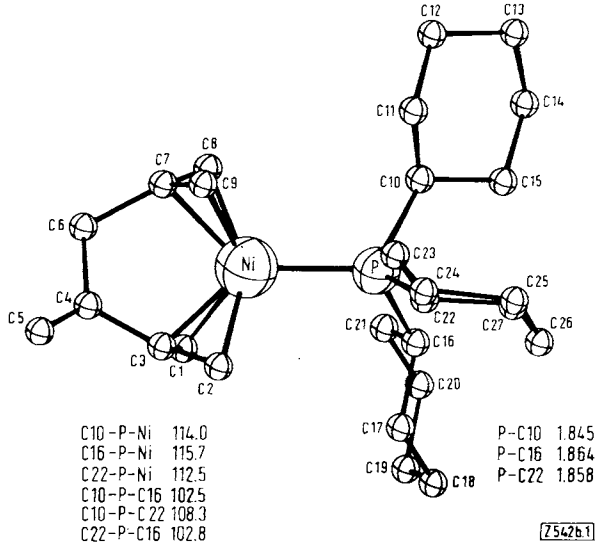


Fig. 1

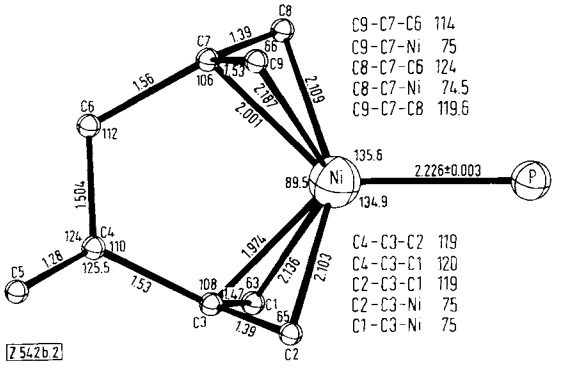


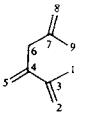
Fig. 2

As we have also found for numerous other examples[5] the coordination of the central atom is trigonal planar with respect to the centers of gravity of the allyl groups; each of the two π-allyl groups occupies a coordination position of the nickel, as does the distorted tricyclohexylphosphane tetrahedron. If the allyl group is considered to occupy two coordination positions as a bidentate ligand there results a square pyramid. The equation of the best plane through C3, C7, Ni, P is

$$-9.671x - 5.911y + 5.180z + 5.425 = 0.$$

All cyclohexyl rings are equatorially bonded and in the chair form; the mean C—C bond length is 1.52 Å, the mean bonding angle 112°.

The interesting asymmetry of the C—C bonds, which is in the same sense in the two π-allyl groups, seems to justify formulation of the ligand as the possible canonical structure *(1)*.



(1)

The allyl group, conjugated with the extremely short (1.28 Å) double bond between C4 and C5, exhibits a tendency towards symmetrization. The angle at C4 shows the metal-ring system of the ligand to be highly strained. The planes through the two allyl groups subtend a dihedral angle of 29.6°.

Received: September 15, 1971 [Z 542b IE]
German version: Angew. Chem. *84*, 121 (1972)

[1] *H. Bönnemann, B. Bogdanović,* and *G. Wilke,* Angew. Chem. *79*, 817 (1967); Angew. Chem. internat. Edit. *6*, 804 (1967).

[2] *M. Englert, P. W. Jolly,* and *G. Wilke,* Angew. Chem. *84*, 120 (1972); Angew. Chem. internat. Edit. *11*, 136 (1972).

[3] Details of data collection and methods of calculation are given in: *C. Krüger,* J. Organometal. Chem. *22*, 697 (1970).

[4] For Ni, P, C we used scattering curves given by *D. T. Cromer* and *J. T. Waber,* Acta Crystallogr. *18*, 104 (1965), and for H that given by *J. McWheeny*: International Tables for X-Ray Crystallography (1962). A list of structure factors and atomic parameters is available from the authors (C. K.) upon request.

[5] *P. W. Jolly, K. Jonas, C. Krüger,* and *Y.-H. Tsay,* J. Organometal. Chem. *33*, 109 (1971); *C. Krüger* and *Y.-H. Tsay,* J. Organometal. Chem., in press.

Absolute Configuration of a 1,2-Disubstituted Ferrocene Derivative with Two Different Chiral Substituents[1]

By *Linda F. Battelle, Robert Bau, George W. Gokel, Ray T. Oyakawa,* and *Ivar Ugi*[*]

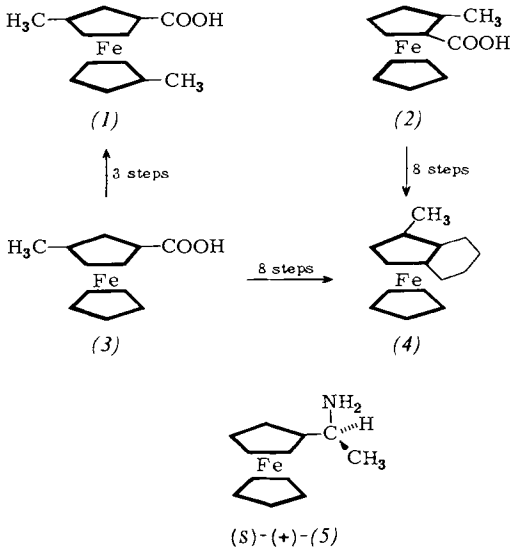
Neither the absolute configuration of a chiral 1,2-disubstituted ferrocene derivative, nor the configuration of a central chiroid with a ferrocenyl ligand has hitherto been determined by X-ray methods. We wish to report the results of such a determination.

The only optically active ferrocene derivative whose configuration has been established by X-ray crystallography is (*S*)-3,1′-dimethylferrocene-1-carboxylic acid *(1)*[2]. Its configuration has recently been correlated with that of (*S*)-2-methylferrocene-1-carboxylic acid *(2)* by converting *(2)* and (*S*)-3-methylferrocene-1-carboxylic acid *(3)* both into the same 1-methyl-2,3-tetramethyleneferrocene *(4)* by sequences of eight steps[3], and by transforming *(3)* into *(1)* by a sequence of three reactions[4]. By this and a pre-

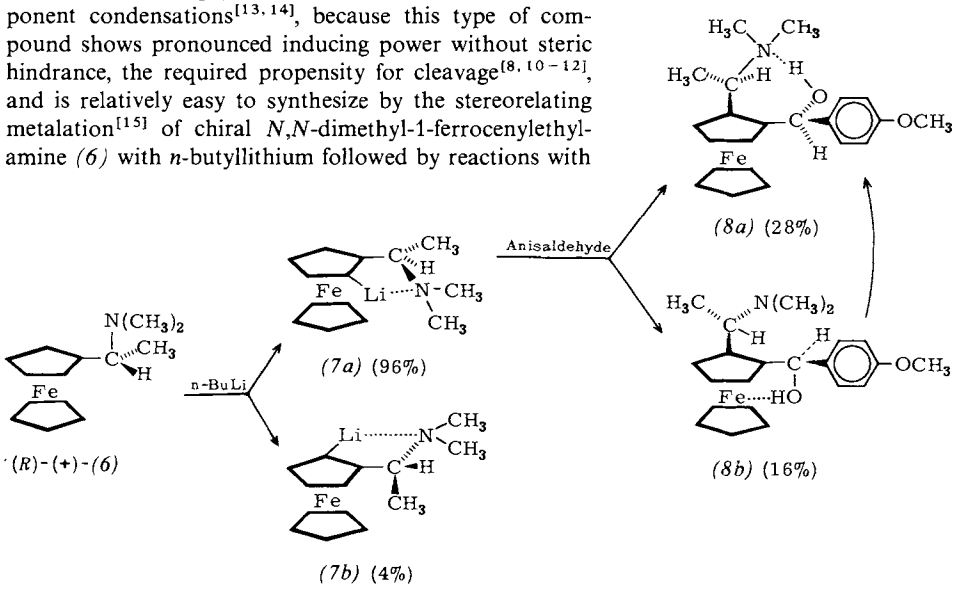
[*] L. F. Battelle, M. A., Prof. Dr. R. Bau, Dr. G. W. Gokel, R. T. Oyakawa, B. S., and Prof. Dr. I. Ugi
Department of Chemistry
University of Southern California
Los Angeles, Calif. 90007 (USA)

ceding series of chemical interconversions[5], the configurations of chiral 1,2-disubstituted ferrocene derivatives with *achiral* substituents are now unambiguously known.

The configurations of central chiroids with a ferrocenyl ligand have not yet been assigned with the same degree of reliability. For example, both the (*R*)-[6] and the (*S*)-configurations[7,8] have been assigned to (+)-1-ferrocenylethylamine *(5)* by optical methods[6] and by stereoselective reactions[7,8], respectively.



Some 1,2-disubstituted ferrocene derivatives show great potential as asymmetrically inducing[9] amine components for stereoselective peptide syntheses[10-12] by four component condensations[13,14], because this type of compound shows pronounced inducing power without steric hindrance, the required propensity for cleavage[8,10-12], and is relatively easy to synthesize by the stereorelating metalation[15] of chiral *N*,*N*-dimethyl-1-ferrocenylethylamine *(6)* with *n*-butyllithium followed by reactions with



suitable electrophiles[15-17] and subsequent retentive nucleophilic substitutions[18-20].

The main product *(7a)* of the metalation of *(6)* reacts with anisaldehyde to form *(8a)* (m.p. 110—111 °C; $[\alpha]_{589}^{22} = -20.8°$, $c = 1.6$, ethanol) and *(8b)* (dark oil, characterized by NMR and IR) which can both be isolated by chromatography (silica gel, J. T. Baker, no. 3405, 60 to 200 mesh; ligroine-acetone (1:1) as eluent); in aqueous solvents *(8b)* rearranges to form *(8a)*, presumably *via* a highly stabilized carbonium ion[18-20].

In order to assign the absolute configurations of the above class of chiral compounds and also in order to prove in an unambiguous manner the assumed stereorelating nature[15] of the metalation of *(6)*, we determined the absolute configurations of all elements of chirality of *(8a)* by X-ray crystallography (see Figure).

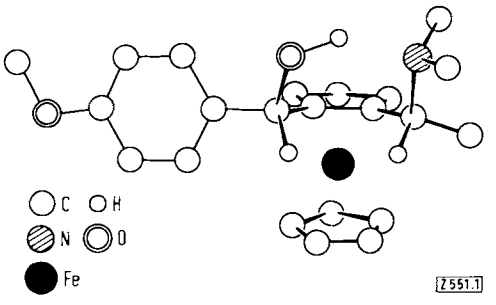


Fig. Molecular structure of *(8a)*.

Crystal data: Monoclinic, space group $P2_1$, $a = 9.77$, $b = 11.15$, $c = 10.56$ Å, $\beta = 120.6°$, $V = 603$ Å^3; d_{calc} (for $Z = 2$) = 1.96 g/ml, d_{exp} (flotation in an aqueous ZnI_2 solution) = 1.92 g/ml. Two quadrants of data were collected on a Nonius CAD-3 automated diffractometer using $Mo_{K\alpha}$ radiation. The structure was solved by conventional heavy-atom techniques[21] and refined to an *R* factor of 6.5%. The opposite configuration refined to an *R* factor of 7.2%. The ratio between the two *R* factors indicates that the probability of the first configuration being correct is better than 99.5%[22]. The configuration about the amine-substituted carbon is (*R*) and that about the hydroxyl-substituted carbon is (*S*). The configuration of the molecule as a whole, with respect to the plane of chirality, is (*S*)[16]. The conformations about the two asymmetric carbons are apparently determined by the hydrogen bond formed between the hydroxyl and amino groups (see Figure). The fact that *(8a)* is the more stable compound seems to be due to this O—H···N hydrogen bonding; an analogous hydrogen bond in *(8b)* is not possible for steric reasons.

Since the stereoselective metalation[15-17], in combination with retentive nucleophilic substitution[18-20], permits the convenient synthesis of a wide variety of ferrocene deriva-

tives having combined planar and central elements of chirality with known configurational relations, the above X-ray result provides access to a large number of optically active ferrocene derivatives with known absolute configurations.

Received: October 4, 1971 [Z 551 IE]
German version: Angew. Chem. *84*, 164 (1972)

---

[1] Stereoselective Synthesis, Part 10. The authors wish to thank the Petroleum Research Foundation (Grant 2059-G3), the National Science Foundation (Grant GP 28927), and the National Institutes of Health (Biomedical Support Grant RR-07012-04) for their support on this project. We would also like to thank the Computer Center of USC for making available its IBM 360/65 computer. — Part 9: *L. F. Battelle, R. Bau, G. Gokel, R. T. Oyakawa,* and *I. Ugi*, J. Amer. Chem. Soc., submitted.

[2] *O. L. Carter, A. T. McPhail,* and *G. A. Sim*, J. Chem. Soc. *A 1967*, 365.

[3] *G. Haller* and *K. Schlögl*, Monatsh. Chem. *98*, 2044 (1967).

[4] *H. Falk* and *K. Schlögl*, Monatsh. Chem. *102*, 33 (1971).

[5] *K. Schlögl*, Top. Stereochem. *1*, 39 (1967).

[6] *K. Schlögl* and *M. Fried*, Monatsh. Chem. *95*, 558 (1964).

[7] *H. Falk, C. Krosa,* and *K. Schlögl*, Monatsh. Chem. *100*, 254 (1969).

[8] *D. Marquarding, P. Hoffmann, H. Heitzer,* and *I. Ugi*, J. Amer. Chem. Soc. *92*, 1969 (1970).

[9] *J. D. Morrison* and *H. S. Mosher*: Asymmetric Organic Reactions. Prentice-Hall, Englewood Cliffs, N. J., 1971.

[10] *I. Ugi*, Rec. Chem. Progr. *30*, 289 (1969).

[11] *G. Gokel, P. Hoffmann, H. Kleimann, H. Klusacek, G. Ludke, D. Marquarding,* and *I. Ugi* in *I. Ugi*: Isonitrile Chemistry. Academic Press, New York 1971, p. 201.

[12] *I. Ugi*, Intra-Science Chem. Rep. *5*, 229 (1971).

[13] *I. Ugi*, Angew. Chem. *74*, 9 (1962); Angew. Chem. internat. Edit. *1*, 8 (1962).

[14] *G. Gokel, G. Lüdke,* and *I. Ugi* in *I. Ugi*: Isonitrile Chemistry. Academic Press, New York 1971, p. 145.

[15] *D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann,* and *I. Ugi*, J. Amer. Chem. Soc. *92*, 5389 (1970).

[16] *D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann,* and *I. Ugi*, Angew. Chem. *82*, 360 (1970); Angew. Chem. internat. Edit. *9*, 371 (1970).

[17] *D. W. Slocum, T. R. Englemann, C. Ernst, C. A. Jennings, W. Jones, B. Koonsvitsky, J. Lewis,* and *P. Shenkin*, J. Chem. Educ. *46*, 144 (1969).

[18] *G. W. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch,* and *I. Ugi*, Angew. Chem. *82*, 77 (1970); Angew. Chem. internat. Edit. *9*, 64 (1970).

[19] *G. W. Gokel* and *I. Ugi*, Angew. Chem. *83*, 178 (1971); Angew. Chem. internat. Edit. *10*, 191 (1971).

[20] *G. W. Gokel* and *I. Ugi*, J. Org. Chem., in preparation.

[21] All the major computations in this paper were done using CRYM, an amalgamated set of crystallographic programs developed by Dr. *R. E. Marsh*'s group at the California Institute of Technology.

[22] *W. C. Hamilton*, Acta Cryst. *18*, 502 (1965).

Polarographic Reduction of Oxygen in the Presence of Phthalocyanine Complexes

By *Werner Beyer* and *Ferdinand von Sturm*[*]

Although the accelerating action of phthalocyanines on oxidations has been known for a long time[1, 2] they have only recently been exploited as catalysts for electrochemical reactions taking place in fuel cells[3–6]. The mechanism of their catalytic effect on the electrode reaction, however, has hitherto remained unknown.

Since the polarographic reduction of O_2 at a mercury electrode occurs in two distinctly separate steps it should be possible to determine the point of attack of the catalyst phthalocyanine, provided that the sparingly soluble compound can be obtained in a solution preferably resembling water that can be subjected to polarographic measurements.

In fact, adequate solubility was found in alkaline alcohol. The measurements reported in the present communication were mainly recorded with a 0.1 M solution of LiOH in methanol as supporting electrolyte with addition of monomeric phthalocyanine.

As is apparent from Figure 1, the catalyst acts already during the first wave of the DC polarogram which is assigned to the reduction of O_2 to H_2O_2. A pronounced maximum is observable with low catalyst concentrations (in the range between 10^{-7} and 10^{-4} M). It is not until a concentration of more than 5×10^{-4} M is reached that the current minimum is suppressed; the four-electron reduction of the O_2 then takes place in a single polarographic wave in contrast to the action of hemin, hemoglobin, and Fe^{3+}[7] (cf. Fig. 1, i). The catalytic effect is displayed by the complexes with Fe, Pt, Mn, and Ni as central atom but not those with Li, Mg, Zn, VO, Co, Ag, nor by metal-free phthalocyanine. The effectiveness decreases along the above series, with the Fe complex exhibiting the highest activity.

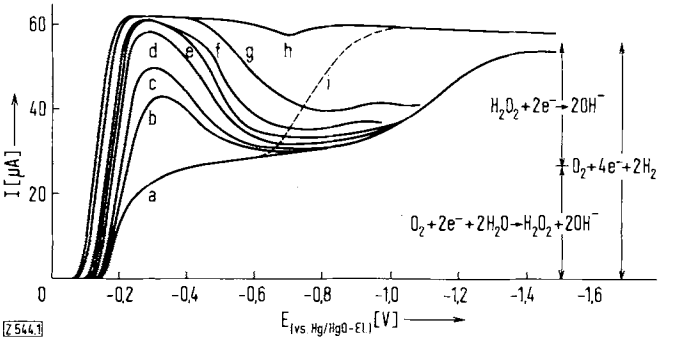


Fig. 1. Polarographic current-voltage curves for oxygen reduction in the presence of the iron(III)-phthalocyanine complex (0.1 M LiOH in methanol, air-saturated, 25 °C).
Fe^{III} concentration: 0 (a); 2.5×10^{-7} M (b); 5.0×10^{-7} M (c); 2.5×10^{-6} M (d); 5.0×10^{-6} (e); 9.5×10^{-6} (f); 5×10^{-5} M (g); 5×10^{-4} M (h); Fe^{3+} concentration: 10^{-3} M (i).

The Co-tetraazaannulene recently described[8] as an electrocatalyst merely increases the steepness of the first polarographic wave. The activity of Fe-tetraazaannulene (for whose preparation we are indebted to Dr. *Todt*), on the other hand, is comparable with that of Fe-phthalocyanine.

The reason for the current minimum after the catalytic wave (see Fig. 1, b to g) was first suspected to lie in an inhibiting adsorption. However, no adsorption-desorption processes could be detected in the potential range of the minimum by electrocapillary curves or by tensammetric studies.

For all the compounds studied two conditions had to be fulfilled before a catalytic reaction took place:

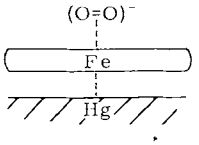
1) The central atom had to be present in the lower valence state (in some cases after a preceding electrochemical reduction);

2) The first electron already had to have been taken up by the oxygen molecule with formation of the peroxide ion O_2^-.

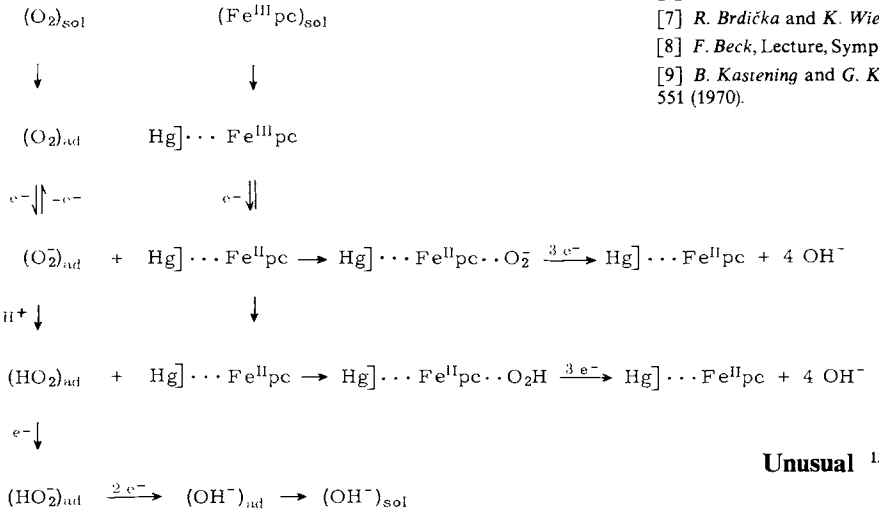
It is therefore assumed that the catalyst actually reacts with partially reduced oxygen, *i.e.* with O_2^-, to form a complex that favors rapid electron exchange. The oxidant remains bound to the electrode surface by way of the same complex molecule until reaction is complete.

[*] Dr. F. von Sturm and Dipl.-Chem. W. Beyer
Forschungslaboratorien der Siemens AG
852 Erlangen 2, Postfach 325 (Germany)

The drop in current after attainment of the current maximum parallels the taking up of the second electron in the uncatalyzed process. This removal of the O_2^- ion or the



protonated HO_2 radical with increasing negative potential in the competing electrode reaction uses up the starting material for the catalytic process. The overall reaction course is envisaged as shown in the following scheme:



In aqueous solution the product of the first incorporation of an electron can only be stabilized by inhibition of the subsequent protonation (*e.g.* by triphenylphosphane oxide) and thus of the taking up of the second electron[9]. In methanolic electrolytes the two steps can be resolved, without the need for an inhibitor, by square-wave polarography (see Fig. 2).

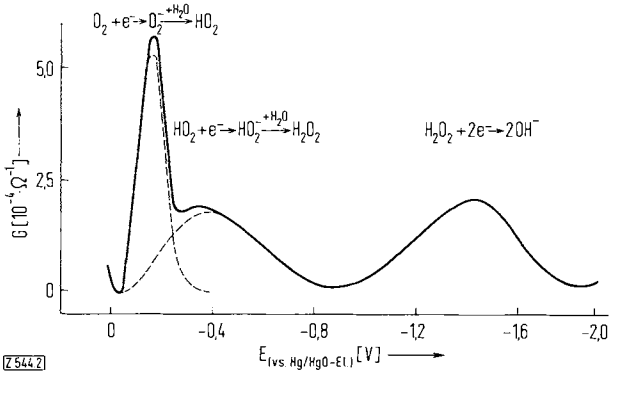


Fig. 2. Square-wave polarogram of oxygen reduction (0.1 M LiOH in methanol), air-saturated, 25 °C; square-wave amplitude 2 mV).

The first step is fast and gives rise to a well developed peak in the square-wave polarogram at −0.175 V. The second electron can only be taken up after completion of the inhibited reaction of peroxide-anion protonation; here the square-wave polarogram exhibits a flat wave at −0.36 V. Addition of water shifts the second wave into the first, thus indicating acceleration of HO_2 formation.

Addition of CN^- ions ($>10^{-6}$ M) deactivates the iron-phthalocyanine complex. This poisoning can be understood in terms of the bridging complex as a displacement of O_2^- by CN^- from the sixth coordination position.

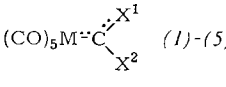
Received: September 9, 1971 [Z 544 IE]
German version: Angew. Chem. *84*, 154 (1972)

[1] *A. H. Cook*, J. Amer. Chem. Soc. *60*, 1761 (1938).
[2] *H. Kropf*, Liebigs Ann. Chem. *637*, 73 (1960).
[3] *R. Jasinski*, J. Electrochem. Soc. *112*, 526 (1965).
[4] *H. Jahnke*, Ber. Bunsenges. Phys. Chem. *72*, 1053 (1968).
[5] *H. Alt, H. Binder, G. Klempert, A. Köhling, W. Lindner*, and *G. Sandstede*, Battelle Information *11*, 64 (1971).
[6] *G. Richter, H. Cnobloch*, and *H. J. Henkel*, US-Pat. 3585079 (1971).
[7] *R. Brdička* and *K. Wiesner*, Naturwissenschaften *31*, 247 (1943).
[8] *F. Beck*, Lecture, Symp. Angew. Elektrochem. Wien, February 1971.
[9] *B. Kastening* and *G. Kazemifard*, Ber. Bunsenges. Phys. Chem. *74*, 551 (1970).

Unusual ^{13}C Chemical Shifts of Transition Metal-Carbene Complexes

By *Cornelius G. Kreiter* and *Victor Formáček*[*]

In order to update our knowledge of the nature of the bonding in transition metal-carbene complexes[1] we have recorded the Pulse-Fourier-Transform ^{13}C-NMR spectra[2] of a few typical compounds. The complexes to be investigated were so chosen that both M as well as X^1 and X^2 in the general formula



(1)-(5)

could be varied to give a comparative series (see Table).

As can be seen from the table the carbene carbon atoms in *(1)—(5)* are extremely deshielded and their signals lie far outside the range in which the ^{13}C-NMR signals of the more common organic compounds appear[2]. The strong deshielding compares very well with the electron deficiency found from other NMR measurements and dipole studies on a complexed carbene carbon[1].

The ^{13}C-NMR signal of the carbene carbon also shifts quite characteristically on changing M, X^1, and X^2 in *(1)* to *(5)*. If the chromium in *(2)* is replaced by tungsten, compound *(3)* is obtained in which the carbene carbon

[*] Priv.-Doz. Dr. C. G. Kreiter
Anorganisch-chemisches Laboratorium
der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)
Dr. V. Formáček
Bruker-Physik A.G., 7501 Karlsruhe-Forchheim (Germany)

is much more shielded. The presence of the *C*-phenyl group in *(1)* instead of the *C*-methyl group in *(2)* has the same effect, since the delocalized aromatic π-electron system of the phenyl group interacts with the vacant p-orbital of the carbene carbon, whose electron deficiency can thus be more effectively lowered than by the methyl group, which only acts inductively[3]. Similarly, a dependence between degree of shielding and nature of heteroatom is observed in compounds *(3)*, *(4)*, and *(5)*. The less electronegative nitrogen in *(5)* clearly confers more negative charge on the carbene carbon than does the more strongly electronegative oxygen in *(3)*.

In the case of *(5)* measurements were carried out on a mixture of the *cis-trans* isomers[4] (65:35). The isomers, which differ from each other only in the orientation of their *C*- and *N*-methyl groups, exhibit different ^{13}C-NMR spectra. The signals for *cis*- and *trans-(5)* in the table were assigned on the basis of intensities. The ^{13}C-NMR signals of the two isomers appear in the same sequence as do the *N*-methyl signals in the ^{1}H-NMR spectrum, *viz.* the signal of the *cis* isomer appears at higher field than that of the *trans* isomer.

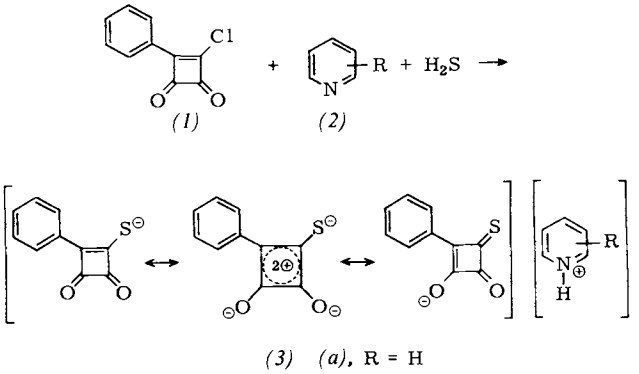
Table. ^{13}C chemical shifts of phenylmethoxycarbenepentacarbonylchromium *(1)*, methylmethoxycarbenepentacarbonylchromium *(2)*, methylmethoxycarbenepentacarbonyltungsten *(3)*, methyl(methylthio)carbenepentacarbonyltungsten *(4)* and methyl(methylamino)carbenepentacarbonyltungsten *(5)*. Measurements on *ca.* 20% solutions in [D_6]-benzene with a Bruker-Multikern Spectrometer HX 90/8 at 22.63 MHz. The chemical shifts are given in ppm relative to TMS as internal standard.

Cpd.	M	X^1	X^2	δC(Carbene)	δC(CO) *trans*	δC(CO) *cis*	$\delta C(X^1)$	$\delta C(X^2)$
(1)	Cr	OCH_3	C_6H_5	−351.42	−224.57	−216.67	−66.62	−153.82 (C-1) −130.26 (C-4) −128.38 (C-2, C-6) −122.89 (C-3, C-5)
(2)	Cr	OCH_3	CH_3	−360.23	−223.76	−216.93	−66.08	−48.10
(3)	W	OCH_3	CH_3	−332.90	−203.62	−197.60	−69.67	−51.51
(4)	W	SCH_3	CH_3	−332.54	−207.40	−198.05	−26.43	−47.11
cis-(5)	W	$NHCH_3$	CH_3	−255.67	−203.44	−198.86	−33.71	−46.39
trans-(5)				−258.73	−203.44	−199.40	−36.68	−41.62

It is worth noting that the $\delta C_{carbene}$ values for *(3)* and *(4)* are virtually equal, thus indicating an almost equivalent degree of charge transfer in the case of oxygen and sulfur. An explanation for this could be the unfavorable overlapping of the large filled p-orbital of the sulfur with the smaller vacant p-orbital of the carbene carbon[5].

In all the carbene complexes investigated, the signal of the *trans* CO-ligands is found to appear downfield from that of the *cis* CO-ligands. It is also observed that most of the ^{13}C-NMR signals of the X^1 and X^2 groups of *(1)*—*(5)* lie outside the range in which signals for these groups in organic molecules characteristically appear. Some of the signals are shifted about 2 ppm downfield; once again the strong electron withdrawing power of the carbene carbon is also apparent.

Received: October 1, 1971 [Z 543 IE]
German version: Angew. Chem. *84*, 155 (1972)



(3) *(a)*, R = H
(b), R = 2-CH_3
(c), R = 4-CH_3

3-Mercapto-4-phenyl-3-cyclobutene-1,2-dione[***]

By *Arthur H. Schmidt, Walter Ried, Peter Pustolemsek,* and *Hans Dietschmann*[*]

We wish to report on the synthesis and properties of 3-mercapto-4-phenyl-3-cyclobutene-1,2-dione (PCB—SH) *(5)*, the first thio analog of the well-known PCB—OH[1].

Because of its expected high acidity and its capability of being transformed into the novel 4-phenyl-3-thiolatocyclobutenediylium 1,2-diolate system[2], compound *(5)* proves to be a very important representative of the phenylcyclobutenedione series.

Dropwise addition of a benzene solution of *(1)* into pyridines *(2)* saturated with hydrogen sulfide leads to formation of the pyridinium salts *(3)*[2], which have been characterized chemically and spectroscopically (see Table).

In agreement with the salt structure, no peaks for the molecular ions appear in the mass spectra of *(3a)*—*(3c)*. On the other hand, a peak due to the anion whose mass is increased by one unit (*m/e* 190) and the peak of the cation both appear with high intensity.—The absence of an IR

[1] *C. G. Kreiter* and *E. O. Fischer*, XXIII. IUPAC-Congress, Boston, 1971.

[2] *E. Breitmaier, G. Jung,* and *W. Voelter*, Angew. Chem. *83*, 659 (1971), Angew. Chem. internat. Edit. *10*, 673 (1971).

[3] *E. O. Fischer, C. G. Kreiter, H. J. Kollmeier, J. Müller,* and *R. D. Fischer*, J. Organometal. Chem. *28*, 237 (1971).

[4] *E. Moser* and *E. O. Fischer*, J. Organometal. Chem. *16*, 275 (1969).

[5] *E. O. Fischer, M. Leupold, C. G. Kreiter,* and *J. Müller*, Chem. Ber. *105*, 150 (1972).

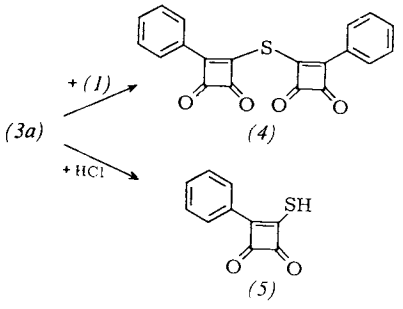
[*] Dr. A. H. Schmidt [**], Prof. Dr. W. Ried, P. Pustoslemsek, and Dipl.-Chem. H. Dietschmann
Institut für Organische Chemie der Universität
6 Frankfurt/Main, Robert-Mayer-Strasse 7—9 (Germany)

[**] Present address: Department of Chemistry, Columbia University, New York, N. Y. 10027 (USA).—A. H. S. thank the Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie for a Liebig-Stipendium.

[***] Reactions with Cyclobutenediones, Part 30.—Part 29: *W. Ried* and *F. Bätz*, Liebigs Ann. Chem., in press.

band at about 1600 cm^{-1} (C=C in the four-membered ring) and the shift of the C=O absorptions to lower wave numbers support the given structure.

(3a) reacts with *(1)* to give the thioether *(4)*[3]. We isolated PCB—SH *(5)* from a suspension of *(3a)*—*(3c)* in concentrated hydrochloric acid. *(5)* forms pale yellow



(4)

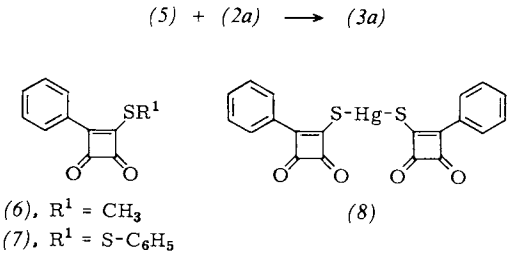
(5)

crystals which are readily soluble in methanol, $CHCl_3$, and CH_2Cl_2 and less readily soluble in CCl_4 and H_2O. According to preliminary measurements, *(5)* is more acidic than PCB—OH, whose pK_a has been determined as 0.37 ± 0.04[1a]. The mass spectrum of *(5)* contains characteristic fragments at $m/e = 162$ ($M^+ - CO$) and $m/e = 134$ ($M^+ - 2CO$) in addition to the molecular ion ($m/e = 190$).

The ^{1}H-NMR spectrum[4] contains two multiplets at $\delta = 7.9$—7.75 ppm (2H) and $\delta = 7.5$—7.4 ppm (3H), assigned to the aromatic protons, and a broad signal at $\delta = 4.18$ ppm whose position is characteristic for SH groups of thiocarboxylic acids[5]. The IR spectrum (KBr) shows the SH band at 2490 cm^{-1} (s) (in CCl_4 at 2530 cm^{-1}) and C=O bands at 1770 (s) and 1750 (s) cm^{-1}. Further bands appear at the following wave numbers: 1810 (w), 1590 (m), 1535 (m), 1480 (m), 1265 (s), 1128 (m), 768 (m), 685 (m) cm^{-1}[6].

The following absorptions occur in the UV spectrum of *(5)* (cyclohexane): $\lambda_{max} = 322$ ($\varepsilon = 16350$), 308 (19100), 298 (shoulder), 276 (shoulder), 267 (shoulder), 248 (5200). In ethanol, absorptions occur whose position and intensity compare with those observed in the UV spectrum of pyridinium salt *(3c)* (see Table), thus indicating the presence of an anion of *(5)*. On the other hand, the spectroscopic findings do not provide any definite proof for the occurrence of a tautomeric hydroxy form of *(5)*.

The acidic character of PCB—SH *(5)* is demonstrated by the formation of the pyridinium salt *(3a)* and by the ready conversion into the *S*-methyl ester *(6)* on reaction with diazomethane. Reaction of *(5)* with phenylsulfenyl chloride leads to the unsymmetrical disulfide *(7)*.



(6), $R^1 = CH_3$
(7), $R^1 = S\text{-}C_6H_5$

(8)

When a solution of *(5)* in THF is treated with an aqueous solution of $HgCl_2$, the mercury salt *(8)* precipitates immediately as fine, pale-yellow crystals. (The properties of the new compounds are summarized in the following Table.)

Table. A few properties of the compounds *(3c)* and *(6)*—*(8)*. Correct elemental analyses and mass spectra have been obtained for all compounds excepting *(8)*.

Cpd.	M. p. (°C) (solvent)	IR (cm^{-1})	UV (solvent) λ_{max} (nm) (ε)	NMR (δ, ppm)	Conditions
(3c)	169 (ethanol)	3160–2200 (br.), (1830); 1750, 1705 (CO)	(ethanol) 361 (13500), 310 (23200), 260 (shoulder), 254 (shoulder), 242 (16000)	9.4–9.2 (br. s, D_2O-exchange), 8.83 u. 7.65 (2H/d; AB System, $J_{AB} = 7$ Hz), 8.55–8.39 (2H/m), 7.42–7.28 (3H/m), 2.55 (3H/s)	100 MHz $CDCl_3$
(6)	151–152 (ethanol)	2940 (CH), (1830); 1770, 1750 (CO), 1600 (CC)	(cyclohexane) 338 (21000), 321 (25080), 310 (shoulder), 285 (11800), 277 (shoulder), 255 (9200)	7.9–7.78 (2H/m), 7.5–7.35 (3H/m), 2.95 (3H/s)	100 MHz $CDCl_3$
(7)	147–149 (methanol/THF)	(1820); 1765, 1755 (CO), 1595 (CC)		8.0–7.65 (2H/m), 7.58–7.32 (3H/m)	60 MHz $CDCl_3$
(8)	286 (dec.)	1760, 1730 (CO), 1595 (CC)			

3-Mercapto-4-phenyl-3-cyclobutene-1,2-dione (PCB—SH) (5)

Anhydrous pyridine (30 ml) is saturated at -15 °C with dry hydrogen sulfide. A solution of *(1)* (1.92 g, 0.01 mol) in anhydrous benzene (30 ml) is then added dropwise with stirring over a period of 15 min. Reaction is allowed to continue for a further 10—15 minutes before the mixture is carefully treated with 40% sulfuric acid until precipitation of gold-yellow crystals of *(3a)* is complete. The crystals

[1] a) *E. J. Smutny, M. C. Caserio,* and *J. D. Roberts,* J. Amer. Chem. Soc. *82,* 1793 (1960); b) *W. Ried, W. Kunkel,* and *G. Isenbruck,* Chem. Ber. *102,* 2688 (1969).

[2] Of the three possible mesomeric formulas for the anion of the salts *(3)* we have chosen the middle one as the more characteristic.

[3] *W. Ried* and *A. H. Schmidt,* Liebigs Ann. Chem. *742,* 116 (1970).

[4] 100 MHz, measured in $CDCl_3$ against HMDSO as internal standard.

[5] a) *G. Gattow* and *R. Engler,* Angew. Chem. *83,* 444 (1971); Angew. Chem. internat. Edit. *10,* 415 (1971); b) High Resolution NMR Spectra Catalog Associates, Palo Alto, California 1962.

[6] Notation: s = strong; m = moderate; w = weak.

are filtered off under suction and recrystallized twice from ethanol; yield 89%, m. p. 156—160 °C.

(3a) (1.35 g, 5 mmol) is added at room temperature to concentrated hydrochloric acid (25 ml); after 3 minutes' stirring the precipitate of *(5)* is recovered by filtration (glass suction filter). The crude crop of *(5)* is recrystallized from $CCl_4/CHCl_3$ (or glacial acetic acid); yield 68—75%, m. p. 149—151 °C.

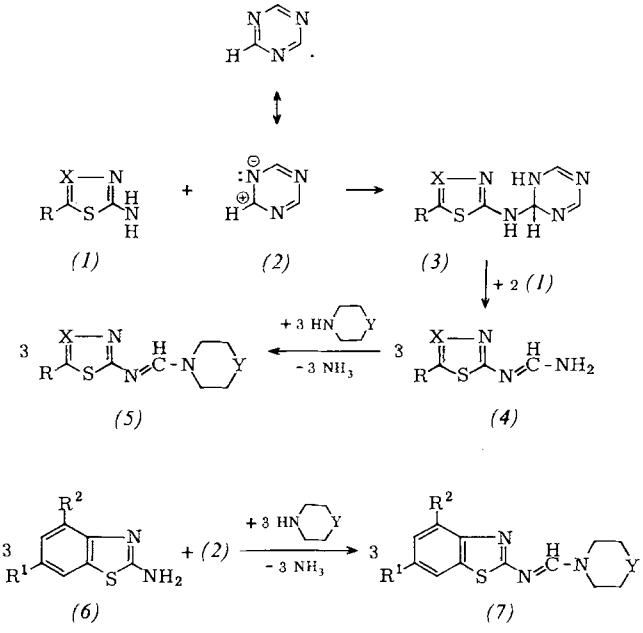
Received: October 18, 1971 [Z 537 IE]
German version: Angew. Chem. *84*, 110 (1972)

Dehydro *N*-Mannich Bases[***]

By *Alfred Kreutzberger* and *Mehmet Umran Uzbek*[*]

In the Mannich reaction an active compound is allowed to react with formaldehyde and an amine. If the active component contains a nitrogen atom bearing a reactive hydrogen, *N*-Mannich bases are formed. Compounds containing a primary amino group, such as urea[1] or benzamide[2], have also found special use in this type of reaction.

We have now found that when *s*-triazine *(2)* is employed instead of formaldehyde, an analogous condensation takes place with formation of *N*-Mannich bases *(5)* having two hydrogen atoms less. This finding is based on the results of a series of investigations on the aminomethinylation reaction, in which *e.g.* anthranilic acid can be converted into 4-quinazolone by reaction with *s*-triazine[3].



(1) *(2)* *(3)* *(4)* *(5)*

(6) *(7)*

Cpd.	X	R	Y	Yield (%)	M. p. (°C)
(5a)	C_6H_5—C	H	CH_2	40	124–125
(5b)	N	HS	CH_2	68	230
(5c)	N	HS	O	71	218

Cpd.	R^1	R^2	Y	Yield (%)	M. p. (°C)
(7a)	Br	H	CH_2	76	114
(7b)	H	Cl	O	83	104–105

[*] Prof. Dr. A. Kreutzberger and Dr. Mehmet Umran Uzbek [**]
Institut für pharmazeutische Chemie der Universität
44 Münster, Hittorfstrasse 58—62 (Germany)

[**] As guest from the Institute of Pharmaceutical Chemistry of the University of Istanbul (Turkey).

[***] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

If 2-aminothiazoles or -thiadiazoles of type *(1)* are used in place of anthranilic acid and its derivatives, either no reaction takes place or, as in the case of 2-amino-4-phenylthiazole *(1a)*, only small yields of the expected *N*,*N'*-disubstituted formamidine derivatives are obtained. When, however, attempts were made to increase the yields by addition of excess amine, *e.g.* piperidine or morpholine, the dehydro *N*-Mannich bases *(5)* were formed, presumably *via* the route shown in the reaction scheme.

2-Aminobenzothiazoles *(6)* can be converted in an analogous way into the dehydro *N*-Mannich bases *(7)*.

The previously described three-component reactions in which the parent compound or derivatives of phenylacetonitrile[4], of picoline *N*-oxides[5], aniline[6], fluorene[7], and phenylhydrazine[7] contain the active hydrogen atom, can also be classed under the present, general type of reaction leading to dehydro Mannich bases.

Received: October 21, 1971 [Z 538 IE]
German version: Angew. Chem. *84*, 109 (1972)

[1] *A. Einhorn* and *E. Spröngerts*, Liebigs Ann. Chem. *361*, 139 (1908).
[2] *H. Hellmann* and *G. Haas*, Chem. Ber. *90*, 50 (1957).
[3] *A. Kreutzberger* and *M. U. Uzbek*, Arch. Pharmaz., in press.
[4] *A. Kreutzberger* and *D. Abel*, Arch. Pharmaz. *301*, 881 (1968).
[5] *A. Kreutzberger* and *D. Abel*, Arch. Pharmaz. *302*, 701 (1969).
[6] *A. Kreutzberger* and *M. F. G. Stevens*, J. Chem. Soc. *C 1969*, 1282.
[7] *A. Kreutzberger* and *D. Abel*, Arch. Pharmaz. *303*, 107 (1970).

Tetraorganofluorophosphoranes

By *Hubert Schmidbaur*, *Karl-Heinz Mitschke*, and *Johann Weidlein*[*]

Of the four conceivable organofluorophosphoranes R_nPF_{5-n} having $n=1$—4 only the types RPF_4, R_2PF_3, and R_3PF_2 are adequately known[1]. Hitherto only scattered references have appeared in the literature[2] concerning tetraorganofluorophosphoranes, which may be assumed to exist only in a ionic isomeric form, as phosphonium fluorides $R_4P^+F^-$. It would appear that $[(C_6H_5)_4P]F$[3] and $[(C_6H_5)_3PC_2H_5]F$[2] are the only representatives ever to have been obtained in a pure state (by halogen exchange from other phosphonium salts in both cases). However, this technique usually runs into considerable experimental difficulties.

Syntheses of pure, salt-free ylides[4, 5] and their silylated derivatives[6] have now opened up a direct route to compounds of formula R_4PF. Addition of anhydrous hydrofluoric acid to corresponding ylides gives the desired products just as smoothly as desilylation of the silyl ylides with subsequent HF addition *in situ*, as formulated for tetramethylfluorophosphorane *(1)*:

[*] Prof. Dr. H. Schmidbaur and Dipl.-Chem. K.-H. Mitschke
Institut für Anorganische Chemie der Universität
87 Würzburg, Landwehr (Germany)
Doz. Dr. J. Weidlein
Institut für Anorganische Chemie der Universität
7 Stuttgart 1, Schellingstrasse 26 (Germany)

$$(CH_3)_3P{=}CH_2 + HF \xrightarrow{-70\,^\circ C} (CH_3)_4PF \quad (1)$$

$$(CH_3)_3P{=}CH{-}Si(CH_3)_3 + 2\,HF \xrightarrow{-40\,^\circ C} (CH_3)_4PF + (CH_3)_3SiF \quad (2)$$

(1)

The second reaction is another example of the preparative significance of desilylation reactions[7]. Reaction occurs at about $-70\,^\circ C$ in diethyl ether to give a high yield (>90%) of a crystalline product that was purified by sublimation at 20 °C/0.1 torr.

Compound *(1)*, which is extremely sensitive to moisture, also sublimes in a sealed tube without melting above 100 °C. The mass spectrum of the sublimate recorded at an excitation energy of 18 eV contains a peak for the ion of greatest mass and intensity at *m/e* 95 which corresponds to the fragment $(CH_3)_3PF^+$. This result confirms the presence of discrete molecules having direct P—F bonds in the gaseous state. A complete redissociation into the components $(CH_3)_3PCH_2$ and HF on sublimation can be ruled out. A similar situation is known to prevail in (molecular) $(CH_3)_4SbF$[8] whose mass spectrum is dominated by the ion $(CH_3)_3SbF^+$

The infrared and Raman spectra of crystalline *(1)* at 25 °C indicate that the substance must be largely ionic in the solid state. A pronounced symmetrical PC_4 stretching vibration at 660 cm^{-1}, which is only observable in the Raman, and a correspondingly strong antisymmetric IR vibration at 783 cm^{-1}, which is seen in the Raman spectrum at the same frequency but at very low intensity, provide clear evidence of ionic structure, as does the absence of a characteristic PF band. However, if $(CH_3)_4PF$ vapor is condensed at 10^{-6} torr on to a AgCl disk cooled to $-160\,^\circ C$ and an IR spectrum is recorded without warming the sample, new bands are observed that are most probably ascribable to a molecular compound or its aggregate. The spectrum of the ionic form appears again on heating.

Apart from water, in which dissociation occurs, the only other suitable solvent for *(1)* is CH_2Cl_2, the resulting solutions also undergoing decomposition. The ^1H-NMR spectrum of freshly prepared solutions contain a doublet at $\delta = -2.2$ ppm (TMS) with $^2J(HCP) = 15$ Hz. This spectrum is unchanged at $-85\,^\circ C$. It appears that *HCPF* coupling, as well as the possibility of distinguishing between differently bonded methyl groups, is ruled out by a rapid fluoride ligand exchange. As expected, the ^{19}F-NMR spectrum contains only a singlet at -4.0 ppm (CF_3COOH, external), thus indicating considerable "fluoride" character.

The molecular nature of a R_4PF compound is seen much more clearly in the case of tri(*n*-butyl)methylfluorophosphorane $(n\text{-}C_4H_9)_3(CH_3)PF$ *(2)* prepared from $(n\text{-}C_4H_9)_3P{=}CH_2$ and HF as a colorless liquid that can be distilled without decomposition (m.p. 11—13 °C; b.p. 74—76 °C/0.1 torr) and also dissolves in nonpolar solvents, in which it is found to have unit molecular weight. Triphenyl(methyl)fluorophosphorane $(C_6H_5)_3(CH_3)PF$ *(3)*, m.p. 116—118 °C, b.p. 150 °C/0.1 torr, which can be prepared in an analogous fashion, exhibits similar properties. No *HCPF* coupling is recorded for these compounds either, even in nonpolar solvents, since intermolecular fluorine exchange apparently has to overcome only a very low activation barrier.

Received: October 27, 1971 [Z 556a IE]
German version: Angew. Chem. *84*, 165 (1972)

Tetramethyl(methoxy)phosphoranes and Related Compounds

By *Hubert Schmidbaur* and *Herbert Stühler*[*]

Although compounds of the type $R_nP(OR')_{5-n}$ have been known for a long time and have been the object of intensive study in recent years, no reliable data have yet become available concerning the existence of simple tetraalkyl(alkoxy)phosphoranes, to say nothing of a knowledge of their structure and bonding. The classical publications by *Ingold et al.*[1] give detailed accounts of the action of alkoxide on phosphonium salts and the resulting degradation—phosphorus analog of the Hoffmann degradation—but the phosphonium alkoxides defied all attempts at isolation, as in numerous other studies[2]. In contrast, there is a wealth of information about prototypes of the formulas $P(OR')_5$, $RP(OR')_4$, $R_2P(OR')_3$, and $R_3P(OR')_2$.

We have now found that tetramethyl(methoxy)phosphorane *(1)* and its homologs are readily available in quantitative yields from the pure, salt-free ylides[3] and alcohols. Thus *(1)* is formed by addition of anhydrous methanol to trimethyl(methylene)phosphorane in diethyl ether or benzene at room temperature as a colorless distillable liquid (m.p. -46 to $-44\,^\circ C$; b.p. 48 °C/30 torr) that gradually decomposes above 130 °C.

$$(CH_3)_3P{=}CH_2 + HOCH_3 \rightleftharpoons (CH_3)_4POCH_3 \quad (1)$$

(1)

The compound hydrolyzes very readily and reacts with halohydrocarbons, carbonyl compounds, and nitriles. It is found to have unit molecular weight in benzene (cryoscopic). Only fragments are seen in the mass spectrum, mainly $(CH_3)_3PO^+$ and its degradation products. This is not very surprising since polyalkoxyphosphoranes have been observed to behave similarly[4].

Under normal conditions, the ^1H-NMR spectrum of toluene solutions shows only two singlets in the expected area ratio; the larger signal is very slightly broadened. At low temperatures the expected doublet splitting is observed ($^2J(HCP) = 14$ Hz). It appears that just enough of the starting materials is in equilibrium with *(1)* at room temperature for rapid proton exchange (NMR time scale) on the $(CH_3)_4P$ group. This is in accord with the finding that the process is decelerated on addition of an excess of methanol. No coupling $^3J(HCOP)$ was observed. This interaction does not occur because the process shown in eq. (1) is accompanied by an exchange of the methoxy groups between the $(CH_3)_4P$ groups, similar to that of the fluorine atoms of $(CH_3)_4PF$[5].

[*] Prof. Dr. H. Schmidbaur and Dipl.-Chem. H. Stühler
Institut für Anorganische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[1] *R. Schmutzler* in *V. Gutmann*: Halogen Chemistry. Academic Press, New York 1969, Vol. II, p. 31.

[2] For a review, see *G. P. Schiemenz, J. Becker*, and *J. Stöckigt*, Chem. Ber. *103*, 2077 (1970).

[3] *G. Urban* and *R. Dötzer*, DAS 1191813 (1965); Chem. Abstr. *63*, 14909d (1965).

[4] *H. Schmidbaur* and *W. Tronich*, Chem. Ber. *101*, 595 (1968); Angew. Chem. *79*, 412 (1967); Angew. Chem. internat. Edit. *6*, 448 (1967).

[5] *R. Köster, D. Simić*, and *M. A. Grassberger*, Liebigs Ann. Chem. *739*, 211 (1970).

[6] *H. Schmidbaur*, Advan. Organometal. Chem. *9*, 260 (1970).

[7] Cf. *H. Schmidbaur* in: 20 Jahre Fonds der Chemischen Industrie. Verlag Chemie, Weinheim 1970, p. 129.

[8] *H. Schmidbaur, K.-H. Mitschke*, and *J. Weidlein*, Chem. Ber. *102*, 4136 (1969). Mass spectra: *H. Schmidbaur*, unpublished.

The IR spectrum of liquid *(1)* is complex owing to the low C_s symmetry assumed for each of the possible structures. However, it does rule out an ionic structure $[(CH_3)_4P]^+OCH_3^-$, as well as significant concentrations of free ylide and methanol, whose presence could be expected from eq. (1). In contrast, real analogies to (covalently bonded) $(CH_3)_4SbOCH_3$[6] are apparent.

With a large excess of methanol, *(1)* gives a colorless crystalline adduct of composition $(CH_3)_4POCH_3 \cdot 2CH_3OH$ and of unknown structure (m. p. 62—64 °C).

$(CH_3)_3P{=}CH_2$ and ethanol give the colorless distillable compound tetramethyl(ethoxy)phosphorane (b. p. 50 °C/30 torr) which exhibits similar spectroscopic properties to *(1)*. The reaction products from isopropanol and *tert*-butanol decompose slowly at room temperature to give phosphane oxides. Similar reactions occur in the case of trimethylsilanol. The last-named alcohols, however, also give highly stable adducts having a greater alcohol content:
$(CH_3)_4POC_2H_5 \cdot 2C_2H_5OH$;
$(CH_3)_4POCH(CH_3)_2 \cdot (CH_3)_2CHOH$; and
$(CH_3)_4POC(CH_3)_3 \cdot (CH_3)_3COH$.

Addition of phenol to $(CH_3)_3P{=}CH_2$ gives crystalline $(CH_3)_4POC_6H_5$ (m. p. 71—75 °C, decomp.) whose NMR spectrum contains a doublet for the $(CH_3)_4P$ group at 25 °C in CH_2Cl_2. The proton exchange analogous to eq. (1) obviously becomes slower with increasing acidity of the alcohol. In contrast, the exchange is accelerated with increasing stability of the ylide: solutions of colorless crystalline triphenyl(methyl)methoxyphosphorane formed on addition of CH_3OH to $(C_6H_5)_3P{=}CH_2$ are weakly tinged with the yellow color of the starting ylide, and the CH_3P doublet in the ^1H-NMR has coalesced to a singlet.

Received: October 27, 1971 [Z 556b IE]
German version: Angew. Chem. *84*, 166 (1972)

[1] *G. W. Fenton* and *C. K. Ingold*, J. Chem. Soc. *1929*, 2342; *L. Hey* and *C. K. Ingold*, *ibid. 1933*, 531.

[2] *E.g.*: *J. Dodonow* and *H. Medox*, Ber. Dt. Chem. Ges. *61*, 907 (1928); *D. D. Coffmann* and *C. S. Marvel*, J. Amer. Chem. Soc. *51*, 3496 (1929); *L. Horner*, *H. Hoffmann*, *H. G. Wippel*, and *G. Hassel*, Chem. Ber. *91*, 52 (1958); *M. Grayson* and *P. T. Keough*, J. Amer. Chem. Soc. *81*, 4803 (1959); *82*, 3919 (1960).

[3] *H. Schmidbaur* and *W. Tronich*, Angew. Chem. *79*, 412 (1967); Angew. Chem. internat. Edit. *6*, 448 (1967); Chem. Ber. *101*, 595 (1968).

[4] *B. C. Chang*, *W. E. Conrad*, *D. B. Denney*, *D. Z. Denney*, *R. Edelmann*, *R. L. Powell*, and *D. W. White*, J. Amer. Chem. Soc. *93*, 4004 (1971).

[5] *H. Schmidbaur*, *K.-H. Mitschke*, and *J. Weidlein*, Angew. Chem. *84*, 165 (1972); Angew. Chem. internat. Edit. *11*, 144 (1972).

[6] *H. Schmidbaur*, *K.-H. Mitschke*, and *J. Weidlein*, Chem. Ber. *102*, 4136 (1969).

Nature of the "Silicon β-Effect" in Allyltrimethylsilane[1]

By *Ulrich Weidner* and *Armin Schweig*[*]

Allylsilanes, $R_3Si{-}CH_2CH{=}CH_2$, exhibit unusual spectral properties and a high reactivity towards electrophiles; furthermore, like other alkylsilanes having β-functions, they are readily fragmented with breakage of the Si—C bond[2]. This "silicon β-effect" has been interpreted in terms of two qualitative models, *viz.* pd conjugation and Si—C hyperconjugation[2]. In the present communication we derive a clear argument in favor of Si—C hyperconjugation from the photoelectron (PE) spectra of trimethylvinylsilane *(1)* and trimethylallylsilane *(2)* and approximate quantum-chemical calculations (CNDO/2 method)[3].

Fig. 1 shows the PE spectra of *(1)* and *(2)*[4] and Fig. 2 the experimental vertical ionization potentials *(IP)* and the

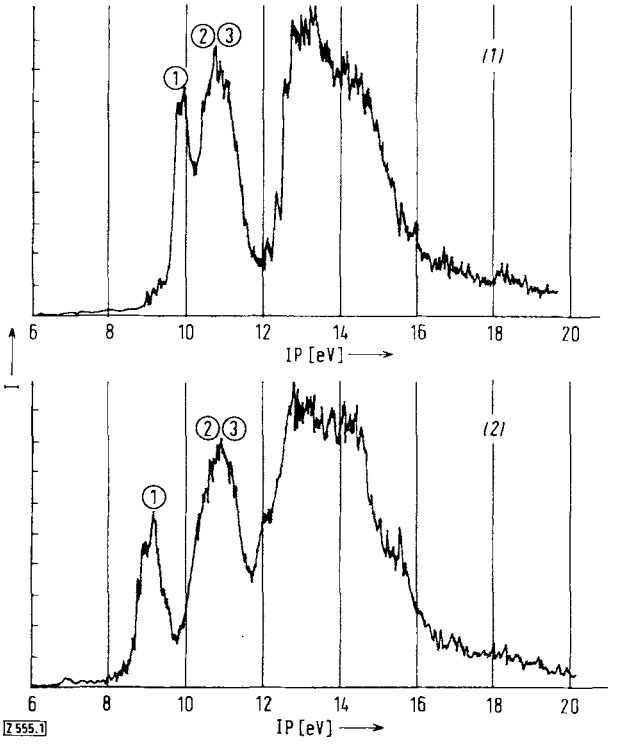


Fig. 1. Photoelectron spectra of trimethylvinylsilane *(1)* and trimethylallylsilane *(2)*.

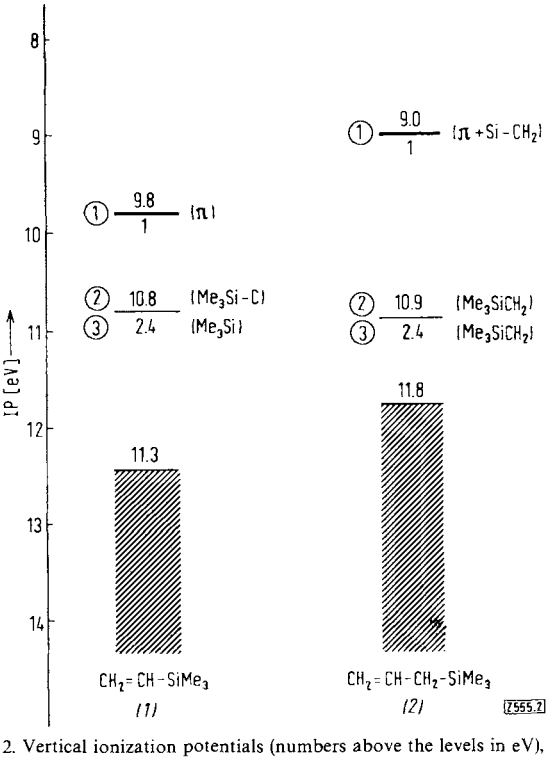


Fig. 2. Vertical ionization potentials (numbers above the levels in eV), relative intensities (numbers under the levels), and assignment of the bands ① and ②③ in the spectra of Fig. 1.

[*] U. Weidner and Prof. Dr. A. Schweig
Physikalisch-chemisches Institut der Universität
355 Marburg, Biegenstrasse 12 (Germany)

relative intensities of the first two bands ① and ②③. A comparison with other vinylsilanes suggested that the HOMO in *(1)* is the π MO having a node between the ethylene π system and the Me_3Si substituents[5]. The band ②③ is due to ionization of the σ MO linking Me_3Si and C, and of a second σ MO localized in the Me_3Si group. The shift of ① by 0.8 eV can be regarded as a characteristic difference between *(2)* and *(1)*[6]. The maximum of the band ②③ remains almost constant in the case of *(2)*. This band is due to ionization of two MOs localized in the σ skeleton of the Me_3SiCH_2 groups[8].

The reason for the unexpected raising of the HOMO in *(2)* is understandable with the aid of Figure 3 which shows the calculated orbital energies for one conformation of *(1)* and two conformations of *(2)*. In *(2a)* the CH_2-Si bond is perpendicular to the ethylenic π-electron clouds but practically parallel to them in *(2b)*; the two conformations undergo mutual interconversion on rotation about the $—CH_2—CH=$ bond. CNDO/2 model calculations were performed for each of the three conformations with and without inclusion of d AOs on the silicon atom (spd and sp basis set respectively). They show that *(2b)* is more stable

Since all three properties that characterize the β-effect—unusual spectral properties (above all bathochromic UV shifts), high reactivity towards electrophiles, and ready fragmentation with breakage of the Si—C bond—are connected with the high energy of the HOMO and the participation of the Si—C bond in the π system we can deduce that the "silicon β-effect" has to be interpreted in terms of Si—C hyperconjugation.

Received: October 11, 1971 [Z 555 IE]
German version: Angew. Chem. *84*, 167 (1972)

[1] Theory and application of photoelectron spectroscopy, Part 4.— We are indebted to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support of this work and to the Deutsches Rechenzentrum, Darmstadt, for carrying out the calculations.— Part 5: ref. [7].

[2] *A. W. P. Jarvie*, Organometal. Chem. Rev. A *6*, 153 (1970). Hyperconjugation as a significant interaction mechanism between an Si—C bond and a π system was first suggested as early as 1954: *C. E. Eaborn* and *S. H. Parker*, J. Chem. Soc. *1954*, 939; *ibid. 1956*, 4858. For later relevant work see: *C. Eaborn*, J. Organometal. Chem. *20*, 49 (1969); *W. Hanstein, H. J. Berwin*, and *T. G. Traylor*, J. Amer. Chem. Soc. *92*, 829 (1970); *C. G. Pitt*, J. Organometal. Chem. *23*, C 35 (1970); Chem. Commun. *1971*, 816.

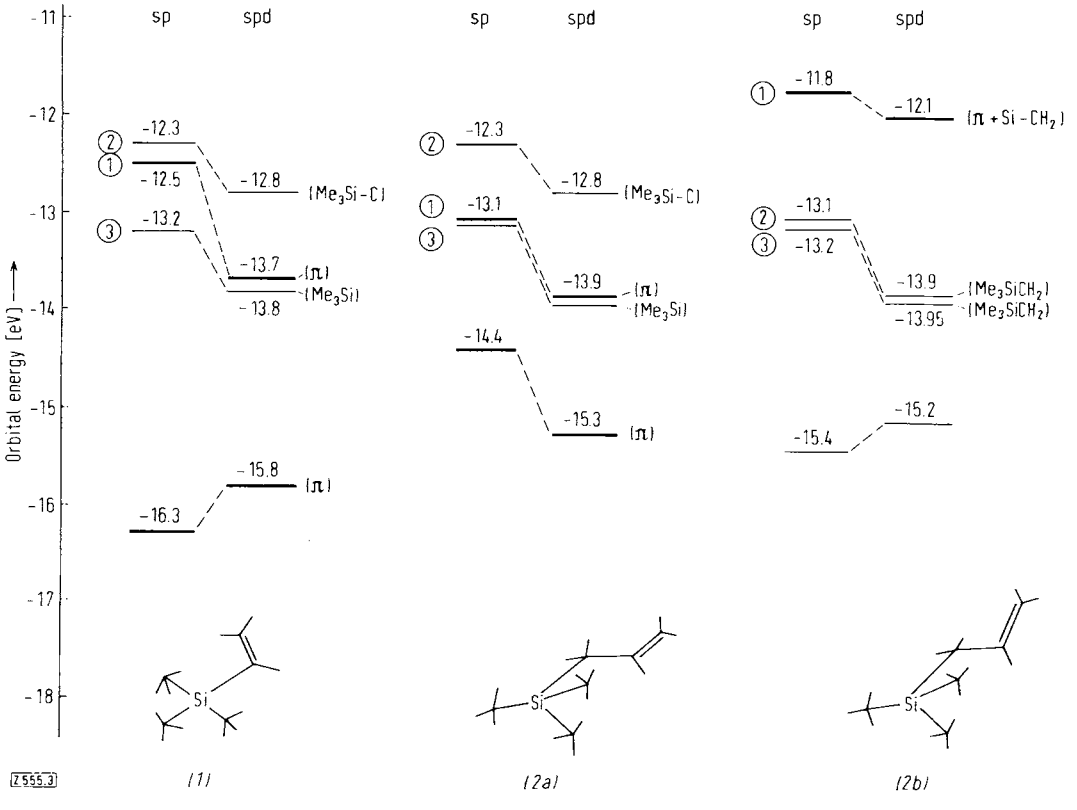


Fig. 3. Calculated orbital energies (in eV) for one conformation of trimethylvinylsilane *(1)* and two conformations *(2a)* and *(2b)* of trimethylallylsilane *(2)*.

than *(2a)* by 5.1 kcal/mol (sp basis set) or 3.3 kcal/mol (spd basis set); *i.e.* the conformation permitting CH_2-Si hyperconjugation is the more stable. It may be seen that the observed elevation of the HOMO can only be explained by conformation *(2b)*. This elevation arises from a coupling of the π-type CH_2-Si σ MO with the ethylenic π system having a node between $—CH_2—CH=$. According to these findings, the elevation of the HOMO on going from *(1)* to *(2)* can be explained unequivocally by Si—C hyperconjugation but not by pd conjugation.

[3] *J. A. Pople* and *D. L. Beveridge*: Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970.

[4] The He I (584 Å) PE spectra were recorded with the PS 16 spectrometer produced by Perkin-Elmer Ltd., Beaconsfield (England).

[5] *U. Weidner* and *A. Schweig*, unpublished results.

[6] Difference measured by mass spectrometry: 10 eV. *H. Bock* and *H. Seidl*, J. Organometal. Chem. *13*, 87 (1968).

[7] *W. Thiel* and *A. Schweig*, Chem. Phys. Lett. *12*, 49 (1971).

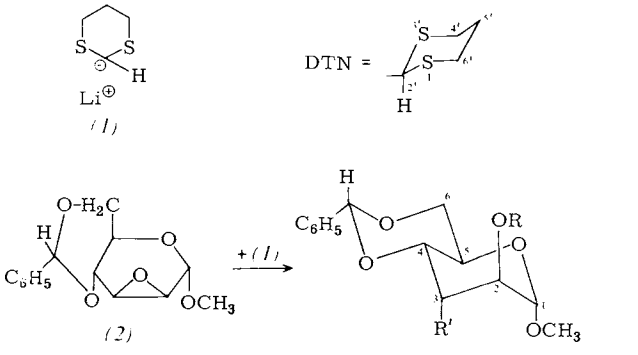
[8] Note added in proof: A more detailed study of the second band in the spectra of *(1)* and *(2)* has revealed that this band probably should be attributed to three MOs.

Synthesis and Pulse Fourier Transform ^{13}C-NMR Spectra of Branched-Chain Carbohydrates[**]

By *Anne-Marie Sepulchre, Gabor Lukacs, Georges Vass,* and *Stephan Dov Gero*[*]

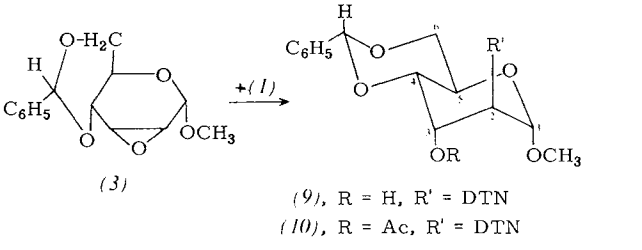
Although much progress has been made recently toward the preparation of branched-chain antibiotic sugars[1], further synthetic approaches seem desirable in this area. Our attention was drawn to the possible exploitation of 2-lithio-1,3-dithiane *(1)*[2] for the synthesis of branched-chain sugars and also for their chain extension. The 1,3-dithianyl side chain allows a variety of chemical modifications leading to functional groups such as CHO, CH_2OH, CH_3, CO, *etc.*

We report here the reaction of *(1)* with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside *(2)*, methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside *(3)*, and 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranoside *(4)*. Reaction of *(2)* with equimolar quantities of *(1)* (R = H) in dry THF solution for three days afforded the highly crystalline methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-(1,3-dithian-2-yl)-α-D-altropyranoside *(5)* in 50% yield, m. p. 195–197 °C, $[\alpha]_D$ +112° (*c* = 2.27; $CHCl_3$). The structure



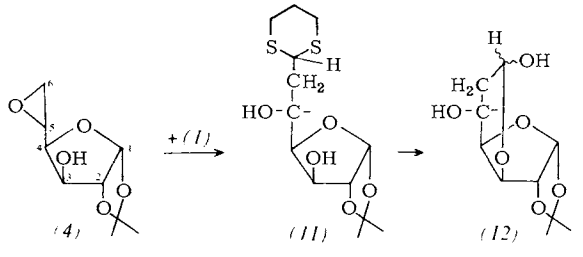
(2)

(5), R = H, R' = DTN
(6), R = Ac, R' = DTN
(7), R = H, R' = CHO
(8), R = H,
R' = CH=N-NH-C_6H_4-NO_2(*p*)



(3)

(9), R = H, R' = DTN
(10), R = Ac, R' = DTN



(4) *(11)* *(12)*

of *(5)* was established from the mass, ^{1}H-NMR, and ^{13}C-NMR spectral data (Table) of its 2-*O*-acetate *(6)*.

Treatment of *(5)* with HgO and BF_3 · ether in aqueous THF[3] gave methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-formyl-α-D-altropyranoside *(7)*, m. p. 125—130 °C, $[\alpha]_D$ +67.4° (*c* = 0.94; $CHCl_3$), 80% yield, which was characterized as its crystalline *p*-nitrophenylhydrazone *(8)*, m. p. 122—124 °C, $[\alpha]_D$ +49.5° (*c* = 0.77; ethyl acetate).

When a solution of *(3)* was treated with equimolar quantities of *(1)* in dry THF solution for three days, followed by direct acetylation of the reaction mixture, methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-(1,3-dithian-2-yl)-α-D-altropyranoside *(10)*, m. p. 78—80 °C, $[\alpha]_D$ +33° (*c* = 0.94; $CHCl_3$), was obtained in 30% yield; the product exhibited a molecular ion peak in the mass spectrum at *m/e* 426. Unreacted epoxide *(3)* was recovered (45%) before acetylation. The structure of *(10)* was deduced unequivocally from its ^{1}H-NMR and ^{13}C-NMR spectral data (Table). Because of the poor solubility of *(3)* and *(1)* in ethereal solvents optimization of the yield of *(10)* was not attempted.

Table. Assignments of the signals in the ^{1}H-broad band decoupled 25.15-MHz PFT ^{13}C-NMR spectra of *(6)* and *(10)*. Accumulation of 700 pulses, pulse width 15.1 μs, pulse interval 1.5 s. δ-values relative to TMS = 0.

Cpd.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	O—CO—	CH_3—	OCH_3—
(6)	103.1	77.2	45.0	71.5 [a]	69.7 [a]	59.6	99.5	169.9	21.1	55.7
(10)	102.2	46.1	74.8	69.7 [b]	69.5 [b]	59.0	99.9	170.5	21.4	55.8

	C-2′	C-4′	C-5′	C-6′	Aromatic C atoms *o*-	*m*-	*p*-	C-1
(6)	44.2	30.2 [c]	25.7	30.6 [c]	128.6 [d]	127 [d]	129.3	138.0
(10)	44.3	27.8 [e]	25.3	28.0 [e]	128.2 [f]	126.1 [f]	129.2	137.6

[a]–[f] These figures may be interchanged.

Opening of the epoxide ring in *(4)* by reaction with *(1)* in dry THF solution for 36 hours furnished 6-deoxy-6-*C*-(1,3-dithian-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose *(11)* in 80% yield, m. p. 98—100 °C, $[\alpha]$ −5.9° (*c* = 1.36; $CHCl_3$). Treatment of *(11)* with HgO and BF_3 · ether gave the known 6-deoxy-1,2-*O*-isopropylidene-α-D-gluco-heptodialdo-1,4-furanose-7,3-pyranose *(12)*[5].

Satisfactory elemental analyses have been obtained for all the compounds described.

Received: August 18, 1971;
supplemented: November 19, 1971 [Z 539a IE]
German version: Angew. Chem. *84*, 111 (1972)

[*] Dr. A. M. Sepulchre, Dr. G. Lukacs, Dr. G. Vass, and Dr. S. D. Gero
Institut de Chimie des Substances Naturelles, C. N. R. S.
91 Gif-sur-Yvette (France)

[**] This work was aided by a grant from the "Ligue Nationale Française contre le Cancer".

[1] *J. S. Brimacombe*, Angew. Chem. *83*, 261 (1971); Angew. Chem. internat. Edit. *10*, 236 (1971).

[2] *E. J. Corey* and *D. Seebach*, Angew. Chem. *77*, 1134 (1965); Angew. Chem. internat. Edit. *4*, 1075 (1965); *D. Seebach*, Synthesis *1969*, 17.

[3] *E. Vedejs* and *P. L. Fuchs*, J. Org. Chem. *36*, 366 (1971).

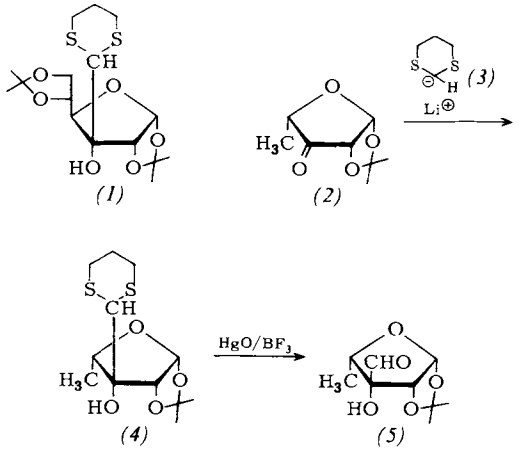
[4] *E. Breitmaier, G. Jung* and *W. Voelter*, Angew. Chem. *83*, 659 (1971); Angew. Chem. internat. Edit. *10*, 673 (1971).

[5] *A. Rosenthal* and *G. Kan*, Carbohydrate Res. *19*, 145 (1971).

Synthesis of Branched Carbohydrates with Aldehyde Side-Chains.—Simple Synthesis of L-Streptose and D-Hamamelose

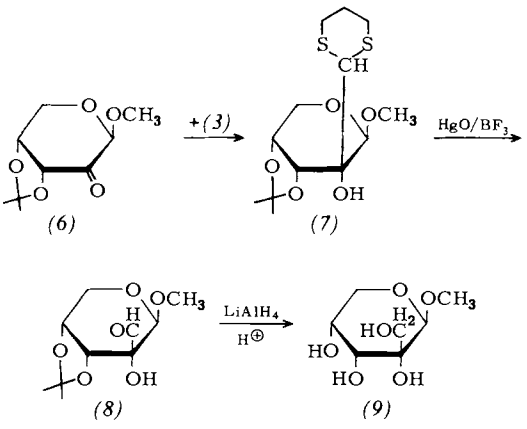
By *Hans Paulsen, Volker Sinnwell,* and *Peter Stadler*[*]

Hitherto, the synthesis of branched sugars with aldehyde or keto groups in the side-chain has remained a problem in the field of carbohydrate chemistry that has not been solved satisfactorily. We have now found that the reagent described by *Seebach*[1], 1,3-dithian-2-yllithium *(3)*, proves to be very useful for the preparation of compounds of this type. Blocked cyclic hexuloses react with *(3)* in good yields to give branched sugars in which the side-chain contains an aldehyde group blocked by mercaptal; *e.g.* reaction of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-ulose with *(3)* gives *(1)* (m.p. 97°C, $[\alpha]_D^{20} = +32.1°$) in 62% yield. As a rule the reaction proceeds stereoselectively and favors formation of the isomer in which the large 1,3-dithiane group is least hindered. Since 1,3-dithiane compounds form excellent crystals they can be prepared in a highly pure state prior to use in the following desulfurization step:

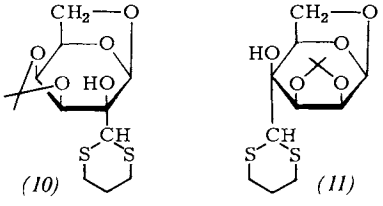


The reaction sequence is probably best illustrated by using the synthesis of L-streptose as example: reaction of the 3-ulose *(2)*[2] with *(3)* affords the dithiane-sugar *(4)* (m.p. 141°C, $[\alpha]_D^{20} = -3.0°$, 89%), which can be desulfurized with HgO/BF_3-ether[3] in THF to give *(5)* (m.p. 80—82°C, $[\alpha]_D^{20} = +43°$, 65%) which crystallizes as the hydrate. Acid hydrolysis of *(5)* yields the free L-streptose (syrup, $[\alpha]_D^{20} = 17.9°$, 90%)[2]. A critical step in the reaction sequence is the desulfurization, *e.g.* *(4)* → *(5)*, which must always be carried out under carefully controlled conditions. The blocked streptose derivative *(4)* is a valuable starting material *e.g.* for the synthesis of glycosides.

The 2-ulose *(6)*[4] reacts with *(3)* stereoselectively to give *(7)* (m.p. 102°C, $[\alpha]_D^{20} = -74.3°$, 78%). Desulfurization of *(7)* leads to the aldehyde-sugar *(8)* (syrup, $[\alpha]_D^{20} = -192°$, 75%), which can be converted by reduction with $LiAlH_4$ in THF and subsequent acid hydrolysis (Amberlite 120 $H^{\oplus}$) into the methyl glycoside of the D-hamamelose *(9)* (m.p. 133°C, $[\alpha]_D^{20} = -149.3°$, 70%)[5]. In the 1,6-anhydro series, reaction of *(3)* with 1,6-anhydro-3,4-*O*-isopropylidene-β-D-lyxohexopyranos-2-ulose[6] leads



to the dithiane-sugar *(10)* (m.p. 158°C, $[\alpha]_D^{20} = +98°$); reaction with 1,6-anhydro-2,3-*O*-isopropylidene-β-lyxo-hexopyranos-4-ulose[6] yields the sugar *(11)* (m.p. 161°C, $[\alpha]_D^{20} = +4.5°$) with a side chain on C-4.



Acyclic blocked aldehyde-sugars also react, but in this case a mixture of isomers is formed. 2,3;4,5-Di-*O*-isopropylidene-D-arabinose affords a crystalline mixture of the corresponding dithiane compounds of D-glucose and D-mannose, the major component being D-glucose, which can be separated by fractional crystallization.

Dithiane derivative (4)

A solution of *(2)* (1.7 g, 10 mmol) in THF (10 ml) is added dropwise with stirring at −78°C to a freshly prepared solution of *(3)* from 1,3-dithiane (1.25 g, 10.5 mmol) in THF (10 ml). The reaction mixture is warmed to room temperature, stirred for 1 hour, and then poured into ice-water (50 ml). The aqueous solution is repeatedly extracted with chloroform. The combined washings are dried over $MgSO_4$, concentrated by evaporation, and the residue remaining after removal of excess 1,3-dithiane by sublimation is recrystallized from ethyl acetate/petroleum ether. *(4)* is obtained in 89% yield (2.6 g) [m.p. 141°C, $[\alpha]_D^{20} = -3.0°$ ($c = 1$ in acetone)].

1,2-O-Isopropylidene-L-streptose (5)

A solution of *(4)* (1.46 g, 5 mmol) in THF (7 ml) is added dropwise with vigorous stirring to a mixture of red HgO (3.9 g, 18 mmol) and BF_3-ether (15 mmol) in aqueous THF (30 ml; 15% H_2O). Cleavage of dithiane is complete after 50 hours' stirring at room temperature. The mixture is

[*] Prof. Dr. H. Paulsen, Dipl.-Chem. V. Sinnwell, and Dipl.-Chem. P. Stadler
Institut für Organische Chemie und Biochemie der Universität
2 Hamburg 13, Papendamm 6 (Germany)

[1] *D. Seebach*, Synthesis *1969*, 17; Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969).

[2] *J. R. Dyer, W. E. McGonigal,* and *K. C. Rice*, J. Amer. Chem. Soc. *87*, 654 (1965).

[3] *E. Vedejs* and *P. L. Fuchs*, J. Org. Chem. *36*, 366 (1971).

[4] *V. M. Parikh* and *J. K. N. Jones*, Can. J. Chem. *43*, 3452 (1965).

[5] *J. J. K. Novák* and *F. Šorm*, Collect. Czechoslov. Chem. Commun. *30*, 3303 (1965).

[6] *K. Heyns, J. Weyer,* and *H. Paulsen*, Chem. Ber. *100*, 2317 (1967).

then treated with 15 ml H_2O and 30 ml acetone. The precipitate that is formed is removed by centrifugation and the centrifugate is concentrated by evaporation and subsequently extracted several times with chloroform. Concentration and drying of the chloroform phase yields a syrup, which, on treatment with a little water and ether, affords *(5)* as the crystalline hydrate. Recrystallization from acetone yields 650 mg of *(5)* (65%), m.p. 80—82°C, $[\alpha]_D^{20} = +42.8°$ ($c = 1.0$ in dioxane).

Received: October 26, 1971 [Z 539b IE]
German version: Angew. Chem. *84*, 112 (1972)

"Electron Lone Pairs" in Organic Sulfides and Disulfides[1]

By *Hans Bock* and *Gerhard Wagner*[*]

Dedicated to Professor O. Glemser on the occasion of his 60th birthday

Hydrogen sulfide is more readily ionized than water; the difference between the first ionization potentials ($IE_1(H_2S) = 10.48$ eV; $IE_1(H_2O) = 12.61$ eV)[2] reflects the more effective screening of the 3p electrons from the positive nuclear charge. The next σ molecular orbital (C_{2v}:$3a_1$) is more strongly bonding in H_2S (∢HSH 92.2°) than in H_2O (∢HOH 104.5°)[3]. The band assigned to the lone pair n_S in the photoelectron (PE) spectrum of hydrogen sulfide[2] is isolated and therefore well suited for the study of intramolecular interactions in organic sulfides: Any substitution on the H_2S molecule must lead to delocalization of the lone pair n_S and thus to a reduced ionization potential IE_1. From a formal viewpoint the following effects can be considered (Fig. 1): Antibonding admixture of σ components (1); n_-/n_+ combination with additional electron pairs (2); and π conjugation (3).

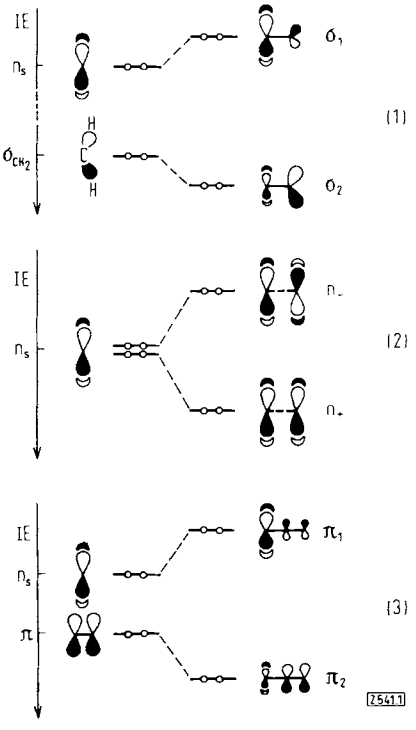


Fig. 1. Qualitative MO schemes for n_S/σ_{CH_2}, n_S/n_S, and n_S/π splitting.

[*] Prof. Dr. H. Bock and Dr. G. Wagner
Institut für Anorganische Chemie der Universität
6 Frankfurt 70, Ludwig-Rehn-Strasse 14 (Germany)

(1) As a result of inductive donor effects and of antibonding admixture of σ_{CH} components in the three-dimensional molecular skeleton (Fig. 1, (1)), alkyl groups lower the n_S ionization energy (Table 1).

Table 1. Vertical PE ionization potentials IE_1 (eV) of sulfides.

	R	IE_1
HSH		10.48 [2]
RSH	CH_3	9.44
RSR	CH_3	8.67
	C_2H_5	8.44
	C_3H_7	8.34
	$CH(CH_3)_2$	8.26
	$C(CH_3)_3$	8.07

Growing chain length and increasing degree of branching of the substituent R further raise the highest molecular orbital with predominating n_S character. These energy changes can also be deduced for dialkyl sulfides from the charge transfer (CT) excitation energies of their σ complexes with tetracyanoethylene (TCNE)[5] according to[4]

$$IE_v\,(\text{eV}) = 3.209 + 2.661 \cdot 10^{-4} \tilde{\nu}_{max}^{CT}\,(\text{cm}^{-1}); \quad SE = 0.011\ \text{eV} \qquad (1)$$

(2) Spatial interaction between sulfur lone pairs in dithiaalkanes (Table 2) causes splitting into an n_- and an n_+ combination (Fig. 1, (2)).

Table 2. Vertical PE ionization potentials $IE_{1,2}$ (eV) of dithiaalkanes [11].

	R	IE_1	IE_2	ΔIE
RSSR	CH_3	8.97	9.21	0.24
	C_2H_5	8.70	8.92	0.22
	C_3H_7	8.62	8.87	0.25
	$CH(CH_3)_2$	8.54	8.76	0.22
	$C(CH_3)_3$	8.17	8.82	0.65
		8.36	9.31	0.95
$RS-CH_2SR$	CH_3	8.65	8.90	0.25
		8.33	8.76	0.43
		9.69	10.16	0.47
$RS-(CH_2)_2-SR$	CH_3	8.64	8.90	0.26
		8.46	8.95	0.49

For a constant interatomic distance S ··· S the splitting is dependent upon the dihedral angle ω. In the case of coplanarity (ω = 0°, 180°) the difference between the first two ionization potentials ΔIE, and also the electronic repulsion neglected in the one-electron MO scheme (Fig. 1, (2)), would reach a maximum. The dihedral angle in dimethyl disulfide is ω = 84.7°[6] and the n_-/n_+ splitting (with admixture of σ_{CH}) therefore amounts to only $\Delta IE = 0.24$ eV. Larger values of ΔIE (Table 2) are observed when the angle is increased by bulky *tert*-butyl groups (ω ≈ 110°) or when it is decreased by fixation in a six-membered ring (ω = 60°[7]). A value of $\Delta IE > 2$ eV can be estimated for ω = 0°.

An increase in the interatomic distance S ··· S by insertion of a CH_2 group reduces the "through-space" interaction between the sulfur lone pairs (Fig. 1, center); at the same time, "through bond" interactions[8] with orbitals of the same symmetry class (Fig. 1, above) should be operative.

Such reasoning provides a qualitative explanation of the varying ΔIE values of the 1,3-dithia compounds (Table 2) on the basis of Figure 2.

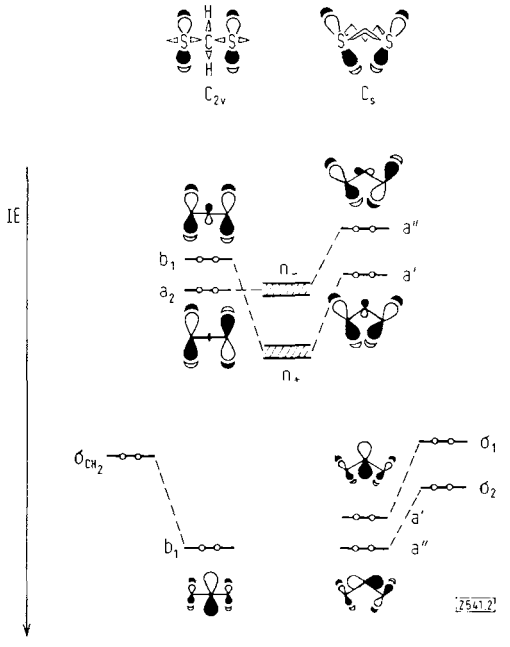


Fig. 2. Qualitative MO schemes for n_S/n_S and n_S/σ interactions in 1,3-dithia compounds.

EHT calculations on the open-chain compound 2,4-dithiapentane in the C_{2v} conformation show the n_+ MO to lie above the n_- MO whose symmetry properties (asymmetric with regard to both mirror planes) rule out admixture of σ_{CH_2} orbitals. In the 1,3-dithiane (C_s) and in bis(thiophosgene) (D_{2h}), however, combinations with molecular orbitals σ_n are symmetry allowed for both n_+ and n_- so that the sequence $IE(n_-) < IE(n_+)$ is retained. Similar differences between the lowest PE ionization potentials are observed (Table 2) in 1,4-dithia compounds, in spite of the large S···S distance ($d_{S\cdots S} \geq 3.5$ Å[9]); this can be interpreted in terms of predominating "through bond" interaction[8].

(3) The delocalization of the sulfur "lone pairs" is particularly clear in thio-substituted π systems[1,4]. The n_S/π conjugation can be described quantitatively by SCF calculations[10] (Fig. 1, (3)) and discussed qualitatively as a perturbation of the π systems. Comparison of the first ionization potentials of dimethyl sulfide (Table 1: 8.67 eV) and of unsubstituted as well as thio-substituted π systems (Table 3) shows, *e.g.*, that the perturbation increases with the number of substituted centers and decreasing energy difference $|IE_\pi - IE_{n_S}|$.

Table 3. Vertical PE ionization potentials IE_i (eV) of π systems and their methylthio derivatives.

	IE_i(X = H)	IE_i(X = SCH_3)
	10.51 [2]	8.45
	10.51	7.96
	9.24	8.07
	9.08 [2]	7.48
	8.55	8.75
	8.15	7.71

The PE ionization potentials IE_1 can only be correlated with the CT excitation energies of the TCNE complexes by the regression

$$IE_v\,(\text{eV}) = 5.769 + 1.335 \cdot 10^{-4}\,\tilde{\nu}_{max}^{CT}\,(\text{cm}^{-1}); \quad SE = 0.017\ \text{eV} \qquad (2)$$

which differs from (1) and which is calibrated with other π systems. Yet more convincing evidence for the delocalization of the sulfur "lone pairs" is provided by the increased ionization energies in the PE spectra which completely confirm, *e.g.* for *trans*-1,2-bis-(methylthio)ethylene, the splitting scheme (Fig. 3) deduced from a symmetry-allowed combination of π- and n orbitals.

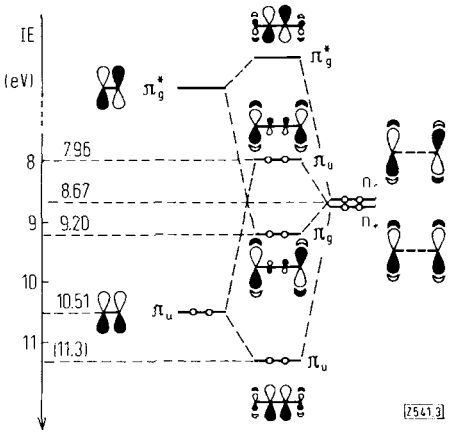


Fig. 3. Qualitative MO scheme for n_S/π interaction in *trans*-1,2-bis-(methylthio)ethylene.

Received: September 6, 1971 [Z 541 IE]
German version: Angew. Chem. *84*, 119 (1972)

[1] Photoelectron spectra and molecular properties. Part 7. — Part 5: *H. Bock, G. Wagner*, and *J. Kroner*, Tetrahedron Lett. *1971*, 3713 (Part 6: Tetrahedron, in press).

[2] *D. W. Turner, C. Baker, A. D. Baker*, and *C. R. Brundle*: Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970.

[3] *B. M. Gimarc*, J. Amer. Chem. Soc. *93*, 593 (1971).

[4] *G. Wagner*, Dissertation, Universität Frankfurt 1971.

[5] *W. M. Moreau* and *K. Weiss*, Nature *208*, 1203 (1965).

[6] *D. Sutter, H. Dreizler*, and *H. D. Rudolph*, Z. Naturforsch. *20a*, 1676 (1965).

[7] *O. Foss, K. Johnsen*, and *T. Reistad*, Acta Chem. Scand. *18*, 2345 (1964).

[8] *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971).

[9] *R. E. Marsh*, Acta Crystallogr. *8*, 91 (1955).

[10] *J. Kroner*, unpublished.

[11] Dr. *S. Kabuss*, Universität Freiburg, kindly supplied 1,2- and 1,4-dithiane, and Prof. Dr. *W. Walter*, Universität Hamburg, dimeric thiophosgene.

2-Cyanoaziridine

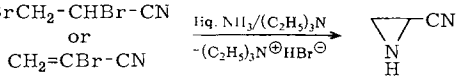
By *Klaus Burzin* and *Klaus Enderer*[*]

Dedicated to Professor Franz Broich on the occasion of his 65th birthday.

Whereas the synthesis of *N*-substituted 2-cyanoaziridines has been reported on a number of occasions[1,2], unsubstituted 2-cyanoaziridine *(1)* has only been postulated

[*] Dr. K. Burzin and Dr. K. Enderer
Forschungslaboratorien der Chemischen Werke Hüls
Aktiengesellschaft
437 Marl (Germany)

as an intermediate in the reaction of 2,3-dichloropropionitrile and of 2-chloro-3-methoxypropionitrile with ammonia[3]. *Gundermann et al.* reported an unsuccessful attempt at synthesizing *(1)*[2]. We have synthesized *(1)* by reaction of 2,3-dibromopropionitrile or 2-bromoacrylonitrile[4] with liquid ammonia[5] in the presence of triethylamine.



The structure of *(1)* follows from elemental analysis and the following spectral data: NMR ($CDCl_3$): $\tau = 8.56$ (1H/broad s), 7.86 (2H/d), 7.44 (1H/q); IR (film): ν(N—H) = 3300 cm^{-1}, ν(C≡N) = 2230 cm^{-1}. Reaction of *(1)* with *p*-nitrobenzoyl chloride in ether in the presence of triethylamine gives 1-*p*-nitrobenzoyl-2-cyanoaziridine [pale yellow crystals, m.p. 95 °C (isopropanol)] in 96% yield. Elemental analysis, IR spectrum, and NMR spectrum are in accord with the given structure.

2-Cyanoaziridine (1)

2,3-Dibromopropionitrile (0.5 mol) or 2-bromoacrylonitrile (0.5 mol) is added dropwise with stirring to liquid ammonia (800 ml) at −30 to −40 °C. After two hours, triethylamine is added in an amount equivalent to the hydrogen bromide released and the resulting mixture is stirred for a further 15—20 hours at −30 to 35 °C. The mixture is then allowed to warm to room temperature, and gently heated to remove last traces of ammonia. The residue is extracted with anhydrous ether (2 × 300 ml). The ethereal solution is concentrated to *ca.* 80 ml and filtered through aluminum oxide (20 g, activity III, neutral). After removal of ether, the residue is distilled[6] at 38—39 °C/0.1 torr through a 10 cm Vigreux column to a colorless oil (yield 65—70%).

Received: September 23, 1971 [Z 535 IE]
German version: Angew. Chem. *84*, 108 (1972)

[1] *V. K. Antonov*, Zh. Obshch. Khim. *29*, 1133 (1959); *V. K. Antonov* and *A. J. Berlin*, ibid. *30*, 151 (1960); *Th. Wagner-Jauregg*, Helv. Chim. Acta *44*, 1237 (1961); *G. Szeimies* and *R. Huisgen*, Chem. Ber. *99*, 491 (1966); *L. Petit* and *P. Touratier*, Bull. Soc. Chim. France *1968*, 1136; *K.-D. Gundermann*, *K. Burzin*, *H. Schulze*, and *F.-J. Sprenger*, Chem. Ber., in press.

[2] *K.-D. Gundermann*, *G. Holtmann*, *H.-J. Rose*, and *H. Schulze*, Chem. Ber. *93*, 1632 (1960).

[3] *K.-D. Gundermann* and *H.-J. Rose*, Chem. Ber. *92*, 1081 (1959).

[4] *H. Brintzinger* and *A. Scholz*, Chem. Ber. *83*, 141 (1950).

[5] A number of 2-alkoxycarbonylaziridines have been prepared by the same method: *E. Kyburz*, *H. Els. St. Majnoni*, *G. Englert*, *C. v. Planta*, *A. Fürst*, and *Pl. A. Plattner*, Helv. Chim. Acta *49*, 359 (1966); *A. Fürst*, *E. Kyburz*, and *St. Majnoni*, German Pat. 1126879 (1962), Hoffmann-La Roche.

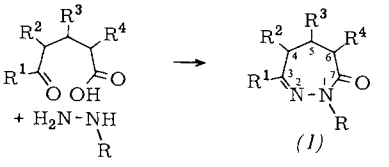
[6] When carrying out the distillation care must be taken to ensure that the bath temperature does not exceed 65 °C, otherwise spontaneous polymerization and consequent destruction of apparatus is likely to take place.

Synthesis of New Diazepinones[**]

By *Camille-Georges Wermuth* and *Jean-Jacques Koenig*[*]

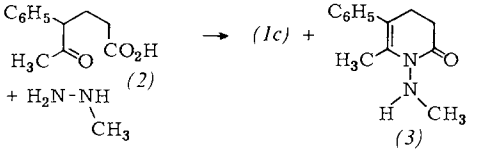
In connection with our studies on pharmacologically active diaza heterocycles[1,2] we have been able to show that the tetrahydrodiazepinones *(1)* are easily prepared by the action of hydrazine on δ-keto acids.

To the best of our knowledge this is the first reported synthesis of these 5,6-dihydro-4*H*-1,2-diazepin-7(1*H*)-ones. Some related compounds, namely a hexahydro derivative[3], a dihydro derivative[4] and a few analogs from the benzodiazepine series[5], have been mentioned in the literature.



(1)	R^1	R^2	R^3	R^4	R	Yield (%)	M.p. (°C)
a	C_6H_5	H	H	H	H	43	157 (C_6H_6)
b	C_6H_5	H	H	CH_3	CH_3	62	89 (hexane)
c	CH_3	C_6H_5	H	H	CH_3	32	55 (pentane)
d	C_6H_5	H	CH_3	H	H	61	161 (C_6H_6)
e	2-Thienyl	H	H	H	CH_3	76	108 ($AcOC_2H_5$ + hexane)

The cyclization represents a general reaction; however, the free δ-keto acids and not the esters must be used. The reaction of unsubstituted hydrazine with δ-keto acids, in which R^1 and R^2 are aliphatic groups leads to a mixture of inseparable compounds. As expected, the cyclization of 4-phenyl-5-oxohexanoic acid *(2)* with methylhydrazine gives the diazepinone *(1c)*; the isomeric 3,4-dihydro-5-phenyl-6-methyl-1-methylamino-2-pyridone *(3)* is formed as by-product [*(1c)*:*(3)* = 4:1]. This side reaction can be explained by the lability of the benzylic hydrogen in *(2)*.



The structure of the products *(1)* was confirmed by spectral analysis and by analytical data: Molecular peak at *m/e* = 188 in the mass spectrum of *(1a)*. UV (C_2H_5OH): 249 nm (ε = 10000) and 292 nm (7900); IR ($CHCl_3$): 3400 cm^{-1} (N—H), 1655 cm^{-1} (C=O), 1600 and 1580 cm^{-1} (C=N and C=C); NMR ($CDCl_3$): δ = 2.4 (4H) for $—CH_2—CH_2—CO$, 2.99 (2H) for CH_2, 7.3 (3H) and 7.5 (2H) for C_6H_5, and 8.83 (1H) for NH (disappears with D_2O). *(3)* is readily differentiated by NMR spectroscopy from the isomer *(1c)* by the absence of the benzyl proton (δ = 4.22 ppm) and presence of a NH proton (δ = 5.1 ppm, exchangeable with D_2O).

[1] *C. G. Wermuth*, *G. Leclerc*, and *J. Schreiber*, Chim. Therap. *1971*, 109.

[2] *C. G. Wermuth* and *M. Flammang*, Tetrahedron Lett. *1971*, 4293.

[3] *S. Hünig*, *L. Geldern*, and *E. Lücke*, Rev. Chim. Acad. Rep. Populaire Roumaine *7*, 935 (1962).

[4] *M. Franck-Neumann* and *G. Leclerc*, Tetrahedron Lett. *1969*, 1063.

[5] *J. O. Halford*, *R. W. Raiford*, and *B. Weissmann*, J. Org. Chem. *26*, 1898 (1961).

[*] Prof. Dr. C. G. Wermuth and Dr. J. J. Koenig
Laboratoire de Chimie Organique—
U. E. R. de Sciences Pharmaceutiques
3, Rue de l'Argonne
F-67 Strasbourg (France)

[**] The diazepinones *(1)* can also be named as 5,6-dihydro-4*H*-1,2-diazepin-3(2*H*)-ones, 7-oxo-4,5,6,7-tetrahydro-1*H*-1,2-diazepines, or 1,2-diaza-7-cyclohepten-3-ones.

Experimental:

A solution of δ-keto acid (0.1 mol) in xylene (500 ml) is heated to boiling under reflux in a two-necked flask fitted with reflux condenser and dropping funnel. Hydrazine (0.11 mol) is then added and the mixture heated under reflux for 4—5 hours, after which time the water is distilled off as xylene/H_2O azeotrope. The solvent is removed by evaporation under vacuum and the residue taken up in chloroform. The chloroform phase is washed twice with 10% $KHCO_3$ solution, then with water, and finally dried over $MgSO_4$. After removal of solvent, the residue is purified by distillation, recrystallization or chromatography.

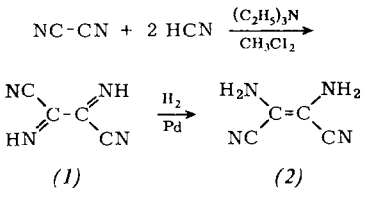
Received: October 4, 1971 [Z 536 IE]
German version: Angew. Chem. *84*, 153 (1972).

CONFERENCE REPORTS

Hydrogen Cyanide Chemistry: Synthesis of Diiminosuccinonitrile[1]

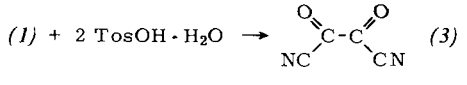
By *Owen W. Webster*[*]

The low temperature, base-catalyzed addition of hydrogen cyanide to cyanogen gives diiminosuccinonitrile *(1)* in high yield.

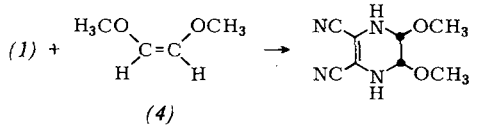


(1) *(2)*

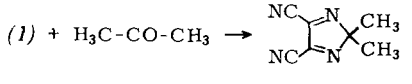
Diiminosuccinonitrile *(1)* is a white, crystalline, air-stable solid that is readily reduced to diaminomaleonitrile *(2)*, the well-known HCN tetramer. *(1)* forms oxalyl cyanide



(3)



(4)



(3) on controlled hydrolysis, adds to electron-rich olefins like *(4)* to give dicyanotetrahydropyrazines, and reacts with ketones such as acetone to produce dicyanoisoimidazoles.

Lecture at Freiburg on October 18, 1971 [VB 331 IE]
German version: Angew. Chem. *84*, 173 (1972)

[*] Dr. O. W. Webster
E. I. Du Pont de Nemours and Company,
Central Research Department, Experimental Station
Wilmington, Delaware 19898 (USA)

[1] *R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard,* and *O. W. Webster*, J. Amer. Chem. Soc. *93*, 4953 (1971).

Comparative Studies of the Topography of the Membranes of Mitochondria and Chloroplasts

By *Günter Hauska*[*]

In *Racker's* laboratory at Cornell University, U.S.A. the reconstitution, from its component parts, of the respiratory chain of mitochondria from succinate to oxygen has been achieved (see[1]). However, it was disappointing that the energy in this artificial electron transport system could not be obtained in chemical form as ATP. Evidently, a specific arrangement of the components in the membrane is necessary for ATP synthesis which is coupled to the electron flux. This topography must be known precisely before one can contemplate the construction of a "synthetic mitochondrion" which might possibly lead to the elucidation of one of the most important energy transformations in nature.

The fact that both surfaces of the membrane can be made accessible was a great help in *Racker's* investigations[1]. In isolated mitochondria the surface which carries the coupling factor 1 (F_1, a reversible ATPase) is on the inside directed towards the matrix, whereas membrane vesicles obtained after ultrasonic treatment have this coupling factor outside, accessible from the medium. These two surfaces have been studied systematically. For example, attempts were made to strip components from the surface without disrupting the membrane structure and then to reattach them. Further, the reaction of the bound components with hydrolytic enzymes, with radioactive, impermeable reagents and, finally, with antibodies was investigated.

The results so far can be summarized in a model (Fig. 1). The coupling factors F_1 to F_6 and succinate dehydrogenase (SDH) are accessible from the M-side (M for matrix). The C-side bears the cytochromes c and c_1. Cytochrome c oxidase (a,a_3) is accessible from both sides. It was assumed that cytochrome b and ubiquinone (Q) extend through the membrane. Protons are pumped from the M- to the C-side when the membrane is excited. Both succinate oxidation and oxygen reduction occur on the M-side (Fig. 1).

The membrane of the chloroplast is similar to the mitochondrial membrane in structure and function (in

[*] Dr. G. Hauska
Abteilung für Biologie, Lehrstuhl für Biochemie der Pflanzen
der Universität Bochum
463 Bochum-Querenburg, Postfach 2148 (Germany)

chloroplasts the excitation of electrons in two photosystems occurs in addition to the electron flux). A few of the differences in the morphology of the two organelles disappear after treatment with ultrasonics or detergents, which also yields vesicles which have the coupling factor 1 of photophosphorylation (CF_1) on the outside and the

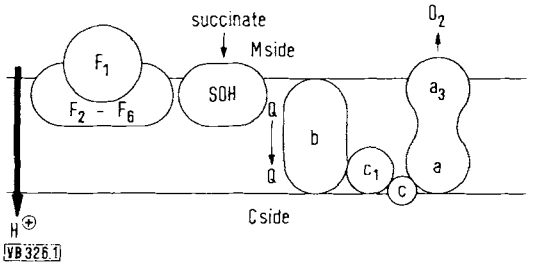


Fig. 1. Model of the mitochondrial membrane.

proton pump directed to the inside. (Bacteria form similar vesicles.) Unfortunately, only one surface of the membrane can be studied directly in chloroplasts since the coupling factor faces the medium immediately after isolation from leaves. It is unclear whether the chloroplast membrane exists *in vivo* with this polarity or whether this is an artifact of isolation. The M-side of the chloroplasts was studied, in the same manner as the mitochondria surfaces. The results are summarized in Fig. 2.

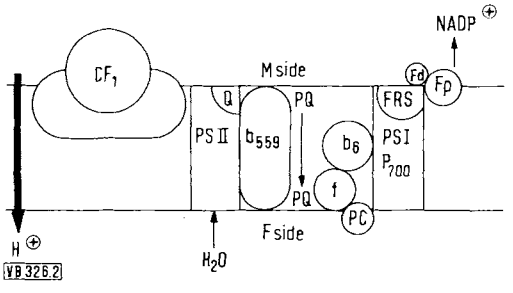


Fig. 2. Model of the chloroplast membrane.

It was assumed that components that are inaccessible are located on the inner surface of the membrane. This seems to be justified, particularly for the hydrophilic plastocyanin (PC)[2]. Coupling factor 1 is found on the M-side[3]. Furthermore, the groups of *Menke* and *Trebst* have found that ferredoxin (Fd)[4], ferredoxin-NADP reductase (Fp)[5] and the reducing end of photosystem I (FRS) (PS = photosystem) are located on this surface. Conversely, cytochrome f and plastocyanin sit on the inside (F-side). It was further assumed that the reaction centers of both photosystems extend through the membrane such that oxygen is formed on the F-side and the reducing end (Q) of photosystem II is located on the M-side. Cytochrome b_{559} is thought to extend through the membrane and plastoquinone (PQ), like ubiquinone, to be dissolved in it. Cytochrome b_6 appears to be tightly linked to photosystem I.

It is obvious that this speculative model is very similar to that for the mitochondrial membrane. In both cases the protein complexes are embedded in layers of lipid.

An analogy between cytochrome c and plastocyanin should also be mentioned. Both of them can react from the M-side with the oxidase and photosystem I respectively, but this artificial electron flux is not accompanied by a phosphorylation. A coupled electron flux is found only when cytochrome c sits on the C-side and plastocyanin on the F-side.

Lecture at Dortmund on October 25, 1971. [VB 326IE]
German version: Angew. Chem. *84*, 123 (1971)

[1] *E. Racker*, Essays in Biochem. *6*, 1 (1970).

[2] *G. Hauska, R. E. McCarty, R. Berzborn*, and *E. Racker*, J. Biol. Chem. *246*, 3524 (1971).

[3] *R. E. McCarty* and *E. Racker*, Brookhaven Symposia in Biology *19*, 202 (1966).

[4] *C. G. Kannangara, D. van Wyk*, and *W. Menke*, Z. Naturforsch. *25b*, 613 (1970).

[5] *R. Berzborn*, Z. Naturforsch. *23b*, 1096 (1968).

[6] *G. Regitz, R. Berzborn*, and *A. Trebst*, Planta *91*, 8 (1970).

Genetic Organization of the Fatty Acid Synthetase Complex of Yeast

By *Eckhart Schweizer*[*]

The multienzyme complex fatty acid synthetase (M.W. 2.3×10^6) can be dissociated into its protein components by denaturing agents but reassociation of the individual components to yield an active complex again has not yet been achieved[1]. What brings about the ordered association of the components *in vivo*? Is it a process which occurs spontaneously or is it specifically controlled, possibly by a particular organization of the genes involved?

On the basis of the meiotic recombination frequency (tetrad analysis) of appropriate mutants it could be shown that the six known fatty acid synthetase *(fas)*genes[2] are located at three unlinked DNA regions on the yeast genome. The first region consists of one gene, the second of three linked genes and the third of two linked genes.

In the course of a systematic biochemical investigation of representative *fas* mutants we have found that the genes for the enoyl reductase and the dehydratase lie in one of the three *fas* regions and the genes for two of the proteins participating in the condensation reaction as well as that for the β-ketoreductase lie in the second *fas* region. Surprisingly, mutants in the DNA region comprising only one *fas* gene yielded a fully active fatty acid synthetase complex in both the overall fatty acid synthetase reaction as well as all the partial reactions studied. Apparently, acetyl CoA carboxylase activity is not impaired in this mutation.

Pleiotropic polar mutations are also encountered in the *fas* regions 2 and 3, in addition to simple structural gene mutations. Evidently, the proteins of both regions are encoded in a polycistronic mRNA. No synthetase-CRM is to be found on immunological assay of a homogenate of pleiotropic *fas* mutants. The activity of other constituent enzymes which are not primarily affected by the polar mutation may also be missing. It is still not known whether this is due to an allosteric inactivation of the protein in question or to a failure of its synthesis.

Since no linkage of functionally related genes has previously been found in yeast or eucaryotes generally, the linkage of the genes of the fatty acid synthetase complex

[*] Doz. Dr. E. Schweizer
Institut für Biochemie der Universität
87 Würzburg, Röntgenring 11 (Germany)

in two or three polycistronic segments of the genome may be of special significance. It is conceivable that a genetic organization of this kind is a necessary requirement not only for aggregate formation but, particularly, for the formation of the "right" protein complex, *i.e.* it is needed to control its stoichiometry and/or architecture. According to this notion the fatty acid synthetase complex of yeast would be assembled from two to three dissimilar component complexes, the synthesis of which is subject, in each case, to the particularly critical control implied in a linked arrangement of their respective genes. It is possible that the synthesis of the component complexes is also subjected to some kind of mutual co-ordination. This could take the form of typical eucaryotic control mechanisms at the translation level.

Lecture at Dortmund on November 8, 1971 [VB 327 IE]
German version: Angew. Chem. *84*, 124 (1972)

[1] *A. Hagen*, Dissertation, Universität München 1963.

[2] *E. Schweizer, L. Kühn*, and *H. Castorph*, Hoppe-Seylers Z. Physiol. Chem. *352*, 377 (1971).

New Aspects of the Hydroformylation Reaction

By *Jürgen Falbe*[*]

The catalytic reaction of olefins with carbon monoxide and hydrogen to give aldehydes was discovered in 1938 by *O. Roelen* (Ruhrchemie). It has become known as hydroformylation, the oxo synthesis, or the Roelen reaction. The development of the petrochemical industry, through which lower olefins have become available in sufficient quantities at reasonable prices, provided the basis for the world-wide exploitation of the oxo synthesis in large production plants. In 1970 the annual world capacity for oxo products amounted to about 2.7×10^6 t.

The initially formed aldehydes are hydrogenated to alcohols that are used primarily as solvents and as starting materials for the production of plasticizers and detergents.

[*] Dr. J. Falbe
Ruhrchemie AG
42 Oberhausen-Holten, Postfach 35 (Germany)

About 80% of available production capacity is utilized for conversion of propylene into butyraldehydes.

However, only about two thirds of the propylene is actually transformed into the desired *n*-butyraldehyde, the rest giving isobutyraldehyde as well as other by-products and further reaction products. The reasons for by-product formation were studied and mechanistic interpretations offered. In order to increase the selectivity of the reaction, the tetracarbonylhydridocobalt used as catalyst was modified by replacing the complexed carbon monoxide by compounds of trivalent phosphorus. Although the use of phosphanes[1] does reduce the amounts of isobutyraldehyde and various higher boiling compounds, hydrogenation of the olefin to the paraffin is promoted. Diphosphacyclopentenones[2] that have been investigated at Ruhrchemie lessen the formation of higher boiling compounds, esters, and alcohols and increase the yield of *n*-butyraldehyde; however, they bring about no reduction in the proportion of isobutyraldehyde. Moreover, the increased catalyst costs incurred by catalyst modification counteract the economic advantages of enhanced selectivity.

Attempts were therefore made to cleave isobutyraldehyde into products that can be used again in the oxo synthesis. It was found that partial oxidation or steam reforming affords a synthesis gas that can be re-used in oxo plants[3]. Isobutyraldehyde can also be cleaved into propylene, carbon monoxide, and hydrogen[4] (reversal of the oxo synthesis) on a fixed-bed noble metal catalyst at 250—350 °C. The reaction products can be recycled into the oxo synthesis. This process has been developed on a pilot-plant scale.

Lecture at Marl on December 22, 1971 [VB 330 IE]
German version: Angew. Chem. *84*, 172 (1972)

[1] *L. G. Cannell, L. M. Slaugh*, and *R. D. Mullineaux*, DAS 1186455 (1960), Shell.

[2] *J. Falbe, H. Tummes, J. Weber*, and *W. Weisheit*, Tetrahedron *27*, 3603 (1971).

[3] *J. Falbe* and *D. Hahn*, German Pat. 1809727 (1968), Ruhrchemie; *F. Schnur, J. Falbe, E. Prött*, and *D. Hahn*, DAS 1767261 (1968), Ruhrchemie.

[4] *J. Falbe, H. Tummes*, and *D. Hahn*, Angew. Chem. *82*, 181 (1970); Angew. Chem. internat. Edit. *9*, 169 (1970); Oil Gas J. of Nov. 23, 1970, p. 59.

SELECTED ABSTRACTS

Paramagnetic anisotropy of transition metal and rare earth compounds and some minerals is surveyed in a paper by *W. deW. Horrocks jr.* and *W. deW. Hall*. Introductory sections on the theory of diamagnetism and paramagnetism are followed by a fairly detailed description of the most simple and versatile method of measuring magnetic anisotropy: *Krishnan*'s critical torque method. Finally, a documentation of compounds is given for which paramagnetic anisotropy data were available up to 1969 and partly into 1970, together with the pertinent references. [Paramagnetic Anisotropy. Coord. Chem. Rev. *6*, 147 to 186 (1971); 228 references, 4 figures, 1 table]

[Rd 423 IE –H]

The photochemistry of α-dicarbonyl compounds in oxygen-free solutions is the subject of a review by *B. M. Monroe*. Cleavage of a C—C bond is favored in the vapor phase, whereas in the condensed phase hydrogen abstraction preferably takes place. Only sufficiently strained compounds or compounds which can afford sufficiently stable radicals give decarbonylation products. The review deals, *inter alia*, with the excited states of α-dicarbonyl compounds and with photochemical reactions of α-diketones, α-keto acids, and α-keto esters. [The Photochemistry of α-Dicarbonyl compounds. Advan. Photochem. *8*, 77–108 (1971); 120 references]

[Rd 438 IE –M]

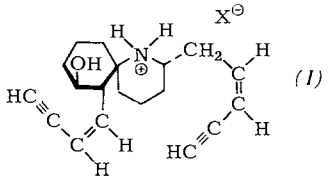
The photochemical and spectroscopic properties of organic molecules in the adsorbed state or in other perturbing polar environments are tabulated by *C. H. Nicholls* and *P. A. Leermakers*. The photochemical behavior of many organic molecules is changed when they are bonded to solid surfaces. This permits the investigation of primary and secondary processes of photochemical reactions. The topics dealt with include, in addition to adsorption itself, the spectra of adsorbed molecules (benzene and derivatives, polycyclic hydrocarbons, ketones, carotinides) and, *inter alia*, their photochemical reactions. [Photochemical and Spectroscopic Properties of Organic Molecules in Adsorbed or other Perturbing Polar Environments. Advan. Photochem. *8*, 315–336 (1971); 60 references, 5 tables]

[Rd 439 IE –M]

Complications in photosensitized reactions are summarized in a report by *P. S. Engel* and *B. M. Monroe*. Choice of sensitizer is very important, since almost all the compounds used as sensitizers are likely to cause complications. The authors give a few rules regarding such a choice. Examples of the complications met with are decomposition of the sensitizers (α- and β-cleavage of ketones, photoenolization, dissociation of halogen compounds), interactions of sensitizer molecules with one another and with substrate (oxetane formation, addition to aromatic hydrocarbons, hydrogen abstraction, reversible energy transfer), and the transfer of energy from a state other than the lowest triplet state (participation of singlet and higher triplet states). [Complications in Photosensitized Reactions. Advan. Photochem. *8*, 245–313 (1971); numerous references, 12 tables, 8 figures]

[Rd 436 IE –M]

New directions of the chemistry of natural products, with particular consideration of the author's own work is the subject of a review by *B. Witkop* in the 13th Paul Karrer lecture. A highlight of the review is a report on histrionicotoxin *(1)*, a component in the poison of the Columbian frog *Dendrobates histrionicus*. *(1)* is the first animal alkaloid containing acetylene residues. Another component, dihydroisohistriotoxin, has one side chain containing an acetylene residue and one containing an allene group; it is the first animal alkaloid with an allene residue.

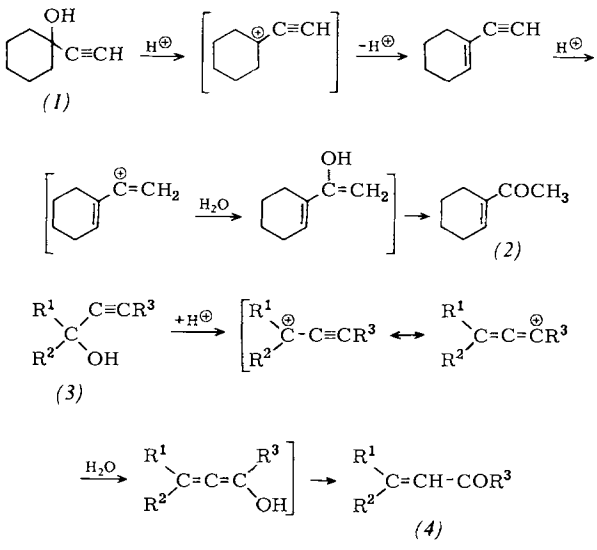


(1)

Other topics dicussed include: batrachotoxin as an auxiliary material in the investigation of Na transport in cell membranes; significance of selective bromocyanide cleavage for the elucidation of protein structure; arene oxides as labile metabolites of aromatic metabolism and their importance as regards long-term toxicology of aromatic medicines and carcinogenic hydrocarbons. [New Directions of the Chemistry of Natural Products: The Organic Chemist as a Pathfinder for Biochemistry and Medicine. Experientia *27*, 1121—1248 (1971); 109 references]

[Rd 448 IE –M]

The Rupe and Meyer-Schuster rearrangements are dealt with by *S. Swaminathan* and *K. V. Narayanan* in a review covering the literature up to the middle of 1968 and in part up to the middle of 1970. The Rupe rearrangement is the acid-catalyzed rearrangement of tertiary α-acetylene alcohols *(1)* to, predominantly, α,β-unsaturated ketones



R^1, R^2 = $C(CH_3)_3$, Aryl; R^3 = H, Alkyl, Aryl

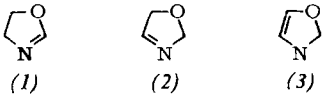
(2); the Meyer-Schuster rearrangement is the isomerization of secondary and tertiary α-acetylene alcohols of type *(3)* to α,β-unsaturated carbonyl compounds *(4)*. A descriptive account of the mechanisms of both rearrangements is supplemented by a discussion of, *inter alia*, substrates and catalysts, and normal and abnormal reaction products. [The Rupe and Meyer-Schuster Rearrangement. Chem. Rev. *71*, 429—438 (1971); 183 references]

[Rd 450 IE –M]

Adsorption and colloidal properties of radioactive elements in trace concentrations are reviewed by *F. Kepák*. Adsorption and colloid formation play a significant role at trace concentrations in solution so that methods of colloid chemistry come to the fore in the study of such small quantities. The author deals, *inter alia*, with ultracentrifugation, ultrafiltration, ion exchange and adsorption, as well as self-diffusion and dialysis. [Adsorption and Colloidal Properties of Radioactive Elements in Trace Concentrations. Chem. Rev. *71*, 357—369 (1971); 170 references]

[Rd 452 IE –M]

A survey of the chemistry of oxazolines from 1949 to 1969 has been authored by *J. A. Frump*. The oxazoline ring, and particularly the 2-oxazoline structure *(1)*, permits the preparation of a large number of derivatives of wide interest.



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

The article considers the preparation of *(1)* from amino alcohols, amides, halo amides, aziridines, epoxides, and Grignard reagents, as well as by the action of $SOCl_2$ on hydroxy amides. Halo-, vinyl-, amino-, mercapto-, and alkoxycarbonyl-oxazolines, as well as oxazolines related to

chloramphenicol and threonine, are discussed in detail. 3-Oxazolines *(2)* and 4-oxazolines *(3)* can also be prepared. Apart from treating stereochemical problems and reactions, the author also goes into technical applications, *e.g.* as protective layers, surface-active agents, fuel and lubricant additives, corrosion inhibitors, textile chemicals, pharmaceuticals, adhesives, and binders. [Oxazolines. Their Preparation, Reactions, and Applications. Chem. Rev. *71*, 483—505 (1971); 398 references]

Rd 453 IE –M]

The function of sulfur in living organisms is the subject of a review by *Z. M. Bacq*. The essential element sulfur is utilized in many forms—ranging from sulfate ions to the mercapto group in amino acids and coenzymes. In seawater and in the soil, sulfur is available as SO_4^{2-} which serves as a suitable source of the element for the synthesis of the sulfur-containing amino acids of proteins.—Space is devoted not only to the utilization of sulfur by plants and animals but also to the general biochemical reactivity of thiols and the mode of action of sulfur-containing compounds that afford protection against radiation. [Some Considerations on the Role of Sulfur in Living Organisms. Internat. J. Sulfur Chem. *6*, 93—101 (1971); 13 references]

[Rd 454 IE –M]

Kinetic data on water exchange between aquo complexes and solvent water are compiled by *J. P. Hunt*. The reactions were followed by monitoring shifts and broadenings of ^{17}O-NMR lines. A compilation of all data available is followed by an attempted systematization of the numerous data on cobalt(II) and nickel(II) complexes. In the author's opinion, there is lack of sufficient data for mechanistic considerations. [Water-Exchange Kinetics in Labile Aquo and Substituted Aquo Transition Metal Ions by Means of ^{17}O-NMR Studies. Coord. Chem. Rev. *7*, 1—10 (1971); 29 references]

[Rd 464 IE –H]

Photochemical reactions of solid coordination compounds are treated in a review by *E. L. Simmons* and *W. W. Wendlandt*. General information about methods of measurement and evaluation of results is followed by sections on redox and ligand substitution reactions. The review concludes with a comparison between thermal dark reactions and photochemical reactions. [Solid-State Photochemical Reactions of Transition-Metal Coordination Compounds. Coord. Chem. Rev. *7*, 11—27 (1971); 88 references]

[Rd 465 IE –H]

Metal complexes of thio-β-diketones are the subject of two reviews, one by *M. Cox* and *J. Darken*, the other by *S. E. Livingstone*. Sections about preparation, structure, and physical properties of the free ligands are followed by descriptions of their metal complexes, including formation, physical and chemical properties, and short accounts of substitution reactions in the chelate ring. Both reviews are written independently and stress different points of their coverage. [Metal Complexes of Thio-β-Diketones. Coord. Chem. Rev. *7*, 29—58 (1971); 99 references. Monothio-β-Diketones and Their Metal Complexes. Coord. Chem. Rev. *7*, 59—80 (1971); 73 references]

[Rd 466 IE –H]

Conductivity measurements in organic solvents are reported by *W. J. Geary* with respect to the electrolytic dissociation of coordination compounds. There are general suggestions about choice of the most suitable solvent and the experimental procedures; detailed accounts (with references to methods of purification) are given of the solvents nitromethane, nitrobenzene, acetone, acetonitrile, dimethylformamide, methanol, and ethanol. Some other solvents are mentioned briefly. A special section is devoted to the toxicity of the various solvents. [The Use of Conductivity Measurements in Organic Solvents for the Characterization of Coordination Compounds. Coord. Chem. Rev. *7*, 81—122 (1971); 377 references]

[Rd 467 IE –H]

BOOK REVIEWS

Organische Chemie (Organic chemistry). By *O. Runquist*. R. Oldenburg Verlag, Munich–Vienna 1970. 1st edit.,
Part 1: Eine programmierte Einführung. Reaktionen I (Programmed introduction. Reactions I), 90 pp., DM 9.80.
Part 2: Reaktionen II (Reactions II), 120 pp., DM 14.80.
Part 3: Nomenklatur (Nomenclature), 101 pp., DM 9.80.

The original American title "Programmed Review of Organic Chemistry" has been incorrectly translated as "Organische Chemie – Eine programmierte Einführung (Organic chemistry—programmed introduction)". Anyone who expects these three volumes to act as an introduction to organic chemistry is thus in for a disappointment. However, if they are regarded (in accordance with the original American title) as a means of testing the knowledge one has gained through reading or attending lectures, then these books will prove to be a useful collection of exercises.

Part 1 (Reactions I) deals with hydrocarbons, alcohols, alkyl halides, Grignard reagents, *etc.* Part 2 (Reactions II) describes more complicated reactions, such as the Hofmann degradation, the Fries rearrangement, the Reformatsky reaction, *etc.* Part 3 (Nomenclature) tests the reader on his ability to assign the correct IUPAC name to an organic formula, and to write out the correct structural formula when given the name. In my opinion this section should have come first.

These books are essentially a series of exercises, a sort of "chemical quiz book". First a fact of general validity (usually an empirical rule) is given, and this is followed by examples of its application. It is thus in no sense a true teaching program. There are also no indications as to the preliminary knowledge expected of the reader. The level of difficulty is about that suitable for chemistry under-

graduates. For such readers it is not important that stoichiometry is not taken into account (*e.g.* in A-13/Part 1).

The presentation of the exercises is lacking in variety, particularly in Part 2. In the answers to Parts 1 and 2, I occasionally missed any consideration of unstable intermediates (*e.g.* in A-242/Part 1).

Sometimes the question bypasses the problem, and the answer appears irrelevant (*e.g.* the answer to question F-206/Part 2, which is very good but not at all what its readers will be expecting).

Despite the deficiencies mentioned, this collection of exercises in organic chemistry is recommended.

Siegfried Nöding [NB 5 IE]

Der Absatz in der Chemischen Industrie. (Marketing in the Chemical Industry). By *H. Köbel* and *J. Schulze*. Springer Verlag, Berlin–Heidelberg–New York, 1970, 1st edit., 732 pp., 259 figures, 156 tables, bound, DM 128.—.

The chemical industry is now showing an increasing tendency to do what other industries have been doing for some time: to align all entrepreneurial activities toward the marketing side. With growing competition resulting from increasing maturity in this industry, the sales prospects have become more and more the bottleneck of commercial success. The development of demand and the situation of markets thus become the most important basis for shaping management decisions from research and development projects to the erection of new plants and the successful opening of markets.

In this book, *Kölbel* and *Schulze* provide for the first time a comprehensive treatment of marketing in the chemical industry. The book is divided into eight main sections, which are based on the practical experience of the authors and their long years of work in the Industrial Chemistry Section of the Institute for Technical Chemistry at the Technische Universität Berlin. The marketing system in the chemical industry is presented by means of branch characterization, classification of products according to marketing aspects, marketing factors as determinants of the marketing system, and the development of chemical marketing. The section on marketing organization and distribution channels shows the possibilities for incorporating the sales function into the company's organization and gives a detailed description of the normal distribution channels in chemistry.

The central point of the whole study is formed by the two sections on the problems and methods of chemical market research, analysis, and forecasting. Particular attention is devoted to the topic of market research for production goods, which so far has received little attention in the literature. The section on forecasting also deals with problems of anticipating trends of technological development.

In the main section on product and program formulation the relationships between research, development, and marketing are studied, together with problems of coordination, followed by details on the determining factors of product development, packaging, quality standards, product marking, and patent and licensing policies. The section on the marketing program formulation is somewhat short, though it includes the problems and aspects of the development of the range of products. In my opinion it does not show sufficiently the relation to the method of direct costing—described in the section on pricing policy—as an instrument for finding the optimal range of goods.

A further section, devoted to application techniques and market development, presents the organization and methods of application techniques in great detail. Examples are shown of the use of the network planning technique for the solution of market development problems. After the section on chemical advertisement, which deals with the fundamentals, advertising factors, target groups, and advertising media, there follows the final section on pricing policy. Emphasis is given here to the determination of prices by costing and pricing in chemical markets.

The comprehensive treatment of the broad marketing field does not allow detailed treatment of special problems. This deficiency is overcome by the extensive lists of lieterature references, mainly of American origin, which have been evaluated by the authors, and which appear at the end of each main section. The clear, detailed arrangement, the large number of illustrative and explanatory examples, and the very detailed subject index should ensure the book's usefulness both for those involved in the fields of marketing, market research, and advertising, and for chemists working in research, development, and production.

Meinhard Forster [NB 6 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of thus issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 4036/4037, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A.J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N.Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P.O. Box 129/149 Germany, Telephone Weinheim (06201) 4031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition
VOLUME 11 · NUMBER 3
MARCH 1972
PAGES 159—248

Chemistry and Biochemistry of Branched-Chain Sugars

By Hans Grisebach and Rolf Schmid[*]

Branched-chain sugars have recently been isolated in larger numbers from microorganisms and higher plants as glycoside components of antibiotics or phenolic compounds. They also occur in plants in cell wall polysaccharides. Sugars with methyl, hydroxymethyl, formyl, hydroxyethyl, and glycoloyl branches have so far been found in nature. Many new methods have been developed for the synthesis of these sugars. With one exception, the branched sugars known at present can be divided biogenetically into three groups. Sugars with methyl branches are formed by C_1 transfer, sugars with hydroxyethyl branches by C_2 transfer to a hexose chain, and sugars with hydroxymethyl or formyl branches by rearrangement of a hexose or pentose chain.

1. Introduction

In the flavone glycoside apiin from parsley *(Apium petroselinum*, synonomous with *Petroselinum hortense)*, *Vongerichten* in 1901 found an unknown sugar, which he named apiose[1]. By oxidation of apiose with bromine, he obtained tetrahydroxyvaleric acid. On reduction with hydriodic acid and phosphorus, this gave a fatty acid, which was regarded as isovaleric acid[2]. *Vongerichten* therefore assumed that apiose has a branched carbon chain. The exact structure of apiose as 3-*C*-hydroxymethyl-D-glyceroaldotetrose was shown later by *O. Th. Schmidt*[3]. A few years after the discovery of apiose, *E. Fischer* and *Freudenberg* discovered a sugar, which they named hamamelose[5], in the hydrolysate of the tannin hamamelitannin[4] from the bark of *Hamamelis virginiana*. *Schmidt et al.* elucidated the constitution and configuration of hamamelose as 2-hydroxymethyl-D-ribose[6].

The discovery of apiose and hamamelose in higher plants attracted little attention at first. These two branched sugars were evidently regarded as rare and unimportant members of the sugar family.

A change came with the start of antibiotic research. More than a dozen branched deoxy sugars have now been discovered as components of antibiotics. The fact that the occurrence of these sugars appears to be confined to the genera *Streptomyces* and *Micromonospora* is probably only a consequence of insufficient investigation of other potentially suitable organisms. It can probably be assumed that sugars of this type will also be found in future in other types of microorganisms; the first example is the discovery of a nucleotide with a branched sugar in *Azotobacter vinelandi*[19].

Apiose and hamamelose have in the meantime been identified in several species in the plant kingdom. A particularly interesting finding is the occurrence of apiose in polysaccharides.

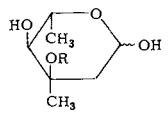
The synthetic chemistry of branched sugars has developed very rapidly during the past few years. One reason for this is the discovery that nucleosides with branched sugars can exhibit cytostatic or virostatic activity.

Some aspects of the chemistry and biochemistry of branched sugars have already been reviewed[7–11]. The present article will be concerned mainly with more recent work.

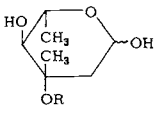
2. Occurrence and Constitution

The branched-chain sugars are best divided on biogenetic grounds into three groups (see Section 5), *i.e.* methyl-branched sugars, hydroxymethyl-branched and formyl-branched sugars, and hydroxyethyl-branched sugars. Only pillarose [2,3,6-trideoxy-2-glycoloylhexopyranos-4-ulose, see *(35)*], does not fit into this scheme.

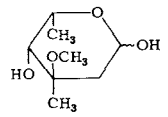
[*] Prof. Dr. H. Grisebach and Dr. R. Schmid
Lehrstuhl für Biochemie der Pflanzen
am Biologischen Institut II der Universität
78 Freiburg, Schänzlestrasse 9 (Germany)



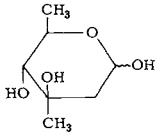
(1a), R = H
(1b), R = CH_3



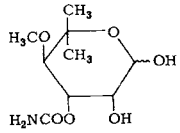
(2a), R = H
(2b), R = Ac



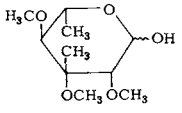
(3)



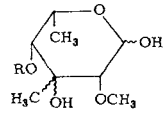
(4)



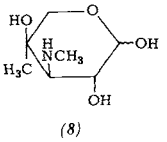
(5)



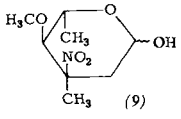
(6)



(7), R = H



(8)



(9)

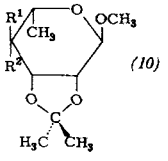
2.1. Methyl-Branched Sugars

The structure and occurrence of the known methyl-branched sugars are listed in Table 1. Sugars of this type have so far been isolated only from microorganisms as glycoside components of antibiotics. They include amino sugars and the nitro sugar L-evernitrose *(9)*. The methyl branch is situated on position 3, 4, or 5 of the hexose chain.

The position of the branch can be deduced from the mass spectrum[24, 25]. The tertiary methyl group is shown by a singlet in the NMR spectrum[26]. Difficulties arise, however, in the determination of the configuration at the branching position.

Indications of the configuration are provided by the IR frequencies of the *tert*-OH group[27], the kinetics of the periodate oxidation[26], chromatographic and electrophoretic mobilities in solvent systems with borate buffer[26, 28] or phenylboric acid[27], formation of cyclic carbonates[26], degradation reactions[29–31], partial stereospecific synthesis (see Section 3), and the formation of bicyclic hemialdals[26, 28]. In the case of nitroalkyl-branched sugars or sugar alcohols, the configuration can be deduced from the ORD and CD spectra[32–34a].

For sugars having a tertiary acetoxy group, the NMR signals of the CH_3CO protons of axial and equatorial acetoxy groups differ by about 0.1 ppm. According to *Lichtenthaler*, this is also true of sugars having a methyl group on the same C atom of the ring. This method can probably also be applied to the methyl signals of the acetamido group of *C*-methyl-branched amino sugars[35].



(10)

In the case of *O*-isopropylideneglycopyranosides *(10)*, the configuration at the branching position can be deduced from the signal of the *endo*-methyl protons of the isopropylidene residue[36]. The signal has a fairly constant position at about $\tau = 8.53$ if the substituent at the branching position is *cis* to the isopropylidene ring [*(10)*, $R^2 = e.g. CH_3$], but lies at $\tau = 8.42$ if the substituent is *trans* to the isopropylidene ring.

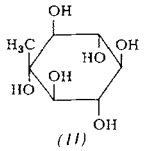
Table 1. Structure and occurrence of methyl-branched sugars.

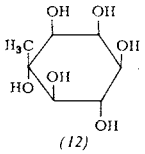
	Trivial name	Systematic name	Occurrence [12]
(1a)	L-Mycarose	2,6-Dideoxy-3-*C*-methyl-L-*ribo*-aldohexopyranose	A few macrolide antibiotics [11] Angolamycin [13] Aureolic acid [16a]
(1b)	L-Cladinose	2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-L-*ribo*-aldohexopyranose	Erythromycin A, B [14]
(2a)	L-Olivomycose	2,6-Dideoxy-3-*C*-methyl-L-*arabino*-aldohexopyranose	Olivomycin [16]
(2b)	L-Chromose B	2,6-Dideoxy-3-*C*-methyl-3-*O*-acetyl-L-*arabino*-aldohexopyranose	Chromomycin A_3 [18]
(3)	L-Arcanose	2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-L-*xylo*-aldohexopyranose	Lankamycin [15]
(4)	D-Evermicose	2,6-Dideoxy-3-*C*-methyl-D-*arabino*-aldohexopyranose	Everninomycin [17, 22a]
(5)	L-Noviose	6-Deoxy-3-*O*-carbamoyl-5-*C*-methyl-4-*O*-methyl-L-*lyxo*-aldohexopyranose	Novobiocin [23]
(6)	L-Nogalose	6-Deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-L-*manno*-aldohexopyranose	Nogalomycin [20, 20a]
(7)	L-Vinelose	6-Deoxy-3-*C*-methyl-2-*O*-methyl-L-(*altro*, *galacto* or *talo*)-aldohexopyranose (R may be CH_3OCH_2CO too)	As Cytidine diphosphate derivative from *Azotobacter vinelandii* [19]
(8)	L-Garosamin	3-Deoxy-3-methylamino-4-*C*-methyl-L-*arabino*-aldopentopyranose	Gentamycin C [21] Sisomicin [21a]
(9)	L-Evernitrose	2,3,6-Trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*ribo*-aldohexopyranose	Everninomycins [22, 22a]

2.2. Methyl-Branched Inositols

In addition to *C*-methyl-branched sugars, the *C*-methyl-inositols laminitol *(12)* and mytilitol *(11)* also occur in nature.

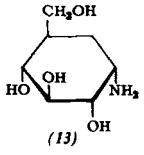
Laminitol was first isolated from the brown alga *Laminaria cloustoni*[37]. This compound was later found in numerous

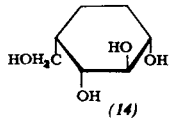

(11)

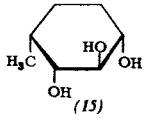

(12)

other red and brown algae[38] and in the green alga *Chlorella fusca*[39]. Mytilitol has been detected in mussels[40] and in red[41] and green algae[39].

Other branched inositols have recently been found in the validamycin antibiotics from *Streptomyces hygroscopicus*


(13)

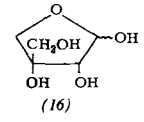

(14)

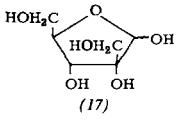

(15)

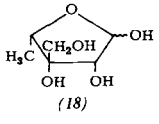
var. limoneus[39a]. These are validamine *(13)*, validatol *(14)*, and deoxyvalidatol *(15)*.

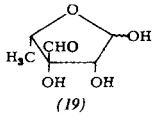
2.3. Sugars with Hydroxymethyl or Formyl Branches

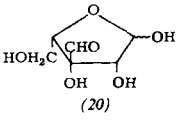
Known sugars of this type are D-apiose *(16)*, D-hamamelose *(17)*, L-dihydrostreptose *(18)*, L-streptose *(19)*, and L-hydroxystreptose *(20)*. The last three of these sugars have so far been found only in members of the streptomycin family[42,43].


(16)

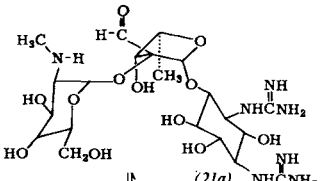

(17)

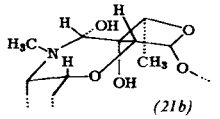

(18)

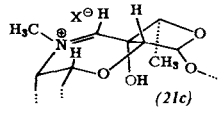

(19)


(20)

The NMR spectrum of streptomycin *(21a)* in D_2O contains no characteristic signal for the aldehyde proton of the streptose between $\tau=0$ and $\tau=2$, but has a sharp one-proton singlet at $\tau=4.98$. It is assumed from these results and from model considerations that the aldehyde group of the streptose forms a carbinolamine *(21b)* with the secondary amino group of *N*-methyl-L-glucosamine[44].

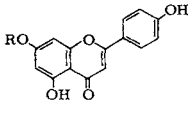

(21a)

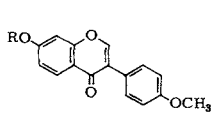

(21b)

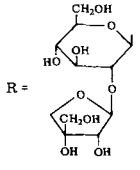

(21c)

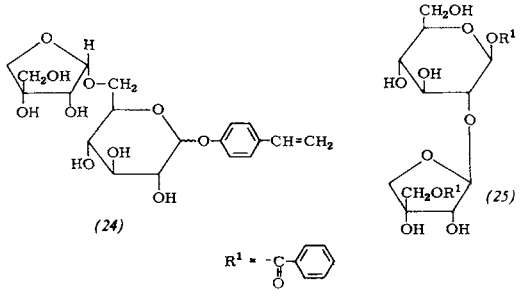
The immonium form *(21c)* that is postulated in equilibrium with *(21b)* is held responsible for the precipitation of polyanions by streptomycin and for its action against certain bacteriophages[44].

As far as is known at present, the occurrence of apiose and hamamelose is confined to plants. D-Apiose is surprisingly widely distributed in the plant kingdom. This sugar is found in the glycosides apiin *(22)* from parsley[1] and Capsicum species[45], lanceolarin *(23)* from *Dahlbergia*


(22)


(23)



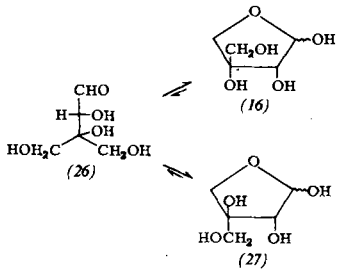

(24)

(25)

lanceolaria[46], furcatin *(24)* from *Viburnum furcatum*[47], and *(25)*, a bitter principle from the leaves of *Daviesia latifolia*[48]. Homoflavoyadorinin B from the leaves of mistletoe *(Viscum album)* is 7,3'-di-*O*-methyl-5,7,3',4'-

tetrahydroxyflavone 4'-*O*-D-glucoapioside[49]. Kaempferol (3,5,7,4'-tetrahydroxyflavone) 3-β-glucoapioside has been isolated from the chick pea *(Cicer arietinum)*[50].

On formation of the furanose ring of D-apiose from the open-chain structure *(26)*, C-3 becomes asymmetric; the two isomers D-apio-D-furanose *(16)* and D-apio-L-furanose *(27)* can be formed.



By permethylation of apiin and comparison of the 2,3,4-tri-*O*-methyl-D-apiofuranose obtained by hydrolysis with a synthetic compound whose configuration on C-3 was known, it was possible to show that apiose is present in apiin in the D-furanose form *(16)*[51].

The occurrence of D-apiose in polysaccharides from aquatic plants is particularly interesting. An almost identical pectin-like polysaccharide (zosterin), which contains D-galacturonic acid, D-galactose, D-xylose, mono-*O*-methyl-D-xylose, L-arabinose and D-apiose, has been found in several grass-wracks (Zosteraceae)[52]. However, it seems doubtful whether this is a single polysaccharide. The action of pectinase on zosterin gave an apiogalacturonan, in which the apiose residues are probably bound to a polygalacturonan. The polysaccharide nucleus of zosterin therefore probably has a structure similar to that of the apiogalacturonans from *Lemna* (see below). In *Helobiae*, walls containing apiose appear to occur mainly in submerged species in salt or brackish water[53].

Apiose also occurs in the cell wall in the genus *Lemna* (duckweeds)[54,55]. Apiogalacturonans from the cell wall of *Lemna minor* have been particularly intensively studied. As was found by *Beck*[56] and by *Kindel et al.*[57,58], the basic skeleton of these polysaccharides consists of an α (1→4)-bound, practically unesterified polygalacturonic acid chain with an apiobiose on C-2 or C-3 of the galacturonic acid (Fig. 1). Since the apiobiose side chains can be removed extremely readily, transannular participation of the free carboxyl group of D-galacturonic acid is assumed in the cleavage of the glycoside linkage[57].

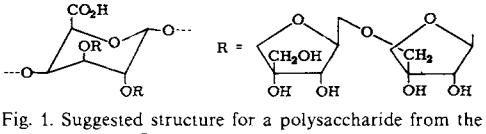
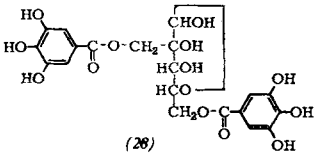


Fig. 1. Suggested structure for a polysaccharide from the cell wall of *Lemna minor* [57].

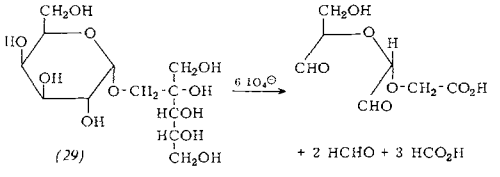
The polysaccharide fractions having a high apiose content are not degraded by pectinase. This may be part of the reason for the high resistance of Zosteraceae to natural decomposition[58].

As well as in aquatic plants, apiose has also been found in a polysaccharide from the lime tree[59].

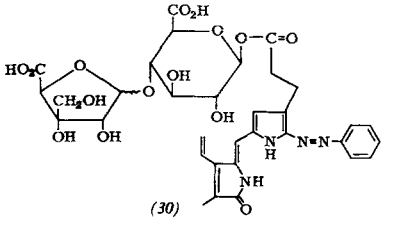
D-Hamamelose *(17)* and the corresponding sugar alcohol D-hamamelitol (2-*C*-hydroxymethyl-D-ribitol) are very widely distributed in the plant kingdom. Hamamelitannin *(28)*[60] has been isolated not only from witch hazel but also from the bark of the sweet chestnut *(Castanea sativa)*[61] and from the bark of the American red oak *(Quercus rubra)*[60].



Free hamamelose also occurs in these plants. This sugar is of general occurrence in genera and orders related to Hamamelis and Castanea[62]. D-Hamamelitol is found in the leaves of *Primula clusiana* as the predominant carbohydrate[63]. Another substance isolated from these leaves is a non-reducing disaccharide named clusianose, which yields D-galactose and D-hamamelitol on hydrolysis. From the results of periodate degradation, it was identified as 1-*O*-α-D-galactopyranosyl hamamelitol *(29)*[64].



Clusianose *(29)*, as well as hamamelitol, is also found in some sections of the genus *Primula*, and can be accumulated in the leaves in quantities comparable with those of sucrose. Since clusianose is formed only very slowly during photosynthesis in $^{14}CO_2$ and undergoes practically no decomposition in the course of four days in the dark, this disaccharide, unlike sucrose, does not appear to be a true storage substance[65].



Branched sugars may also occur in man. Mainly on the basis of mass-spectrometric data, *Kuenzle* proposed the structure *(30)* for a bilirubin conjugate isolated from human bile as the phenylazo derivative[66].

If the structure of this sugar is confirmed, it will show interesting biogenic relations with apiose (see Section 5).

2.4. Sugars with Hydroxyethyl or Glycoloyl Branches

Aldgamycin E, an antibiotic of the macrolide group[67] in which the structure of the macrolide ring is still partly un-

known, has as glycoside component in addition to mycinose *(32)* a 4,6-dideoxy-3-*C*-1'-hydroxyethyl-D-*ribo*-hexose in the form of a cyclic carbonate, D-aldgarose *(31)*[68,69]. The five-membered cyclic carbonate can be recognized from the carbonyl absorption at 1800 cm^{-1} in the IR spectrum. The carbonate group can be readily removed with dilute barium hydroxide. Cleavage of aldgamycin C with periodate (Fig. 2) gives acetaldehyde from the ethyl branch and D-(−)-3-hydroxybutyric acid[69] *(33)* from C-atoms 3—6 of the sugar. The stereochemistry was determined from the NMR spectrum of aldgarose, and only the configuration on C-1' is still unknown[68]. The antibiotic action against *Bac. subtilis* is lost on removal of the aldgarose from the lactone ring[70].

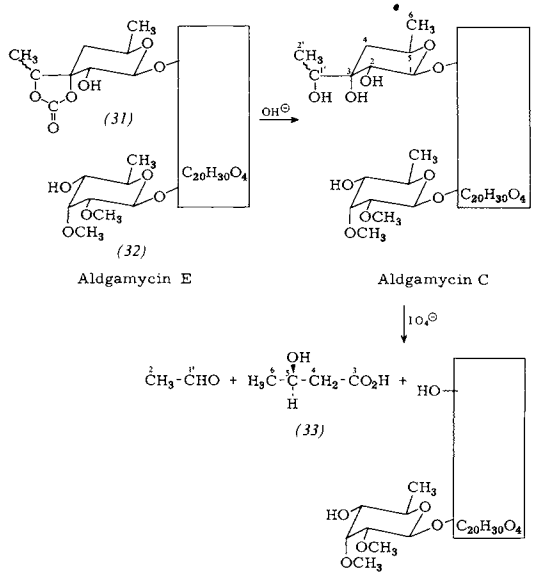
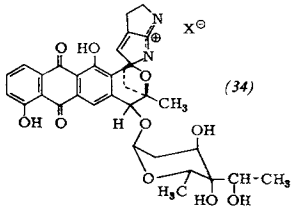
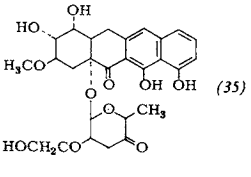


Fig. 2. Partial degradation of aldgamycin E.

The antibiotic isoquinocycline A *(34)*, the constitution of which has been established by X-ray analysis, also contains a sugar with a hydroxyethyl branch. The branch in this case is situated on C-4 of the hexose[71].



Pillarose (2,3,6-trideoxy-2-glycoloylhexopyranos-4-ulose), a keto sugar with a glycoloyl branch, was recently found[73] in pillaromycin A *(35)*[72].



3. Synthesis of Branched-Chain Sugars

Since the publication of the latest reviews[7–10,74,75,124], many new reports on the synthesis of branched sugars have appeared. The preparation of keto sugars, which are very often used as starting compounds, has already been reviewed[9,75a].

The steric course of additions to carbonyl groups or double bonds is particularly important for such syntheses. Whereas it is possible to predict with some certainty which diastereoisomer will be formed in the addition of Grignard compounds to keto sugars (see Section 3.1.1), this is not yet possible for the stereoselective alkylations.

We shall first discuss methods that lead to the formation of sugars of the type RCOH. This will be followed by methods for the formation of deoxy sugars of the types RCNH and RCH. Finally, the synthesis of sugars containing a cyclopropane ring will be discussed. The methods for the synthesis of naturally occurring branched sugars and their diastereoisomers are listed in Table 2.

Table 2. Synthesis of naturally occurring branched sugars and inositols by alkylation of keto sugars.

	Sugar	Alkylating reagent	Ref.
(16)	D-Apiose	Vinyl-MgBr	[87]
		Diazomethane	[96]
		Cyanide	[122]
		Formaldehyde	[159]
		Wittig-reaction	[94]
	L-Apiose	Diazomethane	[97]
		Phenylethynyl-MgBr	[77]
	DL-Apiose	[a]	[160]
(17)	D-Hamamelose	Diazomethane	[98]
	L-Hamamelose	Vinyl-MgBr	[79]
(19)	L-Streptose	Vinyl-MgBr	[83, 85]
	DL-Streptose	[a]	[85]
(1a)	L-Mycarose	Methyl-MgI	[91]
(1b)	L-Mycarose	[a]	[161]
	D-Mycarose	Methyl-MgI	[80]
	D-Cladinose	Methyl-MgI	[80]
	DL-Mycarose	[a]	[162]
	DL-Mycarose	[a]	[163]
D-*(6)*	D-Nogalose	Methyl-MgI	[90]
	D-Vinelose	Methyl-MgI	[88]
	D-Arcanose	Methyl-MgI	[89]
(5)	L-Noviose	Methyl-MgI	[86]
(2a)	L-Olivomycose	Triphenylmethylene-phosphorane	[143]
(11)	Mytilitol	Methyl-MgI	[87a]
(12)	Laminitol	Diazomethane/OsO_4	[87b]

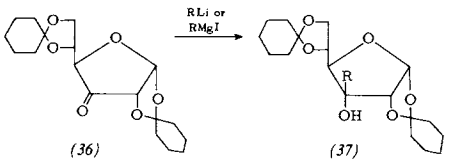
[a] Total syntheses.

3.1. Synthesis of Sugars of the Type RCOH

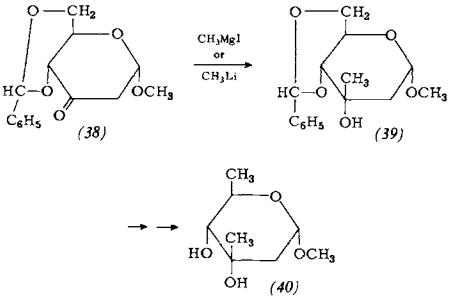
3.1.1. Addition of Organometallic Compounds to Keto Sugars

The reaction of keto sugars with organolithium or organomagnesium compounds proceeds stereoselectively in high yields, and in very many cases even stereospecifically[8–10]. Since this addition leads in a predictable manner to asymmetric products, it has become a standard method for the synthesis of branched sugars and their nucleosides[76–92] (Table 2).

Whereas it was reported earlier that the addition of organolithium compounds[78] can follow a sterically complementary course to the addition of Grignard compounds[79] and lead to diastereoisomers, the *allo*-products *(37)* were isolated in the reaction of *(36)* with both types of reagents[93].



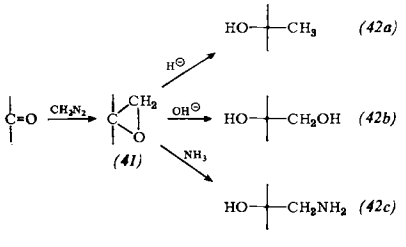
The reaction of *(38)* with methylmagnesium iodide or methyllithium also yields the *ribo*-product *(39)*, which can be converted into D-mycaroside *(40)*[80].



The yields and (within narrow limits) the stereoselectivity of the Grignard reactions depend on the solvent[80,81] and on the halide[81].

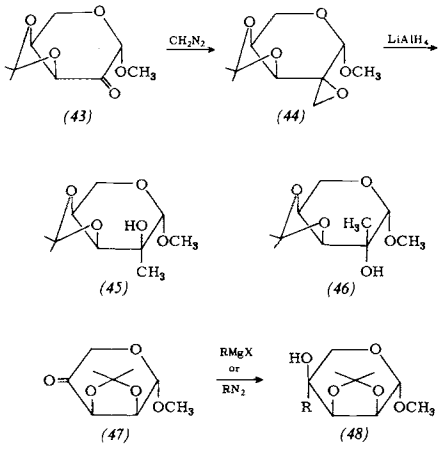
3.1.2. Addition of Diazomethane to Keto Sugars

The reaction of a keto sugar with diazomethane leads to the formation of an epoxide *(41)*, which can be converted into the C-methyl compound *(42a)* by reduction, into the *C*-hydroxymethyl compound *(42b)* by hydrolysis, and into the *C*-aminomethyl compound *(42c)* by ammonolysis.

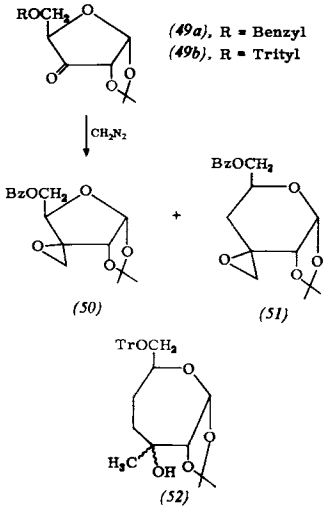


This addition proceeds stereoselectively, and has also frequently been used in recent years for the synthesis of branched-chain sugars[95–98].

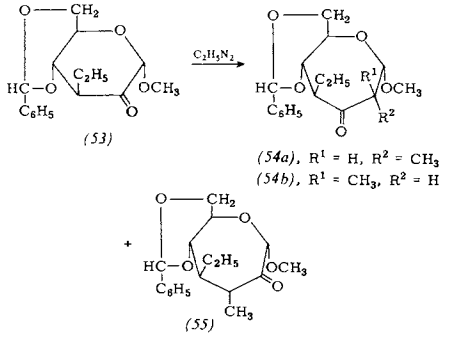
Investigations on the stereochemistry of the reaction led to the following results: Whereas the addition of diazomethane to the keto sugar *(43)* leads mainly to the epoxide *(44)*, which can be reduced to the 2-*C*-methyl compound *(45)* with the *ribo*-configuration[99] (the reaction follows a complementary course to the reaction with methylmagnesium iodide, in which the arabino-compound *(46)* is formed[79]), the reaction of *(47)* both with phenylethynylmagnesium bromide and with diazomethane leads mainly to the *ribo*-compound *(48)*[77].



The reaction can also proceed with ring expansion. Whereas the epoxide *(50)* is formed in the reaction of *(49a)* with diazomethane in ether, the reaction in methanol/ether yields the hexopyranoside *(51)* as the principal product[100].

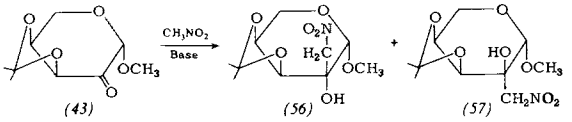


The reduction of the anhydro sugars *(50)* and *(51)* with $LiAlH_4$ yields the 3-*C*-methyl sugars having the *xylo*-configuration. On reaction of the 5-*O*-trityl compound *(49b)* with diazomethane in methanol/ether, a small quantity of the *C*-methylheptose *(52)* formed by double ring expansion was obtained among other products[101]. The addition of diazoethane to the keto sugar *(53)* gave only the ring expansion products *(54a)*, *(54b)*, and *(55)*, but not the expected compound with two ethyl branches[102].



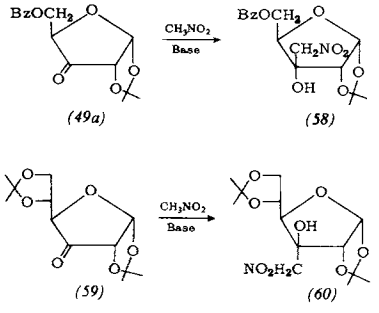
3.1.3. Addition of Nitromethane to Keto Sugars

The base-catalyzed addition of nitromethane to keto sugars leads in good yields to the *C*-nitromethyl compounds, which can be converted into aminomethyl and aminodeoxymethyl sugars[32-34, 103, 104, 138a]. The reaction leads to a mixture of the two anomers. Thus a mixture of the *arabino*-compound *(56)* and the L-*ribo*-compound *(57)* was obtained in the reaction of *(43)* with nitromethane and sodium methoxide[105].



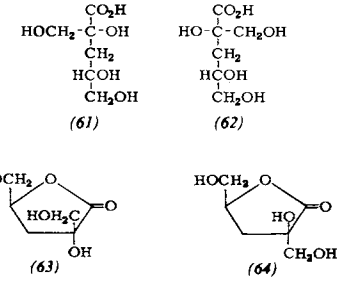
A certain steric control was possible by variation of the temperature. Whereas the isomers *(56)* and *(57)* were formed in a ratio of 1:1 at 0°C, the ratio at 20°C was 3:1. The configuration on C-2 was determined by assignment of the NMR signal of the *endo*-methyl protons of the *O*-isopropylidene residue (see Section 2.1).

Whereas the *ribo* compound *(58)* is formed on addition of nitromethane to *(49a)*, the reaction of the keto sugar *(59)* leads to the *gluco*-isomer *(60)*[33].



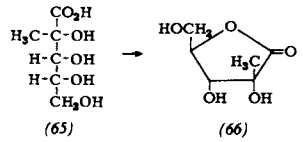
3.1.4. Rearrangements

The treatment of reducing sugars with alkali leads to the formation of saccharic acids[106, 107]. Under the action of calcium hydroxide, 4-*O*-methyl-D-glucose, D-lactose, or D-maltose gives roughly equal quantities of the "α"- and "β"-D-glucoisosaccharic acids *(61)* and *(62)*, from which the γ-lactones *(63)* and *(64)* are readily formed[108].



The configuration of the "α"-glucoisosaccharic acid *(61)*[109] and its lactone *(63)*[110] has been established by X-ray analysis; both were found to be *erythro*-compounds.

When calcium hydroxide is allowed to act on D-fructose, the α-glucosaccharic acid *(65)* is formed in good yields; this compound can also be readily converted into the γ-lactone *(66)*. The β-isomer cannot be detected[108].



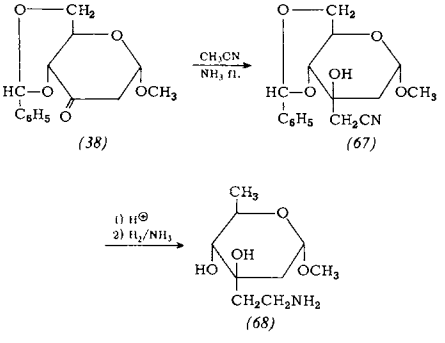
Chemical methods showed the *ribo*-configuration for *(65)*[111], and *(66)* was correlated with the same configuration of D-hamamelose[112].

The lactone *(66)* has been used as a starting material for the synthesis of nucleosides with branched sugars[113-115].

3.1.5. Other Reactions

C-Methyl groups can also be introduced by nucleophilic attack of dimethylsulfoxonium methylide on a keto sugar[96, 116-118].

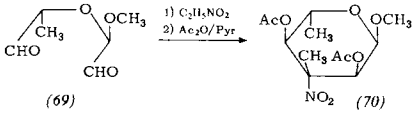
A promising new reaction is that of a keto sugar with acetonitrile in liquid ammonia. Thus reaction of *(38)* leads in very good yields to the *arabino*-cyanomethyl compound *(67)*, which gave the β-aminoethyl compound *(68)* on acid hydrolysis and catalytic reduction in the presence of ammonia[119].



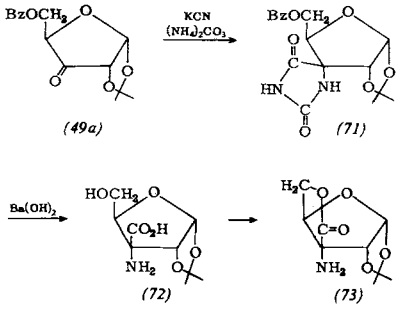
The formation of a branched heptosulonic acid by the cyanohydrin synthesis was described by *Kiliani* as early as 1885[120]. Only occasional use has recently been made of this method[121]. The reason for this is the formation of a mixture of diastereoisomers, the separation of which is time-consuming except in a few cases[122].

3.2. Synthesis of Sugars of the Type $R\overset{|}{C}NH_2$

On reaction of the dialdehyde *(69)* with nitroethane followed by acylation, the methyl-branched nitro sugar *(70)* was isolated in small yields[105, 123]. Reviews on this type of reaction have been published by *Baer*[75] and by *Lichtenthaler*[124].



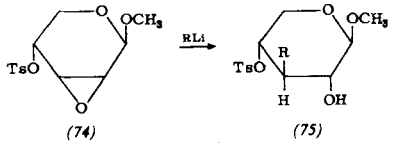
The addition of cyanide to the keto sugar *(49a)* yields the 3-*C*-spiro-5′-hydantoin *(71)* as the principal product. This compound can be converted into the α-amino acid derivative *(72)* by basic hydrolysis. The *ribo*-configuration of *(72)* is shown by the formation of the lactone *(73)*[125].



3.3. Synthesis of Sugars of the Type RCH

3.3.1. Addition of Nucleophiles to Anhydro Sugars[126]

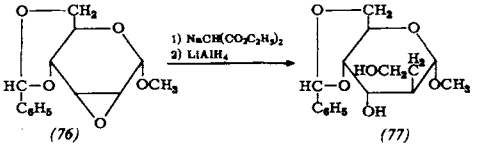
The reaction of *(74)* with phenyllithium, isopropyllithium, or phenylethynyllithium yields only 3-*C*-substituted products having the *xylo*-configuration *(75)*[127].



As expected, therefore, the cleavage of the epoxide ring leads to the product having the substituents on C-2 and C-3 *trans* to each other.

The reaction of 2,3-anhydro sugars with alkyl Grignard compounds can lead to unsaturated halogenated sugars and to 2-C or 3-C-alkylated sugars. The relative yield depends largely on the halogen used[128].

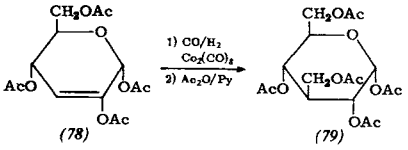
The action of cyanide on 2,3-anhydro sugars leads to a mixture of 2-C- and 3-C-substituted compounds. *trans*-Cleavage of the epoxide ring is normally observed, but the *cis*-product may be formed by subsequent isomerization of the tertiary C atom in the presence of bases[129]. If one of the primary products can be stabilized, this product is preferentially formed[130]. The use of a triethylaluminum-HCN complex in ether favors a stereoselective reaction course[131].



The reaction of the anhydro sugar *(76)* with malonic ester in strongly basic solution followed by reduction with $LiAlH_4$ leads to the hydroxyethyl-branched sugar *(77)* with the *altro*-configuration[132].

3.3.2. Oxo Reaction (Hydro-hydroxymethylation)

Since this reaction was recently reviewed[74], only one example will be mentioned here. If CO and H_2 are allowed

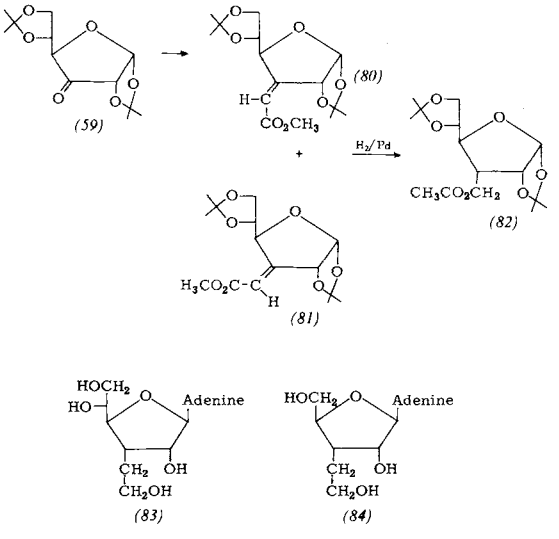


to act on the glycose-ene *(78)* under drastic conditions in the presence of $Co_2(CO)_8$, the *gluco*-compound *(79)* can be isolated in moderate yields after acylation.

3.3.3. Formation of the Branch by Wittig Reaction

Since *Rosenthal* and *Nguyen* first prepared a *C*-alkylated sugar by reaction of a keto sugar with an organophosphorus compound in 1967[133], this method has found increasing use in the synthesis of branched deoxy sugars and their nucleosides[94, 134–141].

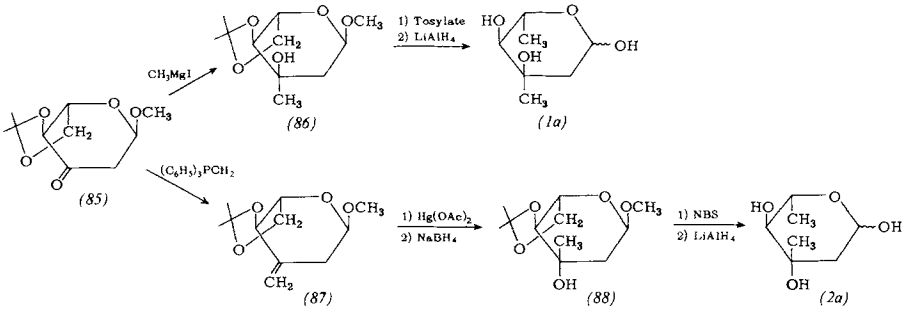
The reaction of *(59)* with methyl dimethoxyphosphonoacetate and potassium *tert*-butoxide at low temperature leads in high yields to the *cis*- and *trans*-methylene sugars *(80)* and *(81)*. The *allo*-product *(82)* is formed on reduction of this mixture with H_2/Pd. The *gluco*-isomer was not detected[133].



It was possible to convert *(82)* into the *allo*- and *ribo*-nucleosides *(83)* and *(84)* by standard methods[142].

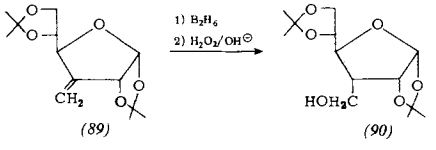
Whereas the branched sugar *(86)* having the L-*ribo*-configuration is formed from the keto sugar *(85)* on reaction with methylmagnesium iodide[91], reaction with triphenylmethylenephosphorane followed by treatment with mercury(II) acetate and sodium tetrahydroborate leads to the branched sugar *(88)* having the *arabino*-configuration. Reaction with tosylate or *N*-bromosuccinimide and reduction led from *(86)* to L-mycarose *(1a)* and from *(88)* to L-olivomycose *(2a)*[143].

The methylene compounds obtained by the Wittig reaction with keto sugars as intermediates allow numerous further reactions[143a]. Thus a hydroxyl group can be introduced



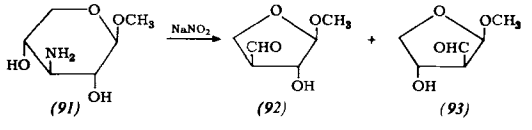
into the compound *(89)* by hydroboration, the product formed being the *allo*-compound *(90)*[135].

Reaction of a methylene sugar with nitryl iodide (NO_2I) leads to nitromethyl-branched sugars[144].



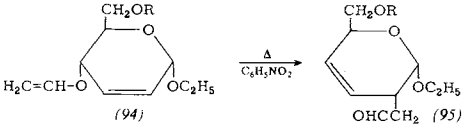
3.3.4. Rearrangements

On treatment of the amino sugar *(91)* with sodium nitrite, the branched aldehyde *(92)* is formed as the main product and *(93)* as a by-product[145].



In earlier attempts to achieve ring contraction by diazotization of amino sugars[146–148] or by thermolysis of *O*-(nitrobenzyl-*p*-sulfonyl)-substituted sugars[148], only the 3-*C*-branched products were identified.

Heating of the unsaturated sugar of the type *(94)* in nitrobenzene leads by allyl shift to the branched aldehyde *(95)*[149].

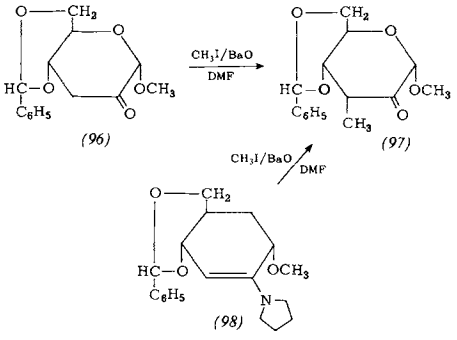


3.3.5. Other Reactions

Methyl iodide can add in good yields to the keto sugar *(96)* with base catalysis to give the compound *(97)*[150]. Epimerization takes place on C-3 even in weakly basic solution. If the enamine *(98)* is used instead of the keto sugar *(96)*, almost quantitative yields are obtained.

Branched sugars can also be obtained by reaction of unsaturated sugars with dienes after the manner of a Diels-Alder reaction[151,152]

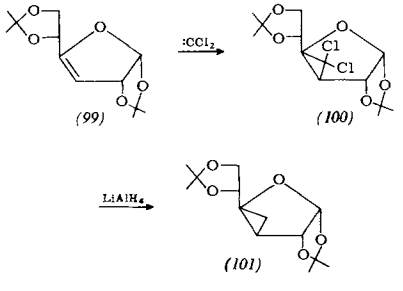
The interesting possibility of using the stereospecificity of enzymatic reactions for the synthesis of branched sugars has so far been realized in only one case. The enzyme 2-deoxy-D-ribose-5-phosphate aldolase (E.C. 4.1.2.4.) can use



propionaldehyde as the substrate instead of the acetaldehyde. Condensation with D-glyceraldehyde-3-phosphate yields 2-methyl-2-deoxy-L-xylose-5-phosphate[153].

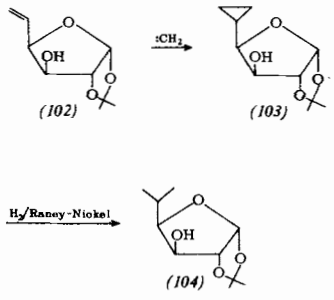
3.4. Synthesis of Sugars Containing a Cyclopropane Ring

The expression "sugars containing a cyclopropane ring" is used here to denote sugars in which two neighboring C atoms are joined by a methylene bridge.



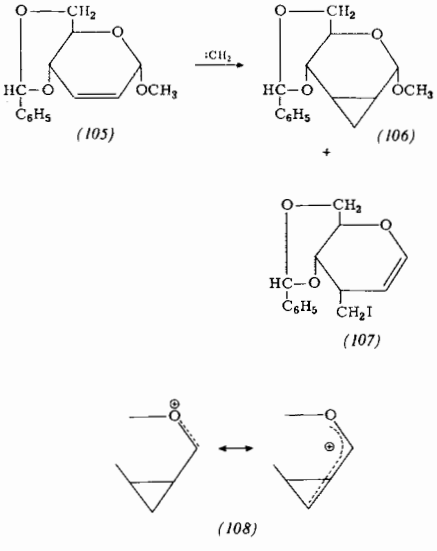
Brimacombe et al. observed the formation of the sugar *(100)* as the only product of the reaction of the unsaturated furanose *(99)* with dichlorocarbene[154]. Reduction of *(100)* with $LiAlH_4$ gave the cyclopropane sugar *(101)*.

The analogous reaction fails to occur with other unsaturated sugars. However, the carbene addition can be achieved in these cases by the use of methylene iodide and zinc/copper in ether (Simmons-Smith reagent)[155]. This reaction leads with *(102)* to the cyclopropyl compound *(103)*,

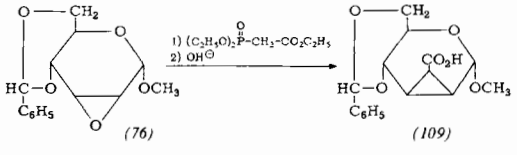


which gives exclusively the isopropyl compound *(104)* on hydrogenation in the presence of Raney nickel. The cyclopropane ring is stable to H_2/Pd, sodium in liquid ammonia, bases, and dilute acids[156].

On addition of carbene to *(105)* by the Simmons-Smith method, the cyclopropyl compound *(106)* having the *allo*-configuration is formed, with the allal *(107)* as a by-product[157]. The ion *(108)* is formed in this reaction as an intermediate.



Another method for the synthesis of sugars containing cyclopropane rings is the reaction of an anhydro sugar with organophosphorus compounds. Thus the reaction of

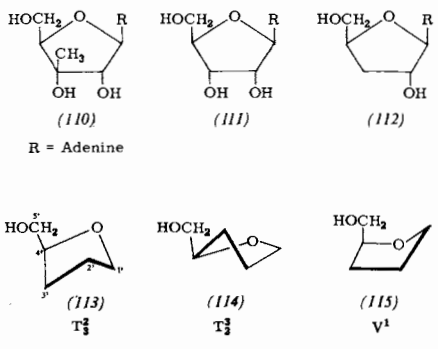


(76) with ethyl diethoxyphosphonoacetate followed by hydrolysis leads to the compound *(109)*, which can undergo many further transformations[158].

4. Conformation of Branched-Chain Sugars

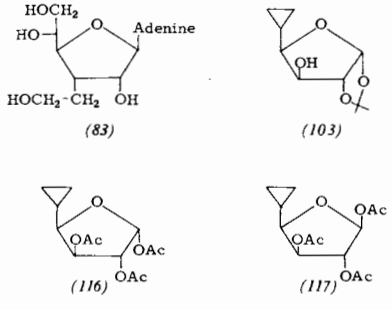
No systematic studies have so far been carried out on the conformation of branched pyranoses. On the other hand, a number of results for branched furanoses have been reported.

The NMR spectrum of 3′-*C*-methyladenosine *(110)* gives a value of 8.2 Hz for the coupling constant $J_{H\text{-}1'—H\text{-}2'}$, whereas the values for adenosine *(111)* and for 3′-deoxyadenosine *(112)* are 6 Hz and 2.3 Hz respectively[76]. The steric interaction in the furan ring decreases in this order. The dihedral angles found for H-1′—H-2′ with the aid of a modified Karplus equation were 151° for *(110)*, 138° for *(111)*, and 116° for *(112)*. These results indicate increasing deformation of the furanose ring on substitution with bulky groups. It can be shown with the aid of a model that *(110)* probably assumes a T_3^2 conformation *(113)*, *i.e.* a twist conformation, in which C-3′ lies below the plane formed by C-4′—O—C-1′, while C-2′ lies above this plane[164].



The size of the dihedral angle H-1′—H-2′ in *(110)* and the correspondingly large angle between the hydroxyl groups on C-2′ and C-3′ are in agreement with the observation that the (quasi-planar) 2′,3′-*O*-isopropylidene ring is formed with much greater difficulty in *(110)* than in *(111)*[76].

In contrast with these results, coupling constants $J_{H\text{-}1—H\text{-}2}$ and $J_{H\text{-}1'—H\text{-}2'}$ of between 0 and 3.5 Hz were found for methyl-3-*C*-methyl-β-D-ribofuranoside[76] and for the 3′-*C*-(2-hydroxyethyl)adenosine derivative *(83)*[142]. The dihedral angle between H-1 and H-2 and between H-1′ and



H-2′ is thus smaller in these cases than in adenosine *(111)*, and the furanoses are probably in the T_2^3 conformation *(114)*.

In the case of the cyclopropane sugars *(103)*, *(116)*, and *(117)*, the coupling constants $J_{H\text{-}1-H\text{-}2}$, $J_{H\text{-}2-H\text{-}3}$, and $J_{H\text{-}3-H\text{-}4}$ indicate a T_2^3 conformation *(114)* for *(103)* and *(117)* and a T_3^2 or v_1 conformation *(115)* for *(116)*[156].

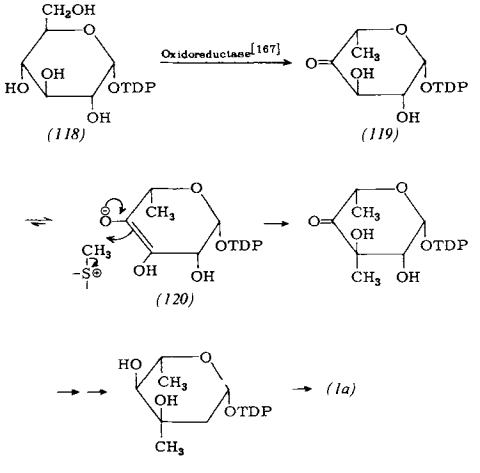
5. Biosynthesis

5.1. Methyl-Branched Sugars

The initially surprising observation that the methyl branch of mycarose *(1a)* comes from the *S*-methyl group of L-methionine (probably *via* *S*-adenosyl-L-methionine) is probably valid for all methyl-branched sugars[111]. This has also been shown experimentally for cladinose and noviose[10, 11].

After incubation of *Streptomyces fradiae* (tylosin former) with methionine deuterated in the *S*-methyl group, mycarose thioacetal was isolated. In the mass spectrum of this compound, the signals of the molecular-ion and of all the fragment ions containing the methyl group on C-3 were accompanied by signals with three mass units higher[165]. It follows that the intact methyl group of methionine is transferred to the hexose chain.

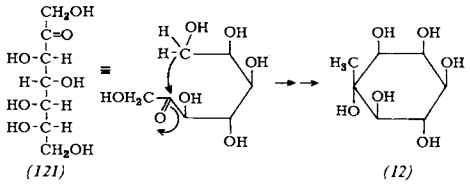
The sugar chain is probably methylated at the stage of a nucleotide-bound 4-keto-6-deoxyhexose, with "active methionine" as the methyl group donor. The formation of thymidine diphosphate 4-keto-6-deoxyhexose *(119)* from TDP-D-glucose *(118)* has been detected in cell-free extracts of *S. fradiae*. Mycarose is also formed with these extracts if *S*-adenosyl-L-methionine and TDP-D-glucose or TDP-4-keto-6-deoxyhexose are present as substrates[166]. The first steps in the biosynthesis of mycarose can therefore be formulated as indicated.



The substitution of *(119)* by the electrophilic methyl group of *S*-adenosylmethionine is formulated here *via* the enol form *(120)*. However, it has not yet been shown that enolization of *(119)* occurs.

5.2. Methyl-Branched Inositols

In contrast with the biosynthesis of methyl-branched sugars, no incorporation of C_1 units was found in the biosynthesis of the *C*-methylinositol laminitol *(12)*. The "best precursor" for laminitol at present is L-*gluco*-heptulose *(121)*[168]. This heptulose has also been detected in small quantities by dilution analysis after application of $^{14}CO_2$ to



Porphyridium[168]. It may therefore be assumed that the methyl group of laminitol comes from C-7 of the heptulose. Experiments with specifically labeled precursors, which would be necessary to confirm this hypothesis, have not yet been carried out.

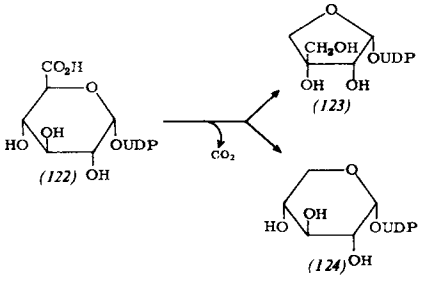
Mytilitol *(11)* appears to be formed in *Chlorella fusca* by epimerization of *(12)*[168a].

5.3. Hydroxymethyl-Branched or Formyl-Branched Sugars

Both hydroxymethyl-branched and formyl-branched sugars are formed by rearrangement of the sugar chain, one C atom being reoriented to form the branch[111]. The biosyntheses of apiose *(16)*, hamamelose *(17)* and streptose *(19)* have been investigated so far. Since no new reports on hamamelose and streptose have been published since the last review[111], only the biosynthesis of apiose will be discussed here.

The biosynthesis of apiose proceeds *via* nucleotide-bound intermediates. The precursor is uridine diphosphate D-glucuronic acid *(122)*; loss of the carboxyl group and branching at C-3 gives UDP-apiose *(123)*[111]. The enzyme that catalyzes this reaction has been partially purified from *Lemna minor*[169, 170] and from cell cultures of parsley[171]. The reaction is NAD^+-dependent.

All the enzyme preparations obtained so far also catalyze the formation of UDP-D-xylose *(124)*. None of the modern separation methods for proteins (chromatography on



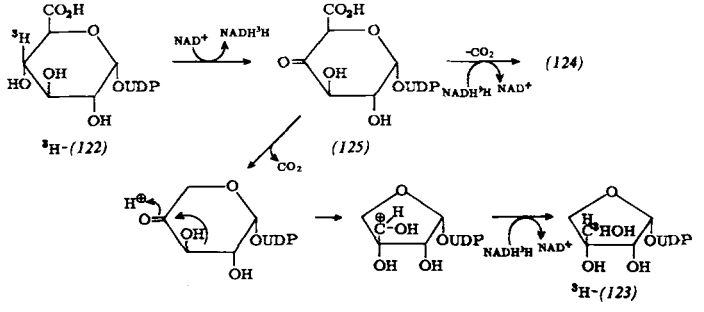
DEAE cellulose, polyacrylamide gel electrophoresis, and electrofocussing) has so far succeeded in separating the two enzymatic activities. They could therefore be due to a multifunctional enzyme.

The activity of this enzyme in parsley and cell cultures is drastically increased by light[172]. Ammonium ions in-

hibit the formation of apiose and stimulate the formation of xylose[170].

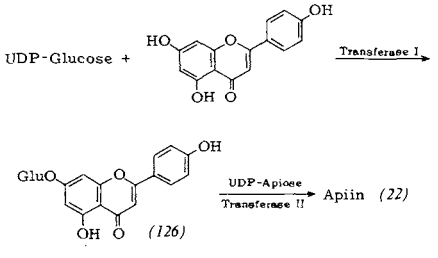
Cell cultures of parsley contain a second enzyme, which catalyzes the reaction UDP-glucuronic acid → UDP-xylose without simultaneous formation of UDP-apiose. This enzyme differs considerably in its properties from the apiose/xylose-forming enzyme. For example, it is not influenced by light[173].

When UDP-glucuronic acid labeled on C-4 with tritium is incubated with the apiose/xylose-forming enzyme, the tritium in the UDP-apiose *(123)* is found entirely on the branch C atom[174]. This result can be explained by a hydride transfer involving NAD^+ in the course of the biosynthesis. This is in agreement with our earlier suggestion that the 4-keto compound *(125)* functions as a common intermediate for apiose and xylose[175].



A variant of the rearrangement to apiose, which starts with the same 4-keto compound, was suggested by *Picken* and *Mendicino*[176].

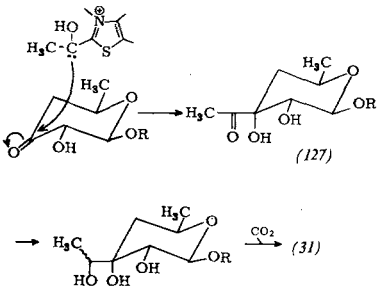
An enzyme that catalyzes the transfer of apiose from UDP-apiose *(123)* to 7-glucosylapigenin *(126)* with formation of apiin *(22)* was partially purified from parsley[177] and cell cultures of this plant and separated from the UDP-glucose: apigenin-7-*O*-glucosyl transferase[178]. According to these results, the two sugars glucose and apiose are linked stepwise to the flavone in the biosynthesis of apiin.



Apiose occurs in polysaccharides in *Lemna* but not in parsley. The transferase responsible for the formation of the polysaccharide containing apiose in *Lemna* (see Section 2.3) is not yet known.

5.4. Hydroxyethyl-Branched Sugars

Among biosyntheses of sugars of this type, that of D-aldgarose *(31)*, a component of aldgamycin, has been investigated. Methionine, ethionine, acetate, and glucose have been ruled out as precursors of the hydroxyethyl branch. On the other hand, specific incorporation of [2-^{14}C]- or [3-^{14}C]-pyruvate into the side chain of aldgarose has been demonstrated[70], while the hexose skeleton comes from D-glucose[69]. It is postulated on the basis of these results that the precursors for the hydroxyethyl branch could be hydroxyethylthiamine pyrophosphate ("active acetaldehyde"), the reaction of which with a 3-ketohexose leads to the intermediate *(127)*. Reduction of the carbonyl group



in *(127)* and formation of the cyclic carbonate would then give aldgarose *(31)*. According to results with [^{14}C]-hydrogen carbonate, the cyclic carbonate is formed at the stage of aldgamycin C by a carboxylation reaction[69, 179].

6. Physiological Action of Branched-Chain Sugars

Very little is known as yet about the physiological action of branched sugars.

Adenosine analogs that are not deaminated to inosine derivatives by adenosine deaminase are of interest as inhibitors of the nucleic acid biosynthesis. It is therefore interesting that 3'-*C*-methyladenosine and 2'-*C*-methyladenosine are not deaminated, or are deaminated very slowly, by adenosine deaminase[113] or by Ehrlich ascites cells[180]. Both adenosines branched in the ribose part inhibit the growth of KB cells[*] in cultures[181].

It is also interesting that 3'-*C*-methyladenosine is phosphorylated to the 5'-triphosphate (the ATP analog) by Ehrlich ascites cells, whereas 5',5'-dimethyladenosine is not[180]. *Walton et al.* have reported on the synthesis and antiviral properties of 2'-*C*-methylcytidine and 3'-*C*-methylcytidine[181]. A number of other nucleosides of branched sugars have been synthesized on the basis of these findings (cf. Section 3), but nothing is yet known about their physiological action.

It is uncertain whether the numerous branched sugars of the antibiotics contribute directly to the antibiotic action[182].

Since some aquatic plants are characterized by apiose-rich cell walls, such cell walls could be connected with the particular conditions of life in the water[53]. Reference has already been made to the resistance of polysaccharides containing apiose toward pectinase (see Section 2.3)[58].

[*] KB cells are human tumor cells from the pharyngeal region.

Our own work in this field has been supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.

Received: April 14, 1971 [A 861 IE]
German version: Angew. Chem. *84*, 192 (1972)
Translated by Express Translation Service, London

[1] *E. Vongerichten*, Liebigs Ann. Chem. *318*, 121 (1901).

[2] *E. Vongerichten*, Liebigs Ann. Chem. *321*, 71 (1902).

[3] *O. Th. Schmidt*, Liebigs Ann. Chem. *483*, 115 (1930).

[4] *F. Grüttner*, Arch. Pharmaz. *236*, 278 (1898).

[5] *E. Fischer* and *K. Freudenberg*, Ber. dtsch. chem. Ges. *45*, 2709 (1912).

[6] *O. Th. Schmidt*, Liebigs Ann. Chem. *476*, 250 (1929); *O. Th. Schmidt* and *K. Heintz*, *ibid. 515*, 77 (1934); *O. Th. Schmidt* and *C. C. Weber-Molster*, *ibid. 515*, 43 (1934).

[7] *F. Shafizadeh*, Advan. Carbohydr. Chem. *11*, 263 (1956).

[8] *W. G. Overend*, Chem. Ind. (London) *1963*, 342 (Syntheses).

[9] *J. S. Brimacombe*, Angew. Chem. *81*, 415 (1969) (Syntheses); Angew. Chem. internat. Edit. *8*, 401 (1969).

[10] *H. Grisebach:* Biosynthetic Patterns in Microorganisms and Higher Plants. Wiley, New York 1967 (Synthesis and Biosynthesis).

[11] *H. Grisebach*, Helv. Chim. Acta *51*, 928 (1968) (Biosynthesis).

[12] *S. Hanessian* and *T. H. Haskell* in *W. Pigman* and *D. Horton:* The Carbohydrates. 2. Edit., Academic Press, New York 1970, Vol. II A, p. 139.

[13] *M. Brufani* and *W. Keller-Schierlein*, Helv. Chim. Acta *49*, 1962 (1966).

[14] *M. Berry*, Quart. Rev. Chem. Soc. *17*, 343 (1963).

[15] *W. Keller-Schierlein* and *G. Roncari*, Helv. Chim. Acta *47*, 78 (1964).

[16] *Yu. A. Berlin, S. E. Esipov, M. N. Kolosov*, and *M. M. Shemyakin*, Tetrahedron Lett. *1966*, 1431, 1643.

[16a] *G. P. Bakhaeva, Yu. A. Berlin, E. F. Boldyreva, O. A. Chuprunova, M. N. Kolosov, V. S. Soifer, T. E. Vasiljeva*, and *I. V. Yartseva*, Tetrahedron Lett. *1968*, 3595.

[17] *A. K. Ganguly* and *O. Z. Sarre*, Chem. Commun. *1969*, 1149.

[18] See [43], p. 18.

[19] *D. Okuda, N. Suzuki*, and *S. Suzuki*, J. Biol. Chem. *242*, 958 (1967); *243*, 6353 (1968).

[20] *P. F. Wiley, F. A. MacKellar, E. L. Caron*, and *R. B. Kelly*, Tetrahedron Lett. *1968*, 663.

[20a] *D. J. Duchamp, P. F. Wiley, V. Hsiung*, and *G. C. Chidester*, J. Org. Chem. *36*, 2670 (1971).

[21] *D. J. Cooper* and *M. D. Yudis*, Chem. Commun. *1967*, 821; *W. Meyer zu Reckendorf* and *E. Bischof*, Tetrahedron Lett. *1970*, 2475; *D. J. Cooper, M. D. Yudis, R. D. Guthrie*, and *A. M. Prior*, J. Chem. Soc. *C 1971*, 961.

[21a] *H. Reimann, R. S. Jaret*, and *D. J. Cooper*, Chem. Commun. *1971*, 924.

[22] *A. K. Ganguly, O. Z. Sarre*, and *H. Reimann*, J. Amer. Chem. Soc. *90*, 7129 (1968).

[22a] *A. K. Ganguly, O. Z. Sarre*, and *S. Szmulewicz*, Chem. Commun. *1971*, 746.

[23] *J. W. Hinman, E. L. Caron*, and *H. Hoeksema*, J. Amer. Chem. Soc. *78*, 2019 (1956).

[24] *A. Rosenthal*, Carbohydr. Res. *8*, 61 (1968).

[25] *D. C. De Jongh* and *S. Hanessian*, J. Amer. Chem. Soc. *88*, 3114 (1966).

[26] *W. Hofheinz, H. Grisebach*, and *H. Friebolin*, Tetrahedron *18*, 1265 (1962).

[27] *R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall*, and *N. R. Williams*, Proc. Chem. Soc. (London) *1963*, 133.

[28] *J. S. Burton, W. G. Overend*, and *N. R. Williams*, J. Chem. Soc. *1965*, 3433.

[29] *W. Keller-Schierlein* and *G. Roncari*, Helv. Chim. Acta *45*, 138 (1962); *47*, 78 (1964).

[30] *D. M. Lemal, P. D. Pacht*, and *R. B. Woodward*, Tetrahedron *18*, 1275 (1962).

[31] *G. Roncari* and *W. Keller-Schierlein*, Helv. Chim. Acta *49*, 705 (1966).

[32] *A. Rosenthal* and *K. S. Ong*, Can. J. Chem. *48*, 3034 (1970).

[33] *A. Rosenthal, K. S. Ong*, and *D. Baker*, Carbohydr. Res. *13*, 113 (1970).

[34] *H. P. Albrecht* and *J. G. Moffat*, Tetrahedron Lett. *1970*, 1063.

[34a] *C. Satoh, A. Kiyomoto*, and *T. Okuda*, Carbohydr. Res. *5*, 140 (1967).

[35] *F. W. Lichtenthaler* and *P. Emig*, Tetrahedron Lett. *1967*, 577; Carbohydr. Res. *7*, 121 (1968).

[36] *R. D. King* and *W. G. Overend*, Carbohydr. Res. *9*, 423 (1969).

[37] *B. Lindberg* and *J. McPherson*, Acta Chem. Scand. *8*, 1875 (1954); *B. Lindberg* and *B. Wickberg*, Ark. Kemi *13*, 447 (1959).

[38] *R. G. Schweiger*, Arch. Biochem. Biophys. *118*, 383 (1967).

[39] *G. Wöber* and *O. Hoffmann-Ostenhof*, Monatsh. Chem. *100*, 369 (1969).

[39a] *S. Hori, T. Iwasa, E. Mizuta*, and *Y. Kameda*, J. Antibiotics *24*, 59 (1971).

[40] *D. Ackermann*, Ber. dtsch. chem. Ges. *54*, 1938 (1921).

[41] *B. Wickberg*, Acta Chem. Scand. *11*, 506 (1957).

[42] *M. W. Miller:* The Pfizer Handbook of Microbial Metabolites. McGraw-Hill, New York 1961, p. 37, 38.

[43] *H. Umezawa:* Recent Advances in Chemistry and Biochemistry of Antibiotics. Microbial Chemistry Research Foundation, Tokyo 1964, p. 67.

[44] *J. Aronson, W. L. Meyer*, and *T. D. Brock*, Nature *202*, 555 (1964).

[45] *R. Rangoonwala* and *H. Friedrich*, Naturwissenschaften *54*, 368 (1967).

[46] *A. Malhotra, V. V. S. Murti*, and *T. R. Seshadri*, Tetrahedron *23*, 405 (1967).

[47] *S. Hattori* and *H. Imaseki*, J. Amer. Chem. Soc. *81*, 4424 (1959).

[48] *B. Hanson, I. Johansson*, and *B. Lindberg*, Acta Chem. Scand. *20*, 2358 (1966).

[49] *N. Ohta* and *K. Tagishita*, Agr. Biol. Chem. (Japan) *34*, 900 (1970); Chem. Abstr. *74*, 983a (1971).

[50] *W. Hösel* and *W. Barz*, Phytochem. *9*, 2053 (1970).

[51] *R. K. Hulyalkar, J. K. N. Jones*, and *M. B. Perry*, Can. J. Chem. *43*, 2085 (1965); *D. H. Ball, F. H. Bissett, I. L. Klundt*, and *L. Long, jr.*, Carbohydr. Res. *17*, 165 (1971).

[52] *Yu. S. Ovodov, R. G. Ovodova, O. D. Bondarenko*, and *I. S. Krasikova*, Carbohydr. Res. *18*, 311 (1968) and literature cited therein.

[53] *C. F. van Beusekom*, Phytochem. *6*, 573 (1967).

[54] *R. B. Duff*, Biochem. J. *94*, 768 (1965).

[55] *E. Beck* and *O. Kandler*, Z. Naturforsch. *20b*, 62 (1965).

[56] *E. Beck*, Z. Pflanzenphysiol. *57*, 444 (1967).

[57] *D. A. Hart* and *P. K. Kindel*, Biochemistry *9*, 2190 (1970).

[58] *D. A. Hart* and *P. K. Kindel*, Biochem. J. *116*, 569 (1970).

[59] *J. S. D. Bacon*, Biochem. J. *89*, 103P (1963).

[60] *W. Mayer, W. Kunz*, and *F. Loebich*, Liebigs Ann. Chem. *688*, 232 (1965).

[61] *W. Mayer* and *W. Kunz*, Naturwissenschaften *46*, 206 (1959).

[62] *H. van Scherpenberg, W. Gröbner*, and *O. Kandler:* Beiträge zur Biochemie und Physiologie von Naturstoffen. VEB G. Fischer, Jena 1965, p. 387.

[63] *J. Sellmair, E. Beck*, and *O. Kandler*, Z. Pflanzenphysiol. *59*, 70 (1968).

[64] *E. Beck*, Z. Pflanzenphysiol. *61*, 360 (1969).

[65] *J. Sellmair, E. Beck*, and *O. Kandler*, Z. Pflanzenphysiol. *61*, 338 (1969).

[66] *C. C. Kuenzle*, Biochem. J. *119*, 411 (1970).

[67] See [43], p. 44.

[68] *G. A. Ellestad, M. P. Kunstmann, J. E. Lancaster, L. A. Mitscher*, and *G. Morton*, Tetrahedron *23*, 3893 (1967).

[69] *R. Schmid* and *H. Grisebach*, Z. Naturforsch. *25b*, 1259 (1970).

[70] *R. Schmid, H. Grisebach*, and *W. Karl*, Europ. J. Biochem. *14*, 243 (1970).

[71] *A. Tulinsky*, J. Amer. Chem. Soc. *86*, 5368 (1964); *D. B. Cosulich, J. H. Mowat, R. W. Broschard, J. B. Patrick*, and *W. E. Meyer*, Tetrahedron Lett. *1963*, 453.

[72] *M. Asai, E. Mizuta, K. Mizuno, A. Miyake*, and *S. Tatsuoka*, Chem. Pharm. Bull. (Japan) *18*, 1720 (1970); Chem. Abstr. *73*, 120 865q (1970).

[73] *M. Asai*, Chem. Pharm. Bull. (Japan) *18*, 1713 (1970); Chem. Abstr. *73*, 120 833c (1970).

[74] *A. Rosenthal*, Advan. Carbohydr. Chem. *23*, 59 (1968).

[75] *H. H. Baer*, Advan. Carbohydr. Chem. *24*, 67 (1969).

[75a] *R. F. Butterworth* and *S. Hanessian*, Synthesis *1971*, 70.

[76] *R. F. Nutt, M. J. Dickinson, F. W. Holly*, and *E. Walton*, J. Org. Chem. *33*, 1789 (1968).

[77] *W. G. Overend, A. C. White*, and *N. R. Williams*, Carbohydr. Res. *15*, 185 (1970).

[78] *A. A. J. Feast, W. G. Overend*, and *N. R. Williams*, J. Chem. Soc. *1966*, 303.

[79] *J. S. Burton, W. G. Overend*, and *N. R. Williams*, J. Chem. Soc. *1965*, 3433.

[80] *B. Flaherty, W. G. Overend*, and *N. R. Williams*, J. Chem. Soc. *1966*, 398.

[81] *T. D. Inch*, Carbohydr. Res. *5*, 45 (1967).

[82] *T. D. Inch, P. V. Ley*, and *P. Rich*, Chem. Commun. *1967*, 865.

[83] *B. M. Gough, S. W. Gunner, W. G. Overend*, and *N. R. Williams*, Carbohydr. Res. *14*, 173 (1970).

[84] *B. R. Baker* and *D. H. Buss*, J. Org. Chem. *31*, 217 (1966).

[85] *J. R. Dyer, W. E. McGonigal*, and *K. C. Rice*, J. Amer. Chem. Soc. *87*, 654 (1965).

[86] *B. P. Vaterlaus, J. Kiss*, and *H. Spiegelberg*, Helv. Chim. Acta *47*, 381 (1964).

[87] *J. M. J. Tronchet* and *J. Tronchet*, C.R. Acad. Sci. Paris *C 267*, 626 (1968).

[87a] *T. Posternak*, Helv. Chim. Acta *27*, 457 (1944).

[87b] *T. Posternak* and *J. G. Falbriard*, Helv. Chim. Acta *44*, 2080 (1962).

[88] *G. B. Howarth, W. A. Szarek*, and *J. K. N. Jones*, Can. J. Chem. *46*, 3375 (1968).

[89] *G. B. Howarth, W. A. Szarek*, and *J. K. N. Jones*, Carbohydr. Res. *7*, 284 (1968).

[90] *G. B. Howarth, W. A. Szarek*, and *J. K. N. Jones*, Can. J. Chem. *46*, 3691 (1968).

[91] *G. B. Howarth* and *J. K. N. Jones*, Can. J. Chem. *45*, 2253 (1967).

[92] *P. J. Harper* and *A. Hampton*, J. Org. Chem. *35*, 1688 (1970).

[93] *R. D. Rees, K. James, A. R. Tatchell*, and *R. H. Williams*, J. Chem. Soc. *C 1968*, 2716.

[94] *J. M. J. Tronchet, J. M. Bourgeois, J. M. Chalet, R. Graf, R. Guruy*, and *J. Tronchet*, Helv. Chim. Acta *54*, 687 (1971).

[95] *W. G. Overend*, Advan. Chem. Ser. *74*, 141 (1968).

[96] *A. D. Ezekiel, W. G. Overend*, and *N. R. Williams*, Tetrahedron Lett. *1969*, 1635.

[97] *F. Weygand* and *R. Schmiechen*, Chem. Ber. *92*, 535 (1959).

[98] *W. G. Overend* and *N. R. Williams*, J. Chem. Soc. *1965*, 3446.

[99] *R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall*, and *N. R. Williams*, J. Chem. Soc. *C 1968*, 1091.

[100] *S. Nahar, W. G. Overend*, and *N. R. Williams*, Chem. Ind. (London) *1967*, 2114.

[101] *J. P. Horwitz, N. Mody*, and *R. Gasser*, J. Org. Chem. *35*, 2335 (1970).

[102] *T. D. Inch, G. J. Lewis, R. P. Peel*, and *N. R. Williams*, Chem. Commun. *1970*, 1549.

[103] *A. Rosenthal* and *K. S. Ong*, Tetrahedron Lett. *1969*, 3981.

[104] *G. J. Lourens*, Carbohydr. Res. *17*, 35 (1971).

[105] *S. W. Gunner, R. D. King, W. G. Overend*, and *N. R. Williams*, J. Chem. Soc. *C 1970*, 1954.

[106] *J. C. Sowden*, Advan. Carbohydr. Chem. *12*, 35 (1957).

[107] *R. L. Whistler* and *J. N. BeMiller*, Advan. Carbohydr. Chem. *13*, 289 (1958).

[108] *A. A. J. Feast, B. Lindberg*, and *O. Theander*, Acta Chem. Scand. *19*, 1127 (1965).

[109] *P. E. Werner, R. Norreston*, and *O. Römquist*, Acta Cryst. *B 25*, 714 (1969).

[110] *D. L. Hughes* and *J. Trotter*, J. Chem. Soc. *B 1970*, 983.

[111] *J. C. Sowden* and *D. R. Strobach*, J. Amer. Chem. Soc. *82*, 3707 (1960).

[112] *A. B. Foster, T. D. Inch, J. Lehmann*, and *J. M. Webber*, J. Chem. Soc. *1964*, 948.

[113] *E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmermann*, and *F. W. Holly*, J. Amer. Chem. Soc. *88*, 4524 (1966).

[114] *S. R. Jenkins, B. Arison*, and *E. Walton*, J. Org. Chem. *33*, 2490 (1968).

[115] *J. J. Novák, I. Šmejkal*, and *F. Šorm*, Tetrahedron Lett. *1969*, 1627.

[116] *D. H. Ball, F. A. Carey, I. L. Klundt*, and *L. Long*, Carbohydr. Res. *10*, 121 (1969).

[117] *J. H. Jordaan* and *S. Smedley*, Carbohydr. Res. *16*, 177 (1971).

[118] *R. D. King, W. G. Overend, J. Wells*, and *N. R. Williams*, Chem. Commun. *1967*, 726.

[119] *A. Rosenthal* and *G. Schöllnhammer*, Carbohydr. Res. *15*, 421 (1970).

[120] *H. Kiliani*, Ber. dtsch. chem. Ges. *18*, 3066 (1885).

[121] *R. J. Woods* and *A. C. Neish*, Can. J. Chem. *31*, 471 (1953).

[122] *P. A. J. Gorin* and *A. S. Perlin*, Can. J. Chem. *36*, 480 (1958).

[123] *S. W. Gunner, W. G. Overend*, and *N. R. Williams*, Chem. Ind. (London) *1964*, 1523.

[124] *F. W. Lichtenthaler*, Fortschr. chem. Forsch. *14*, 556 (1970).

[125] *H. Yanagisawa, M. Kinoshita, S. Nakada*, and *S. Umezawa*, Bull. Chem. Soc. Jap. *43*, 246 (1970).

[126] *M. Sharma* and *R. K. Brown*, Can. J. Chem. *46*, 757 (1968).

[127] *A. A. J. Feast, W. G. Overend*, and *N. R. Williams*, J. Chem. Soc. *C 1965*, 7378.

[128] *T. D. Inch* and *G. J. Lewis*, Carbohydr. Res. *15*, 1 (1970).

[129] *N. R. Williams*, Chem. Commun. *1967*, 1012.

[130] *P. W. Austin, J. G. Buchanan*, and *E. M. Oakes*, Chem. Commun. *1965*, 374.

[131] *B. E. Davidson, R. D. Guthrie*, and *A. T. McPhail*, Chem. Commun. *1968*, 1273.

[132] *L. I. Kudryashov, M. A. Chlenov*, and *N. K. Kochetkov*, Izv. Akad. Nauk SSSR Ser. Khim. *1*, 75 (1965); Chem. Abstr. *62*, 14793h (1965).

[133] *A. Rosenthal* and *L. Nguyen*, Tetrahedron Lett. *1967*, 2393.

[134] *A. Rosenthal* and *P. Catsoulacos*, Can. J. Chem. *46*, 2868 (1968).

[135] *A. Rosenthal* and *M. Sprinzl*, Can. J. Chem. *47*, 4477 (1969).

[136] *A. Rosenthal* and *M. Sprinzl*, Can. J. Chem. *47*, 3941 (1969).

[137] *A. Rosenthal* and *M. Sprinzl*, Can. J. Chem. *48*, 3253 (1970).

[138] *A. Rosenthal* and *D. A. Baker*, Tetrahedron Lett. *1969*, 397.

[138a] *A. Rosenthal, M. Sprinzl*, and *D. A. Baker*, Tetrahedron Lett. *1970*, 4233.

[139] *J. M. J. Tronchet, J. M. Bourgeois, R. Graf*, and *J. Tronchet*, C.R. Acad. Sci. Paris *C 269*, 420 (1969).

[140] *J. M. Tronchet* and *J. M. Chalet*, Helv. Chim. Acta *53*, 364 (1970).

[141] *J. M. Tronchet* and *J. M. Bourgeois*, Helv. Chim. Acta *53*, 1463 (1970).

[142] *A. Rosenthal* and *L. Nguyen*, J. Org. Chem. *34*, 1029 (1969).

[143] *E. H. Williams, W. A. Szarek*, and *J. K. N. Jones*, Can. J. Chem. *47*, 4467 (1969).

[143a] *A. Rosenthal* and *M. Sprinzl*, Carbohydr. Res. *16*, 337 (1971).

[144] *W. A. Szarek, J. S. Jewell, I. Szczerek*, and *J. K. N. Jones*, Can. J. Chem. *47*, 4473 (1969).

[145] *E. J. Reist, D. F. Calkins*, and *L. Goodman*, J. Amer. Chem. Soc. *90*, 3852 (1968).

[146] *S. Inoue* and *H. Ogawa*, Chem. Pharm. Bull. (Tokyo) *8*, 79 (1960); Chem. Abstr. *55*, 6385d (1961).

[147] *E. J. Reist*, Chem. Ind. (London) *1967*, 1957.

[148] *P. W. Austin, J. G. Buchanan*, and *R. M. Saunders*, J. Chem. Soc. *C 1967*, 372.

[149] *R. J. Ferrier* and *N. Vethaviyasar*, Chem. Commun. *1970*, 1385.

[150] *R. F. Butterworth, W. G. Overend*, and *N. R. Williams*, Tetrahedron Lett. *1968*, 3239.

[151] *T. D. Inch* and *D. Rich*, Carbohydr. Res. *6*, 244 (1968).

[152] *W. A. Szarek* and *J. S. Jewell*, Can. J. Chem. *48*, 1030 (1970).

[153] *O. M. Rosen, P. Hoffee*, and *B. L. Horecker*, J. Biol. Chem. *240*, 1517 (1965).

[154] *J. S. Brimacombe, E. M. Evans, E. J. Forbes, A. B. Foster*, and *J. M. Webber*, Carbohydr. Res. *4*, 239 (1967).

[155] *E. L. Albano, D. Horton*, and *J. H. Lauterbach*, Chem. Commun. *1968*, 357.

[156] *D. Horton* and *C. G. Tindall jr.*, Carbohydr. Res. *8*, 328 (1960); *15*, 215 (1970).

[157] *B. Fraser-Reid* and *B. Radatus*, Can. J. Chem. *47*, 4095 (1969); *48*, 2146 (1970).

[158] *W. Meyer zu Reckendorf* and *U. Kamprath-Scholtz*, Angew. Chem. *80*, 152 (1968); Angew. Chem. internat. Edit. *7*, 142 (1968).

[159] *D. T. Williams* and *J. K. N. Jones*, Can. J. Chem. *42*, 69 (1964).

[160] *R. A. Raphael* and *C. M. Roxburgh*, J. Chem. Soc. *1955*, 3405.

[161] *D. M. Lemal, P. D. Pacht*, and *R. B. Woodward*, Tetrahedron *18*, 1275 (1962).

[162] *H. Grisebach, W. Hofheinz*, and *N. Doerr*, Chem. Ber. *96*, 1823 (1963).

[163] *F. Korte, U. Claussen*, and *K. Gohring*, Tetrahedron *18*, 1257 (1962).

[164] *L. D. Hall*, Chem. Ind. (London) *1963*, 950.

[165] *H. Pape, R. Schmid, H. Grisebach*, and *H. Achenbach*, Europ. J. Biochem. *10*, 479 (1969).

[166] *H. Pape*, unpublished results.

[167] *R. Okazaki, T. Okazaki, J. L. Strominger*, and *A. M. Michelson*, J. Biol. Chem. *237*, 3014 (1962); *H. Zarkowsky, E. Lipkin*, and *L. Glaser*, *ibid. 245*, 6599 (1970); *S. F. Wang* and *O. Gabriel*, *ibid. 245*, 8 (1970).

[168] *G. Wöber* and *O. Hoffmann-Ostenhof*, Europ. J. Biochem. *17*, 393 (1970).

[168a] *G. Wöber* and *O. Hoffman-Ostenhof*, Monatsh. Chem. *101*, 1861 (1970).

[169] *H. Sandermann jr.* and *H. Grisebach*, Biochim. Biophys. Acta *208*, 173 (1970).

[170] *E. Wellmann* and *H. Grisebach*, Biochim. Biophys. Acta *235*, 389 (1971).

[171] *D. Baron, E. Wellmann*, and *H. Grisebach*, Biochim. Biophys. Acta *258*, 310 (1972).

[172] *K. Hahlbrock, J. Ebel, R. Ortmann, A. Sutter, E. Wellmann*, and *H. Grisebach*, Biochim. Biophys. Acta *244*, 7 (1971).

[173] *E. Wellmann, D. Baron*, and *H. Grisebach*, Biochim. Biophys. Acta *244*, 1 (1971).

[174] *W. Kelleher* and *H. Grisebach*, Europ. J. Biochem. *23*, 136 (1971); cf. *H. Grisebach* and *U. Döbereiner*, Z. Naturforsch. *21b*, 429 (1966).

[175] *H. Grisebach* and *U. Döbereiner*, Biochem. Biophys. Res. Commun. *17*, 737 (1964).

[176] *J. M. Picken* and *J. Mendicino*, J. Biol. Chem. *242*, 1629 (1967).

[177] *R. Ortmann, H. Sandermann jr.*, and *H. Grisebach*, FEBS Lett. *7*, 164 (1970).

[178] *A. Sutter, R. Ortmann*, and *H. Grisebach*, Biochim. Biophys. Acta *258*, 71 (1972).

[179] *R. Schmid*, unpublished results.

[180] *H. T. Shigeura* and *S. D. Sampson*, Nature *215*, 419 (1967).

[181] *E. Walton, S. R. Jenkins, R. F. Nutt*, and *F. W. Holly*, J. Med. Chem. *12*, 306 (1969).

[182] See *e.g. J. M. Wilhelm, N. L. Oleinick*, and *J. W. Corcoran*: Antimicrobial Agents and Chemotherapy, 1970. American Society for Microbiology, Bethesda, Md. 1971, p. 236.

Mechanisms of Reactions in the Solid State

By Kurt Hardel[*]

The reaction of two solid phases X and Y to give a solid compound XY_ν is taken as an example for the discussion of transport mechanisms and reaction steps. The following methods of investigation are discussed: determination of the rate law, marker experiments, and calculation of the reaction rate. It is pointed out that the investigation of powder reactions leads to problematic conclusions.

1. Introduction

If a solid phase X is in contact with a solid phase Y at a temperature at which the mobilities of the particles in the solid state are sufficiently high, X and Y can react to form one or more solid reaction products $XY_{\nu 1}$, $XY_{\nu 2}$, *etc.* which separate the reactants from each other. A process of this kind is a solid-state reaction. The reactants X and Y may be elements or compounds. Generally the reaction is exothermic, since the entropy of reaction of solids is low. Similar features are valid for reactions between several solid phases, X_1, X_2, *etc.* and several solid phases Y_1, Y_2, *etc.* to form one or more solid reaction products.

If one considers only the reaction of a single solid phase X with a single solid phase Y, the following reaction types can be distinguished:

1. Formation of one or more compounds;

2. Formation of a continuous series of solid solutions between the reactants;

3. Formation of a series of solid solutions with a miscibility gap;

4. Double reaction, *e.g.* $PbS_{(s)}+CdO_{(s)}\rightarrow PbO_{(s)}+CdS_{(s)}$[1];

5. Superposition of the solid-state reaction by an additional decomposition of one reactant with formation of a gas, *e. g.*

$$BaCO_{3(s)} + WO_{3(s)} \rightarrow BaWO_{4(s)} + CO_{2(g)}$$

Only the relatively well-studied reaction type 1 will be discussed, specifically the formation of a single compound XY_ν with a small homogeneity range. X and Y will be binary ionic compounds having the same anion, and XY_ν will be a ternary ionic compound. The reaction mechanisms and the principal methods of investigation are discussed for this simple case. Examples may be found in the literature cited.

2. Reaction Mechanisms

At the beginning of the reaction, the following reaction step may be assumed:

(I) Exchange processes of particles at the interface between the two reactants and formation of the reaction product (phase boundary reaction).

If the reaction product is a ternary compound and if the contact between the solids is ideal, there are three conceivable transport mechanisms after the formation of a homogeneous, pore-free reaction layer; these mechanisms, which

[*] Prof. Dr.-Ing. K. Hardel
Institut für Anorganische und Analytische Chemie der Technischen Universität
1 Berlin 12, Strasse des 17. Juni 135 (Germany)

should be regarded as limiting cases, are shown schematically in Figure 1 for spinel formation from the oxides. A distinction is to be made between the migration of cations and anions through the reaction product in the same direction and countertransport of cations[2]. For the case in which the cations and anions of the substance AO migrate in the same direction through the reaction product to the reactant B_2O_3 (Fig. 1), further reaction steps are as follows:

(II) Transfer of the particles through the interface 1 between the reactant AO and the reaction product (phase boundary reaction).

(III) Diffusion of the cations and anions of the substance AO through the reaction product, specifically volume diffusion or diffusion *via* grain boundaries and dislocations of the crystallites of the reaction product.

(IV) Reaction of the cations and anions of the substance AO at the interface 2 with the reactant B_2O_3 to form the reaction product (phase boundary reaction).

Analogous reaction steps may be assumed for migration of the cations and anions of the substance B_2O_3 through the reaction product in the same direction and for countertransport of cations (Fig. 1).

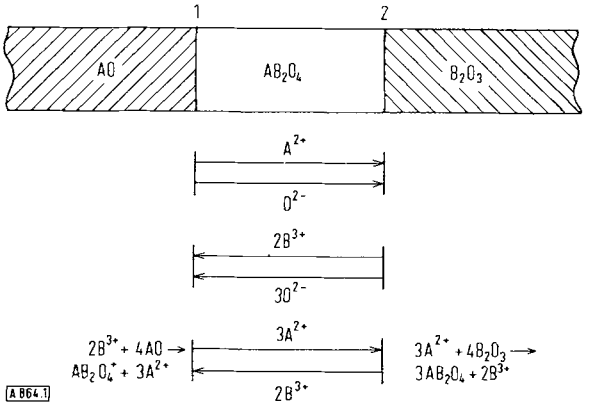


Fig. 1. Transport mechanisms with ideal contact between the solids.

If the contact between the reactants or between one of the reactants and the reaction product is insufficient, or if the reaction layer contains pores, other transport mechanisms are possible; these are the transport of one reactant *via* the gas phase or the transport of the nonmetallic component *via* the gas phase with simultaneous migration of cations and of electrons or defect electrons through the reaction layer (Fig. 2).

Exchange processes of particles at the interface at the beginning of the reaction have been confirmed by LEED investigations[3].

The mechanism of the formation of the reaction product in steps (I) and (IV) has not yet been sufficiently elucidated. It is to be supposed that because of the limited solubility of the reaction product in the reactant, supersaturation of the reactant with the reaction product can occur in the phase boundary reaction (I) or (IV), with consequent heterogeneous nucleation and crystal growth. The heterogeneous nucleation is possible at the interface and in the vicinity of the interface at two-dimensional and one-dimensional defects, at vacancies, or at impurities[4]. In the spinel formation from the oxides, the following mechanism has been proposed for the case of countertransport of cations and for the structural relationship between the reaction product and one of the reactants[5]: After transfer through the interface between the reaction product and the reactant (Fig. 1), the small cations diffuse into the reactant and occupy the sites of the cation lattice of the reaction product, while the anion lattice of this reactant is transformed into the anion lattice of the reaction product by alteration of the stacking sequence of the lattice planes. This occurs by migration of partial dislocations.

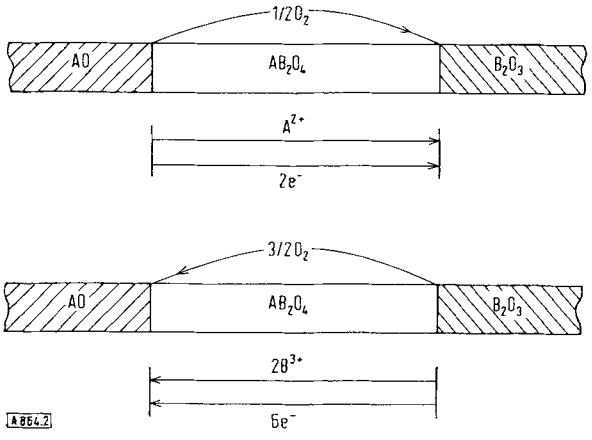


Fig. 2. Transport mechanisms for the case in which contact between the solids is inadequate and the partial pressure of the nonmetallic component is sufficiently high.

Reaction step (II), *i.e.* the finite rate of the transfer of the particles through the interface between one reactant and the reaction product (Fig. 1), can be detected[6]. Deviations from thermodynamic equilibrium at the interface may inhibit the transfer of the particles through the interface, with the result that this becomes the rate-determining step of the reaction.

The volume diffusion through the reaction product, which depends only on the concentration of point defects, has been extensively studied. Reaction layers that are at least several μm thick, and in which the volume diffusion is often the rate-determining step of the reaction at sufficiently high reaction temperatures, are relatively easy to investigate. If the reaction product is a ternary compound and if it is assumed that the particles migrate independently of one another and that the ion currents are related only by the electroneutrality condition, it is possible to distinguish the three diffusion mechanisms shown schematically in Figure 1. Since the component diffusion coefficients of the various types of ions are generally different, the rate of the solid-state reaction is determined by the type of ion whose mobility lies between the mobilities of the other two types. With counterdiffusion of cations, for example, the mobility of the type of cation that diffuses more slowly is rate-determining[7].

If the reaction temperature is not so high that volume diffusion predominates, the diffusion of the particles *via* the

grain boundaries and dislocations ("dislocation pipes") of the crystallites of the product can become the rate-determining step of the reaction. In this case, the reaction rate depends on the relative orientation of neighboring crystallites of the product[8] and on the size of the coherent crystal regions. The reaction rate increases with decreasing average crystallite size or with decreasing average size of the coherent regions of the product[9-11]. If the product is a ternary compound, it is possible, in analogy with volume diffusion, to discuss diffusion of cations and anions in the same direction or counterdiffusion of cations.

If it is established that the formation of the reaction product in step (IV) is coupled throughout the reaction with nucleation processes at the interface between the product and the reactant (Fig. 1), it is possible that the average crystallite size of the reaction product depends on the rate of nucleation of the product at this interface. If grain boundary diffusion through the reaction product is rate-determining, it is thus necessary to check whether factors that affect the rate of nucleation of the reaction product at the interface between the reactant and the product lead to a change in the average crystallite size of the product, and hence to a change in the reaction rate. Such factors would be the crystal structure, the crystallographic orientation, and the defect structure of the reactant, as well as contamination of the reactant with impurities[12-14]. The mechanism has not yet been proved beyond doubt[9].

Where contact between the solid substances is inadequate, the influence of the gas phase on the solid-state reaction must be taken into account. If gaps in which a certain partial pressure of the reactant is produced remain between one of the reactants and the reaction layer during the reaction, and if the reaction temperature is so high that this partial pressure is not negligible, the mass transport takes place *via* the gas phase. For sufficiently thin reaction layers, the evaporation of the reactant, the transport in the gas phase, and the condensation on the reaction product may become rate-determining[5]. This can also be observed[15]. With thick layers of reaction product, however, diffusion through the product is the rate-determining step of the reaction.

If partial conductivity of electrons or defect electrons in the reaction product is not negligible, and if the partial pressure of the nonmetallic component is sufficiently high, the nonmetallic component may be transported *via* the gas phase in cases of insufficient contact between the solid substances or in cases where the reaction layer contains pores, while electroneutrality is maintained by an electron or defect electron current through the reaction product. For the example of spinel formation from the oxides, Figure 2 shows schematically the transport of oxygen through the gas phase with simultaneous transport of the cation A^{2+} or B^{3+} and of electrons through the spinel layer. It is assumed that the particles migrate independently of one another and that the ion and electron or defect electron currents are coupled only by the condition of electroneutrality. The rate-determining step is the diffusion of the cations A^{2+} or B^{3+} through the reaction product. If the oxygen partial pressure is decreased to such an extent that there are no longer sufficient oxygen molecules available for the reaction at the interface, another transport mechanism must come into effect[16].

With good contact between the solid substances, if the partial pressure of the nonmetallic component is sufficiently high, one may find the special case that the reaction product is formed not only between the reactants but also on part of the surface of one of these substances[17]. It is then possible that counterdiffusion of cations occurs in the interior of the reaction layer (Fig. 1), whereas in the zones near the surface, cations and electrons or defect electrons migrate through the reaction product, and the nonmetallic component is simultaneously transported *via* the gas phase (Fig. 2).

The rate-determining step of these reactions depends mainly on the experimental conditions under which the solid-state reaction takes place. The transport mechanism is mainly determined by the experimental conditions, the mobilities of the various types of ions in the reaction product, and the electronic properties of the product.

3. Methods of Investigation

It is assumed in the following discussion that the reaction is isothermic. This condition is satisfied if the mass fraction of the reaction product formed per unit time is relatively small. This assumption is generally permissible in solid-state reactions of the type specified in Section 1.

The principal methods used to investigate the mechanisms of such solid-state reactions are the following:

1. determination of the rate law to establish the rate-determining step of the reaction;

2. marking the interface between the reactants before the beginning of the reaction to establish the transport mechanism;

3. calculation of the reaction rate if the volume diffusion through the product is the rate-determining step. It is possible in this way to decide which of the diffusing types of ions determines the rate of the reaction.

3.1. Determination of the Rate Law

If the phase boundary reaction (II) or (IV) is the rate-determining step, the reaction rate is independent of the thickness Δx of the reaction layer; one obtains a linear rate law, which can be expressed in the form

$$\Delta x = l' t \tag{1}$$

if the reaction cross section remains constant and if the growth of the reaction layer can be treated as a one-dimensional problem. l' is the rate constant and t is the reaction time.

If nucleation is the rate-determining step, one can again obtain a linear rate law, which is the first approximation of the exponential law of nucleus formation, and which can be represented, after the formation of a homogeneous reaction layer, in the form of equation (1). The exponential law is the frequently used equation for the rate of nucleation.

To establish whether the rate-determining step is the phase boundary reaction (II) or (IV) or the nucleation of the reaction product, it is necessary to use further methods of investigation. In the case of nucleation, it may be possible to use microscopy or electron microscopy as the additional method of investigation, if it is possible to separate the reaction layer from one of the reactants without destruction.

If volume diffusion through the reaction product is rate-determining, the reaction rate decreases with increasing thickness Δx of the reaction layer. The process then follows the parabolic rate law, which can be expressed, for a constant reaction cross section, *i. e.* for one-dimensional growth of the single-phase reaction layer, in the form

$$\Delta x^2 = 2k't \qquad (2)$$

k' is the rate constant and t is the reaction time.

Equation (2) also describes the growth of the reaction layer if, instead of the volume diffusion, the rate-determining step is the diffusion *via* the grain boundaries and dislocations of the crystallites of the product, provided that the flux equation[18] can be applied to the ion currents[19].

It is possible to decide between rate-determining volume diffusion and rate-determining diffusion *via* the grain boundaries and dislocations if the reaction rate is found to depend on the average crystallite size or on the average size of the coherent regions of the reaction product. The average crystallite size can be determined with the aid of the microscope or the electron microscope; the average size of the coherently scattering crystal regions can be determined from X-ray line broadening. An indication which of the two diffusion mechanisms predominates can also be obtained by comparison of the activation energies of the two processes. The activation energy of the diffusion *via* grain boundaries and dislocations of the crystallites of the product is relatively low.

Deviations from the parabolic rate law (2) at the beginning of the reaction, *i. e.* if the reaction layer is thin, can also be attributed, in cases of insufficient contact between one of the reactants and the reaction layer, to the evaporation, condensation, or transport of one of the reactants in the gas phase[5]. With sufficiently thin reaction layers, transport *via* the gas phase becomes rate-determining, and a linear rate law (1) is to be expected if the diffusion path in the gas phase remains constant during the reaction[15].

3.1.1. Investigation of Powder Reactions

Though powder reactions are of great importance in preparative solid-state chemistry and in industry, the definite establishment of a rate law for these reactions is difficult, since the growth of the reaction layer is a three-dimensional problem, the thickness of the reaction layer cannot be measured directly, and the reaction cross section changes during the reaction. The investigation is further complicated by other parameters, such as the grain size, the grain size distribution, the porosity of the grains, and the packing density. The determination of the mechanism of powder reactions is therefore problematic[20], even when diffusion processes through the reaction product are rate-determining and the frequently used equations of *Jander*[21] and of *Serin* and *Ellickson*[22] can be applied.

3.1.2. Investigation of Reaction Layers with Plane-Parallel Interfaces

If the reactants are used in compact form, specifically as a single-crystal or as a sintered specimen with plane contact surfaces, the reaction product is formed between the reactants as a layer with a constant reaction cross section and with plane-parallel interfaces. In this case, the growth of the reaction layer may be treated as a one-dimensional problem. For reaction layers whose thickness Δx is at least several μm, Δx can be measured directly by microscopic observation of sections normal to the reaction cross section, and the rate law can thus be determined. This procedure is frequently used.

Using one reactant single-crystalline or as a sintered sample and the second reactant as a cover layer deposited onto the plane substrate, *e. g.* by evaporation *in vacuo* or by sputtering, optimum contact between the reactants can be achieved under suitable experimental conditions. The reaction product is then generally also formed under the cover layer as a homogeneous layer with a constant reaction cross section and plane-parallel interfaces, so that the growth of the reaction layer may be treated as a one-dimensional problem. Since only a thin cover layer is applied to the substrate in this method, the procedure is suitable for the determination of the rate law for thin reaction layers up to a maximum of a few 10^4 Å thick. This method yields information about the initial stages of a solid-state reaction, for example about the reaction steps (I) to (IV) that can become rate-determining in the case of thin reaction layers. Very little is known about the initial stages of solid-state reactions[9, 15], apart from the problematic results obtained by the investigation of powder reactions.

However, the thickness of the thin reaction layers cannot be measured microscopically. In some cases, the cover layer of one of the reactants can be quantitatively removed from the reaction layer by means of a suitable solvent; if the density of the reaction product and the cross section of the reaction layer are known, the thickness Δx of the single-phase reaction layer can then be found by weighing, and the rate law can be determined. In other cases, it is possible to use a procedure[23] based on the measurement of the thickness Δx of the thin reaction layer XY_ν (maximum thickness several 10^3 Å) between the substrate X of one reactant (at least a few millimeters thick) and the thin cover layer Y of the other reactant by X-ray fluorescence analysis (Fig. 3).

The intensity of the X-ray fluorescent radiation of an element in the sample is determined before the beginning of the reaction, *i. e.* without the reaction layer XY_ν, and after the reaction time t, *i. e.* with the reaction layer XY_ν, with monochromatic X-rays; the thickness Δx of the reaction layer after the reaction time t can then be found from the change in intensity, and the rate law can be determined. The intensity I of the X-ray fluorescent radiation is obtained by

surface measurement without destruction of the sample. The following conditions must be satisfied:

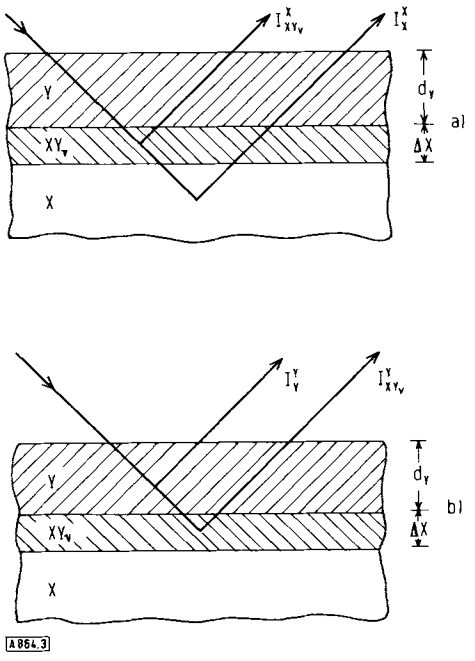


Fig. 3. Excitation of X-ray fluorescent radiation in the sample.

1. The reaction layer is in the form of a homogeneous layer with plane-parallel interfaces. The roughness of the phase boundaries is disregarded.

2. In the quasi-binary system of the reactants X and Y, only one compound XY_ν is formed, or the layer thicknesses of any other compounds formed in this system are negligible. The homogeneity ranges of the reactants and of the reaction product are small.

3. The cover layer Y contains an element Y that does not occur in the substrate X, or *vice versa*.

4. The X-ray fluorescent radiation of the excited element is sufficiently absorbed by passage through the sample.

Two methods of measurement can then be distinguished, depending on whether the X-ray fluorescence of the element X is excited in the substrate X and in the reaction layer XY_ν under the cover layer Y (Fig. 3a) or whether the X-ray fluorescence of the element Y is excited in the cover layer Y and in the reaction layer XY_ν (Fig. 3b). For both cases, it is possible to give functions for the determination of the thickness Δx of the reaction layer under the cover layer[*] if the absorption coefficient of the X-rays can be determined by investigation of the cover layer Y without the reaction layer XY_ν and of the reaction layer XY_ν without the cover layer Y. The more favorable of the two methods (Fig. 3a or Fig. 3b) is chosen for experimental studies. It is advisable to excite the element in the sample whose X-ray fluorescent radiation is most strongly absorbed on passage through the sample, in particular an element with a relatively low atomic number that emits long-wave X-rays.

[*] Cf. eq. (12) or (6) in Ref. [23].

The method has been successfully tested by measurement of the thickness Δx of thin layers of Pb_2SiO_4 up to several 10^3 Å thick[24]. The Pb_2SiO_4 layer was situated between a quartz single crystal or a quartz glass substrate and a thin cover layer of PbO. The Δx values found by X-ray fluorescence analysis agreed with those found by weighing after the removal of the PbO cover layers.

3.2. Marker Experiments

If the reactants are used as single crystals or as sintered samples with plane contact surfaces, it is possible to determine the transport mechanism on which the solid-state reaction is based by marking the interface before the beginning of the reaction with wires or foils of inert material, *e.g.* platinum, a few μm thick (Fig. 4a). By microscopic observation of the position of these markers after the reaction in sections normal to the reaction cross section, it is possible to distinguish the cases shown in Figures 4b to 4d for spinel formation from the oxides. If the position of these markers after the reaction is assumed to indicate the position of the interface between the reactants before the reaction and if the homogeneity ranges of the reaction product and of the reactants may be disregarded, the experiments can be interpreted as follows:

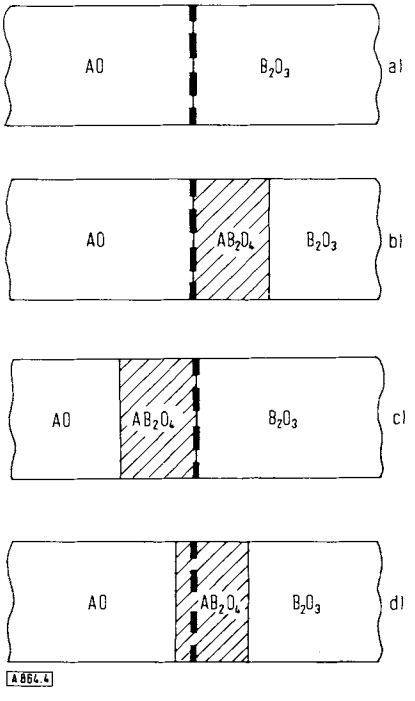


Fig. 4. Position of the markers before (a) and after (b to d) the reaction.

1. If the inert markers are situated in the interface between one reactant and the reaction product (Figs. 4b and 4c), this indicates transport of the cations and anions of this reactant in the same direction through the reaction product (Fig. 1) or migration of cations and of electrons or defect electrons through the reaction layer in conjunction with transport of the nonmetallic component *via* the gas phase (Fig. 2).

2. If the inert markers are situated inside the reaction layer (Fig. 4d), this points to countertransport of cations (Fig. 1). In spinel formation from the oxides, the marker then divides the spinel layer in the ratio 1:3, since according to Fig. 1 only 1 mole of spinel is formed at interface 1, while 3 moles are formed at interface 2.

If the transport of a reactant *via* the gas phase is involved, a reaction layer is formed on one of the reactants even when the compact reactants are separated before the reaction by platinum wires a few hundred μm thick and when this separation is maintained during the reaction.

However, the condition that the position of the interface before the reaction is still indicated by the inert markers after the reaction is frequently not satisfied. It is better to use natural markers. For example, one of the reactants may be used single-crystalline, the cross section of this sample being large in relation to the cross section of the compact sample of the other reactant; the parts of the surface of the single crystal on which no reaction has occurred can then be used as a natural marker. If the reactants differ in their porosity or if one is monocrystalline and the other polycrystalline, the change in porosity or the monocrystallinity or polycrystallinity of the reaction layer may be used as a natural marker.

Experiments with markers are not possible if the reaction layers are less than a few μm thick. In such cases, the results of marker experiments with thick reaction layers must be used to obtain information about the transport mechanism. The same is true of powder reactions.

3.3. Calculation of the Reaction Rate

If the volume diffusion through the product is the rate-determining step, the transport mechanism found from marker experiments can be checked and confirmed by comparing the rate constant of the parabolic rate law calculated on the basis of this transport mechanism with the measured rate constant. The rate of such a solid-state reaction can be calculated for a small spinel phase width[18] if the following conditions are satisfied:

1. The reaction is isothermal and isobaric. The partial pressure of the nonmetallic component is constant, so that the disorder type of the reaction product does not change.

2. The homogeneity ranges of the reactants and of the single-phase reaction product are small.

3. The reactants and the reaction product contain no pores. The contact at the interfaces is ideal.

4. Local thermodynamic equilibrium exists within the reaction layer. This means that the point defects are responsible for the transport of the particles through the reaction layer. The reaction temperature must therefore be so high that the diffusion *via* the grain boundaries and dislocations of the crystallites of the product is negligible.

5. Thermodynamic equilibrium is maintained at the interfaces during the reaction, so that the transfer of the particles through the interfaces is not inhibited. This condition is generally satisfied for sufficiently thick reaction layers.

6. The particles migrate independently of one another. The ion and the electron or defect electron currents are coupled only by the condition of electroneutrality.

If the mobilities of the various types of ions in the lattice of the product differ sufficiently from one another, certain diffusion mechanisms occur.

If the oxygen ions have the lowest mobility in the spinel lattice, counterdiffusion of cations (Fig. 1) occurs when contact between the solids is ideal. The diffusion of the type of cation having the lower mobility is then the rate-determining step. If this is *e.g.* the ion A^{2+} and if the homogeneity range of the spinel is small, the rational reaction constant k can be calculated from the following equation[18]:

$$k = \gamma c_A n_A^{-1} D_A(a_{AO} = 1) \quad [1 - \exp(n_A \Delta G^0 / RT)] \tag{3}$$

γ is a numerical factor of the order of 1, c_A is the molar concentration of the ion A^{2+} in the reaction product, R is the gas constant, and T is the absolute temperature. $D_A(a_{AO}=1)$ is the self-diffusion coefficient of the ionic species A^{2+} in the reaction product when the activity of the reactant AO in the reaction product is 1. ΔG^0 is the standard free energy of the reaction $AO + B_2O_3 = AB_2O_4$. The reaction constant k is related to the rate constant k' of the parabolic rate law (2), which can be determined experimentally by $k = k'/\tilde{V}$, where $\tilde{V}$ is the equivalent volume of the reaction product.

ΔG^0 can be measured with the aid of galvanic solid-state cells. $D_A(a_{AO}=1)$ must be determined for the case where the reaction product is in equilibrium with AO, *i.e.* the activity of AO in the reaction product is unity. n_A can be determined from the equation[18]

$$\frac{D_A(a_{AO}=1)}{D_A(a_{B_2O_3}=1)} = \exp(n_A \Delta G^0 / RT) \tag{4}$$

where $D_A(a_{B_2O_3}=1)$ is the self-diffusion coefficient of the ions A^{2+} in the reaction product if the reaction product is in equilibrium with B_2O_3, *i.e.* the activity of B_2O_3 in the reaction product is unity. n_A has also been calculated for a number of disorder types[18, 25].

4. Closing Remarks

The transport mechanisms and reaction steps discussed here are also valid in principle when several ternary compounds are formed instead of one in the quasi-binary system of the two reactants.

The knowledge of the mechanisms of solid-state reactions can lead to new synthetic pathways in preparative solid-state chemistry. However, our knowledge of the kinetics of

these reactions is still limited. In particular, the following problems are to be clarified:

1. the initial stages of solid-state reactions;
2. the mechanisms of reaction types 4 and 5 in Section 1.

Received April 20, 1971 [A 864 IE]
German version: Angew. Chem. *84*, 227 (1972)
Translated by Express Translation Service, London

[1] *V. Leute*, Z. Phys. Chem. (Frankfurt am Main) *59*, 76, 91 (1968).
[2] *C. Wagner*, Z. Phys. Chem., Abt. *B 34*, 309 (1936).
[3] *C. W. Tucker*, Surface Sci. *5*, 179 (1966).
[4] *E. Hornbogen* in *A. C. Zettlemoyer*: Nucleation. M. Dekker, New York 1969, p. 309.
[5] *H. G. Sockel* and *H. Schmalzried*, Mater. Sci. Res. *3*, 61 (1966).
[6] *H. Rickert* and *K.-H. Tostmann*, Werkst. Korros. *21*, 965 (1970).
[7] *F. S. Petit, E. H. Randklev*, and *E. J. Felten*, J. Amer. Ceram. Soc. *49*, 199 (1966).
[8] *M. R. Achter* and *R. Smoluchowski*, J. Appl. Phys. *22*, 1260 (1951).
[9] *K. Hardel* and *B. Strocka*, Z. Phys. Chem. (Frankfurt am Main) *67*, 8 (1969).
[10] *J. F. Laurent* and *J. Bénard*, J. Phys. Chem. Solids *7*, 218 (1958).
[11] *H. J. De Bruin, G. M. Watson*, and *C. M. Blood*, J. Appl. Phys. *37*, 4543 (1966).
[12] *J. W. Matthews*, Phil. Mag. *12*, 1143 (1965).
[13] *G. R. Hennig*, Appl. Phys. Lett. *4*, 52 (1964).
[14] *J. L. Robins* and *T. N. Rhodin*, Surface Sci. *2*, 346 (1964).
[15] *K. Hardel*, Z. Phys. Chem. (Frankfurt am Main) *65*, 86 (1969).
[16] *H. Schmalzried*, Z. Phys. Chem. (Frankfurt am Main) *33*, 111 (1962).
[17] *H. Rickert* and *C. Wagner*, Z. Elektrochem., Ber. Bunsenges. Phys. Chem. *66*, 502 (1962).
[18] *H. Schmalzried*, Progr. Solid State Chem. *2*, 265 (1965).
[19] *L. G. Harrison*, Trans. Faraday Soc. *57*, 1191 (1961).
[20] *W. Komatsu*, Reactivity Solids, 5th Int. Sympos., Munich 1964, *1965*, 182.
[21] *W. Jander*, Z. Anorg. Allg. Chem. *163*, 1 (1927).
[22] *B. Serin* and *R. T. Ellickson*, J. Chem. Phys. *9*, 742 (1941).
[23] *K. Hardel*, Z. Phys. Chem. (Frankfurt am Main) *62*, 328 (1968).
[24] *K. Hardel* and *B. Strocka*, unpublished results.
[25] *H. Schmalzried* and *C. Wagner*, Z. Phys. Chem. (Frankfurt am Main) *31*, 198 (1962).

Chemistry of the Positron and of Positronium[1]

By Hans J. Ache[*]

In this progress report, the properties and behavior of the positron ("positive electron", anti-electron) and of the positronium, a "hydrogen atom" containing a positron instead of a proton, are considered from the chemist's viewpoint. Examples are given to demonstrate the development of positronium chemistry, in aqueous solution and in the gaseous, liquid, and solid phases, with its problems and possibilities.

1. Introduction

The reactions of the hydrogen atom and of the proton have been the subject of numerous investigations and must be familiar to every chemist. The reactions of deuterium and of tritium, the heavy hydrogen isotopes with masses 2 and 3 respectively, which are often used as "labeled" hydrogen atoms for the investigation of reaction mechanisms, are also extensively known.

It is probably not so well known, however, that there is an "atom" that can be regarded as an analog of the hydrogen atom, but in which the proton is replaced by a positron, and which thus represents the lightest isotope of hydrogen. This particle, which is known as a positronium, has a very limited lifetime (of the order of 10^{-7} to 10^{-10} s) before it decays with emission of two or three photons.

Despite this short lifetime, which rules out conventional product analysis as used *e.g.* in the reactions of deuterium or tritium, it is an excellent "labeled" hydrogen atom for the investigation of chemical and physical processes in matter; this is because its lifetime and the mechanism of its decay process are determined by the chemical and physical state of the environment. The positron-electron annihilation process is one of the few known nuclear processes whose course depends in a characteristic manner on the chemical and physical structure of the environment. These elementary particles can therefore serve as nuclear probes, and can provide a great deal of information about the properties of the surrounding matter.

At present there are essentially four nuclear processes that satisfy these conditions: 1. the Mössbauer effect; 2. the positron-electron annihilation process; 3. the angular distribution between two successive γ quanta in the emission of γ cascades; and 4. the depolarization of muons and muonium formation.

Whereas *e.g.* the Mössbauer effect has had a firm place in analytical chemistry for several years, the part that the positron or positronium can play in the solution of chemical problems is still largely unknown.

The physico-chemical aspects of the interaction between the positron and matter will therefore be examined below,

[*] Dr. H. J. Ache, Professor of Chemistry
Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061 (USA)

and some examples will be given to demonstrate the importance of this new nuclear method to chemistry[2–5]. The fact that a positronium atom occurs as an intermediate in many cases before the final annihilation of the positron also allows the study of a series of interesting reactions of this unusual "atom".

2. Annihilation of the "Free" Positron

The positron, which is sometimes also referred to as a positive electron or anti-electron, has the same mass and electric charge as the electron, but the sign of its charge is positive. Its spin, like that of the electron, is $1/2\,\hbar$; it belongs to the class of leptons and obeys the Fermi-Dirac statistics.

It is preferentially formed in the radioactive decay of nuclides in which the proton/neutron ratio is greater than one.

The fate of the positron in matter is determined by the fact that sooner or later it interacts with an electron, resulting in annihilation of both particles. The energy liberated in this process generally appears in the form of "annihilation radiation". The number of photons emitted is determined by the orientation of the spins of the positron and the electron at the instant of annihilation.

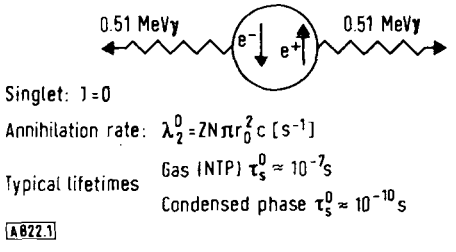


Fig. 1. Two-quantum annihilation of a positron (schematic). J = total spin momentum; Z = atomic number; N = number of particles per unit volume; r_0 = classical electron radius; c = velocity of light.

If the spins of the positron and of the electron are antiparallel, *i.e.* if a singlet system exists ($^1S_0$), the selection rules for the conservation of energy, momentum, and

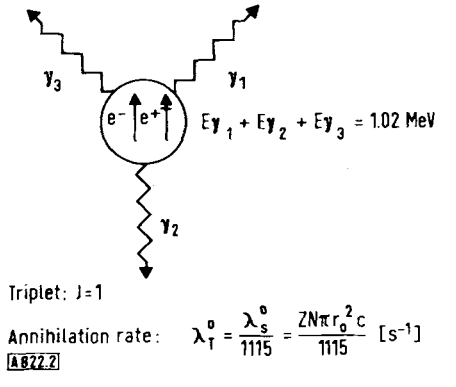


Fig. 2. Three-quantum annihilation of a positron (schematic).

parity require the emission of two γ quanta, each having the energy mc^2 (m = rest mass of the electron, c = velocity of light) or 0.51 MeV. The angular distribution between the two γ quanta depends on the kinetic energy of the positron-electron system (Fig. 1). If the system is at absolute rest at the instant of annihilation, the two photons are emitted in exactly opposite directions; in practice, however, the system usually still has a small content of kinetic energy, which can lead to deviations of a few milliradians (mrad) from the ideal angular distribution of 180°.

If the spins are parallel [triplet system ($^3S_1$)], the selection rules can be satisfied only by the emission of an odd number of photons (usually three). The distribution of the angles between three γ quanta and the distribution of the annihilation energy of 1.02 MeV over the three γ quanta are much more complicated than in two-quantum annihilation (Figs. 2 and 3).

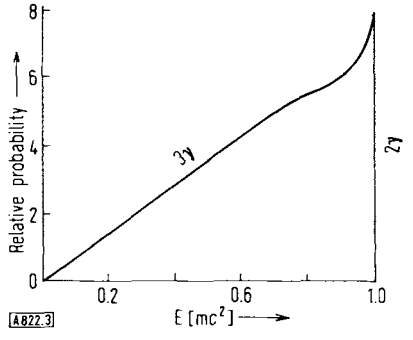


Fig. 3. γ-Energy spectrum of the positron-electron annihilation as a function of the alternatives: two-quantum or three-quantum decay [11].

The cross section for the two-quantum annihilation of a free positron having velocity v with a free electron at rest was calculated by *Dirac*[6]:

$$\sigma_D = \sigma_{2\gamma} = \frac{\pi r_0^2}{\gamma+1}\left[\frac{\gamma^2+4\gamma+1}{\gamma^2-1}\ln(\gamma+\sqrt{\gamma^2-1}) - \frac{\gamma+3}{\sqrt{\gamma^2-1}}\right] \quad (1)$$

$$\gamma = 1/\sqrt{1-\beta^2}\,; \qquad \beta = v/c \quad (2)$$

r_0 = classical radius of the electron or positron = $e^2/mc^2 = 2.8\cdot10^{-13}$ cm

If v is small in relation to c, equation (1) simplifies to:

$$\sigma_D = \frac{\pi r_0^2}{\beta} = \frac{\pi r_0^2 c}{v} \quad (3)$$

from which it is easy to see that the probability of annihilation of the positron increases with decreasing velocity of the particle. The annihilation constant of the free positron in matter ($\lambda_{2\gamma}$) and its average lifetime (τ_D) are found from equation (3), for the case of two-quantum annihilation, to be:

$$1/\tau_D = \lambda_{2\gamma} = ZN\pi r_0^2 c = ZN\sigma_D v\ [s^{-1}] \quad (4)$$

(Z = atomic number of the substrate; N = number of atoms per cm³; τ_D = Dirac lifetime)

Better agreement with the experimental findings can be obtained if Z in equation (4) is replaced by the quantity Z_{eff} (the number of electrons in the outer shells).

The ratio of the three-quantum to the two-quantum annihilation constants was calculated by *Ore*[11], and is:

$$\lambda_{3\gamma}/\lambda_{2\gamma} = 1/1115 \qquad (5)$$

Since the relative probabilities of the formation of triplet or singlet states on meeting of a positron and an electron are given by the number of possible quantum states in the two systems, which is $2J_T+1$, *i.e.* 3, in the case of the triplet (parallel spins, total momentum $J_T=1$) and $2J_S+1$, *i.e.* 1, in the case of the singlet (anti-parallel spins, $J_S=0$), the ratio of the cross sections of the two annihilation modes is given by the equation:

$$\sigma_{3\gamma}/\sigma_{2\gamma} = \frac{\lambda_{3\gamma}}{\lambda_{2\gamma}}\frac{2J_T+1}{2J_S+1} = \frac{1}{1115}\cdot 3 = 1/372 \qquad (6)$$

Positrons formed as a result of a nuclear decay process generally have kinetic energies of several hundred eV to a few MeV, which they lose by successive collisions with atoms or molecules of the environment.

A schematic representation of the fate of positrons in argon as a function of their kinetic energy is shown in Figure 4[7].

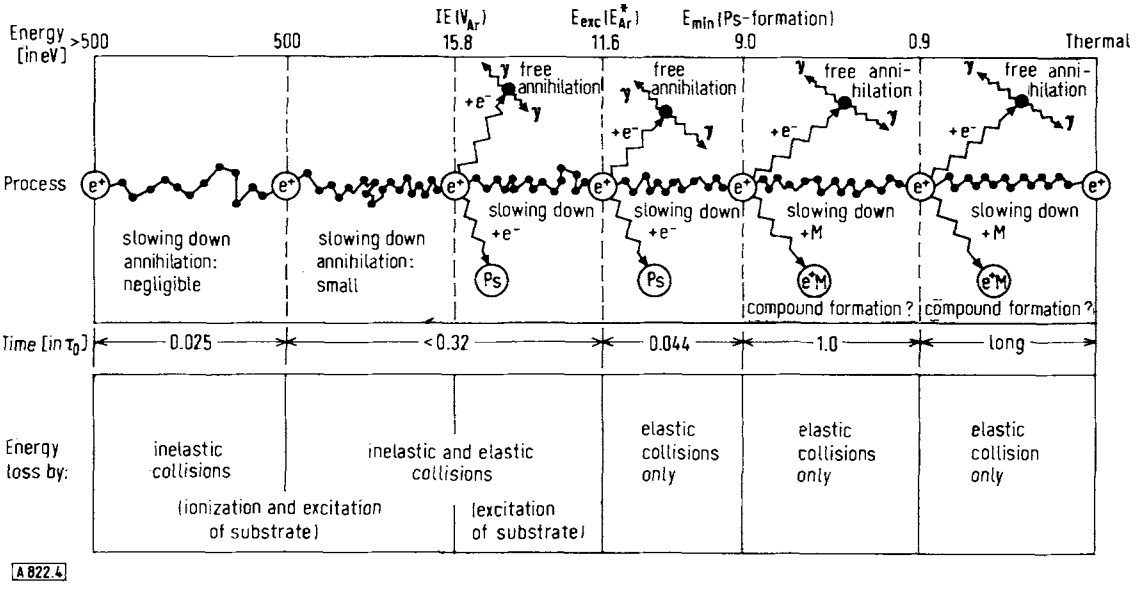


Fig. 4. Fate of positrons in argon as a function of their kinetic energy.

The cross section for the annihilation of positrons is extremely small in comparison with the cross sections for energy transfer *via* ionization or electron excitation in collisions with substrate molecules or atoms; less than 5% of all positrons are annihilated before reaching an energy level of about 5—10 eV.

A comparison of the "Dirac" lifetime calculated from equation (4) with the time required by the positrons to reduce their kinetic energy from an initial value of 0.5 MeV to thermal energies leads to the same result. If τ_D is compared with the time scale in Figure 4, it is found that positrons in argon require only about 8.74×10^{-8} s or 0.32 τ_D for their kinetic energy to fall below 20 eV, *i.e.* only a small fraction of all positrons is annihilated at higher energies.

3. Positronium Formation

The experimentally observed ratio of three-quantum to two-quantum annihilation usually differs considerably from the value of 1/372 found from quantum mechanics [equation (6)]. It follows that the annihilation of the *free* positron cannot be the only process that leads to the disappearance of positrons.

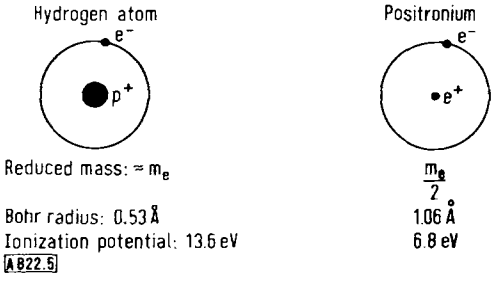


Fig. 5. Characteristics of hydrogen and positronium atoms.

The possibility that the positron could enter into combination (though only very short-lived) with an electron was considered by *Mohorovic*[8] as early as 1934. However, it

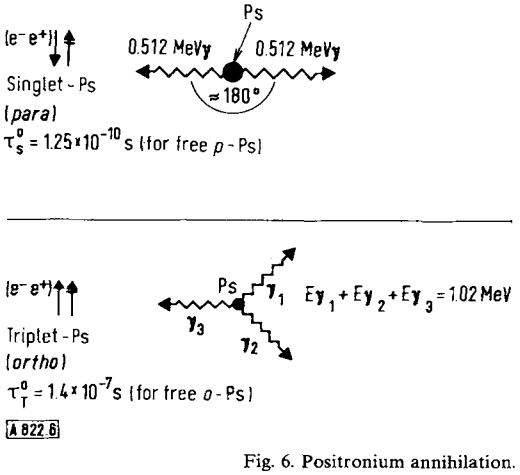


Fig. 6. Positronium annihilation.

was not until 17 years later that *Deutsch*[9, 10] was able to detect the combination, which is known as positronium (e^+e^- or Ps), experimentally.

The properties of positronium can be best described if it is considered as an analog of the hydrogen atom in which the proton has been replaced by a positron. On the basis of the simple Bohr model of the atom, the Ps atom has half the reduced mass of the H atom, so that in comparison with the H atom, the Bohr radius is doubled (1.06 Å) and the ionization potential is halved (6.8 eV) (Fig. 5).

Positronium can exist in two ground states, *i. e.* as a triplet (*ortho*-Ps), with parallel orientation of the positron and electron spins, and as a singlet (*para*-Ps), with antiparallel spins (Fig. 6). The ratio in which *o*-Ps and *p*-Ps are formed is again determined by the number of possible quantum states in which the two systems can occur (see Section 2), with the result that *o*-Ps is formed in 75% of cases and *p*-Ps in 25%.

Corresponding to the annihilation of the free positron, the rules for the conservation of energy, momentum, and parity require a three-quantum annihilation on decomposition of *o*-Ps and a two-quantum annihilation for *p*-Ps.

The average lifetime of *free* *p*-Ps is $\tau_S^0 = 1.25 \times 10^{-10}$ s, while that of *free* *o*-Ps is $\tau_T^0 = 1.4 \times 10^{-7}$ s[11].

The relatively long lifetime of *o*-Ps makes it possible to follow both its formation and its reactions and to use it as a "labeled" hydrogen atom for the elucidation of chemical and physical processes in matter.

4. The "Ore Model"

As was indicated in Figure 4, positronium formation takes place in an energy range of a few eV. This process can be illustrated by the example of a gaseous system, where it is easiest to follow.

The formation of Ps can be formulated as follows:

$$e^+ + M \longrightarrow Ps + M^+ \tag{7}$$

If the ionization potential V of the substrate molecule (M) is greater than 6.8 eV, the bonding energy of the positron and the electron in the ground state of the Ps atom, the formation of Ps is an endothermic reaction with a threshold energy of $Q = (V - 6.8)$ eV, *i. e.* only positrons having a kinetic energy $E_{kin} > (V - 6.8)$ eV can form positronium in this way. This determines the lower energy limit, $(V - 6.8)$ eV, of the Ps formation.

However, if E_{kin}, the kinetic energy of the positrons, is greater than V, the probability of Ps formation is low in comparison with the cross section of reactions that lead to ionization of the substrate molecule, *e. g.*

$$e^+ + M \longrightarrow e^+ + M^+ + e^- \tag{8}$$

and only a few Ps atoms will therefore be formed.

A further reaction that competes with the Ps formation is the electronic excitation of the substrate molecules by the positron, which can occur as long as E_{kin} is greater than E^*, the energy of the first excitation potential of M.

$$e^+ + M \longrightarrow e^+ + M^* \tag{9}$$

It follows that in gases, the major part of the positronium is formed from positrons with kinetic energies between the first (electronic) excitation potential of the substrate molecule (upper limit) and $(V - 6.8)$ eV (lower limit).

This model of the Ps formation was first developed by *Ore*[12], and the energy range in which the Ps formation is most probable is named the "Ore gap" after this author.

The fraction of Ps-forming positrons will be largely dependent on the number of collisions with the substrate molecules within this energy range, *i. e.* it will be a function of the width of the Ore gap. On the basis of the following greatly simplified assumptions:

1. all positrons reach the upper energy limit for Ps formation, E_{max}, without being annihilated;

2. statistical distribution of the kinetic energy of the positrons in the range between E_{max} and $E = 0$;

3. all positrons whose kinetic energy lies in the Ore gap form Ps,

the fraction of these positrons is given by

$$P^0 = \frac{E_{max} - E_{min}}{E_{max}} \tag{10}$$

$E_{max} - E_{min}$ = width of the "Ore gap".

Depending on whether the first excitation potential or the ionization potential of the substrate is taken as the upper energy limit, one obtains for P^0, the fraction of Ps formed:

$$6.8/V > P^0 > (E^* - (V - 6.8))/E^*$$

The validity of the simple Ore model is limited in the case of condensed phases, since the limits of the Ore gap are then determined not only by the ionization and excitation potentials but also by dissociation energies and intermolecular forces, such as dipole-dipole interactions.

For example, *Ferrell*[13] calculated that the upper limit of the Ore gap for the solid phase is $E_{max} = E^* - Q_{e^-}$ and the lower limit is $E_{min} = V - 6.8 - Q_{Ps}$, where E^* = lower limit of the conductivity band; $V - E^* = Q_{e^-}$ = electron affinity; Q_{e^+} = positron affinity; Q_{Ps} = positronium affinity; Δ_0 = Ore gap, calculated for the same substance in the gas phase.

The Ore gap in the solid phase is thus defined as

$$\Delta = (E^* - Q_{e^+}) - (V - 6.8 - Q_{Ps}) = \Delta_0 - (Q_{e^+} - Q_{Ps}) \tag{11}$$

For ionic crystals of the metal halide type (NaCl, KBr, *etc.*), where $Q_{e^+} = 3$—5 eV and $Q_{Ps} < 0$, we find $\Delta = 0$, *i. e.* Ps formation is thermodynamically impossible in such crystals.

The interaction between the positron (or positronium) and matter can be investigated on the basis of two fundamental phenomena: 1. inhibition of Ps formation and 2. reactions of the Ps atom formed (quenching).

5. Inhibition of Positronium Formation

All processes that reduce the formation of Ps will be included in this category. The Ore model is based on the simplified assumption that all positrons whose kinetic energy lies in the Ore gap produce Ps. In practice, however, the Ps formation process in the Ore gap has to compete with all other processes that can cause moderation of the positron to energies below the lower Ore limit. The most important of these are elastic and inelastic collisions with substrate molecules, the energy transferred in the second case possibly stimulating molecular vibrations and rotations. This category also includes processes that lead to positron capture by addition of positrons to the substrate molecule AB.

$$e^+ + AB \longrightarrow e^+AB \text{ or } A + e^+B \qquad (12)$$

If the compound formation occurs above or within the Ore gap, the captured positrons are no longer available for the formation of Ps, the yield of which is therefore decreased (Fig. 7). (The positron bound in the complex is annihilated mainly with emission of two quanta with an annihilation constant that is characteristic of this complex.)

Little is known at present about the fraction of the po that form complexes in the Ore range. From the inv tion of the annihilation of positrons in argon, *Tao e* conclude that approximately 18 to 23 % of all positron an e^+Ar complex in the Ore range.

Since the processes mentioned here, such as elastic s ing, stimulation of molecular vibrations and rotati the eV range, and the addition of low-energy electr positrons) to molecules, are of the greatest importa the understanding of elementary processes in rac chemistry, the study of Ps formation should be capa yielding valuable new knowledge in this little-invest field.

6. Reactions of the Positronium Atom (Quen

The average lifetime of *free o*-Ps, *i.e.* 1.4×10^{-7} s, is re ly long, but only a small fraction of all *o*-Ps atoms r this age in condensed matter, since the positrons car into a series of reactions in the substrate, all of whic to a decrease in their average lifetime. These include

1. annihilation of Ps with "foreign" electrons on co with substrate molecules (pick-off annihilation);

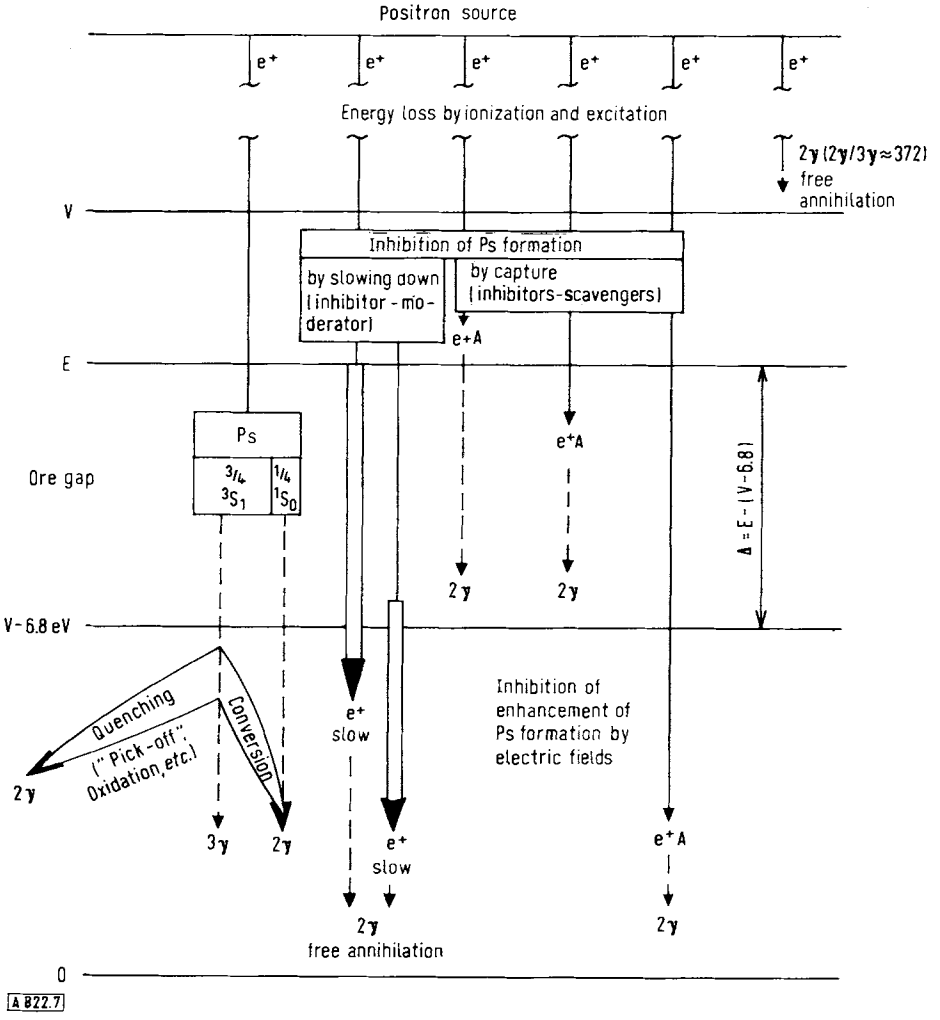
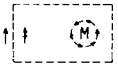
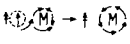
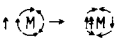


Fig. 7. Schematic survey of the processes of positronium formation and annihilation to illustrate the Ore model and possible deviations from it [3].

2. *ortho-para*-conversion: under the influence of paramagnetic particles, *e.g.* paramagnetic ions in solution, a spin conversion from *ortho* to *para* or *vice versa* can occur;

3. chemical reactions of Ps; addition, substitution, oxidation, compound formation.

The above reactions and their effects on the various annihilation parameters are shown schematically in Figure 8.

Reaction	Mechanism	Average lifetime of products [s]	Photons emitted	Average lifetime of *o*-Ps appears to be
"Pick-off"		—	$2\gamma/3\gamma = 372/1$	shorter [a]
Conversion		1.25×10^{-10} (*p*-Ps)	2γ	shorter [a]
Oxidation		$\approx 0.5 \times 10^{-10}$ [b]	$2\gamma/3\gamma = 372/1$	shorter [a]
Compound formation		$\approx 0.5 \times 10^{-10}$ [c]	$2\gamma/3\gamma = 372/1$	shorter [a]

[a] Intrinsic lifetime $\tau_T^0 = 1.4 \times 10^{-7}$ s. [b] Free positron in condensed phase. [c] Complex

A822.8

Fig. 8. Reactions of *ortho*-positronium (quenching).

6.1. Pick-Off Annihilation

The pick-off annihilation of *o*-Ps atoms can be best described by assuming that at some instant after the formation of *o*-Ps, the positron is removed from the *o*-Ps under the influence of the "electron cloud" of a substrate molecule, and is then annihilated as a free positron together with an electron of the substrate molecule. The result is a decrease in the lifetime of Ps in relation to the characteristic value τ_T^0. Since the same rules apply in this annihilation process as in the annihilation of the free positron, two-photon emission predominates here in contrast with the three-quantum decomposition of *o*-Ps. Increased pick-off annihilation therefore results in a decrease in the three-quantum annihilation probability (Fig. 8).

p-Ps atoms can naturally also be annihilated by pick-off. However, since their average lifetime τ_S^0 is only 1.25×10^{-10} s, they usually undergo self-annihilation before they can enter into any reactions.

The pick-off annihilation of Ps is a process that can generally occur in all substances. The experimental observation[3] that the pick-off annihilation constant in gaseous systems or even in solutions is determined mainly by the molar density of the substance, and not by the average electron density, confirms the view that on collision of Ps with a molecule, the entire "electron cloud" of the molecule enters into interaction with the Ps before an electron of the substrate molecule is annihilated together with the positron.

The kinetics of the pick-off annihilation of *o*-Ps in gases corresponds to the relation[3]:

$$1/\tau_T = \lambda_T = \lambda_T^0 + \sigma_p n v \qquad (13)$$

τ_T = average lifetime of *o*-Ps in the substrate [s]
λ_T = experimental annihilation constant of *o*-Ps in the substrate [s^{-1}]
λ_T^0 = self-annihilation constant of *free* *o*-Ps [s^{-1}]
n = molecular concentration of the substrate [cm^{-3}]
v = velocity of *o*-Ps in the substrate [cm s^{-1}]
σ_p = characteristic cross section for pick-off annihilation of *o*-Ps per collision with a substrate molecule [cm^2].

The lifetime of positronium therefore decreases with increasing molar density of the substance. Since it is also a function of the velocity v, it decreases with rising temperature.

In gases, where $\lambda_T^0 \gg \sigma_p n v$ under normal conditions (1 atm, 25 °C), pick-off annihilation is only of minor importance, and the average lifetime of free *o*-Ps is usually found, *i.e.* when no other reactions lead to faster annihilation. The contribution of pick-off to the annihilation process as a whole increases only at higher pressures or temperatures, and it may then considerably decrease the average lifetime of *o*-Ps.

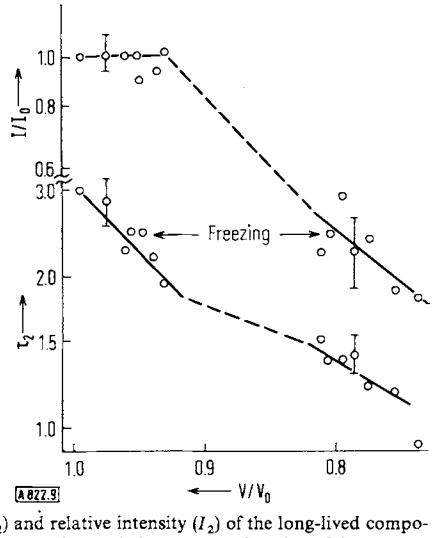
In the condensed phase, on the other hand, the temperature dependence is reversed. This observation is the basis of the free volume model[15-18], which correlates the lifetime of positronium with the "free volume" available in the lattice for the formation and accommodation of the Ps atom.

Brandt, *Berko*, and *Walker* have calculated the lifetime of Ps in molecular crystals, and found the following relation[15]:

$$\tau = \tau_0 [1 + F(P_0 r_0^2, V^*)] \qquad (14)$$

τ_0, P_0 = characteristic constants for lattice type and compound
r_0 = classical electron radius
$V^* = V_1/V_0$ = reduced free cell volume
V_1 = volume of the lattice cell (at temperature T_1)
V_0 = volume of the lattice cell at $T_0 = 0$ °K

In this model, V_0 is regarded as the volume that is not accessible to the Ps; the "free volume" available to the Ps at a given temperature T_1 is calculated as $V_1 - V_0$; F is a function of V^*, and increases linearly with V_1. The lifetime of Ps in a given substance is therefore inversely proportional to the density of this substance, as is confirmed by experiments[19] in which the density of the material was altered by compression (Fig. 9). Since a temperature rise is usually accompanied by a decrease in density, it leads in many condensed systems to an increase in the lifetime of Ps.



A822.9

Fig. 9. Lifetime (τ_2) and relative intensity (I_2) of the long-lived component of the positron annihilation in benzene as a function of the pressure (V_0 = volume at 30 °C/1 atm) [19].

In addition to this density effect, a separate temperature effect, which shortens the lifetime of Ps, was also observed[20]. Such a temperature effect can be explained by the

increase in the thermal vibrations of the atoms in the crystal lattice at higher temperatures, which leads to density variations; the volume available to the Ps atoms is thus reduced, and their lifetime is shortened. The density effect and the temperature effect act in opposite directions, and may lead to maxima in the lifetime, as shown in Figure 10, where the observed lifetime of *o*-Ps in Teflon is plotted as a function of V^*.

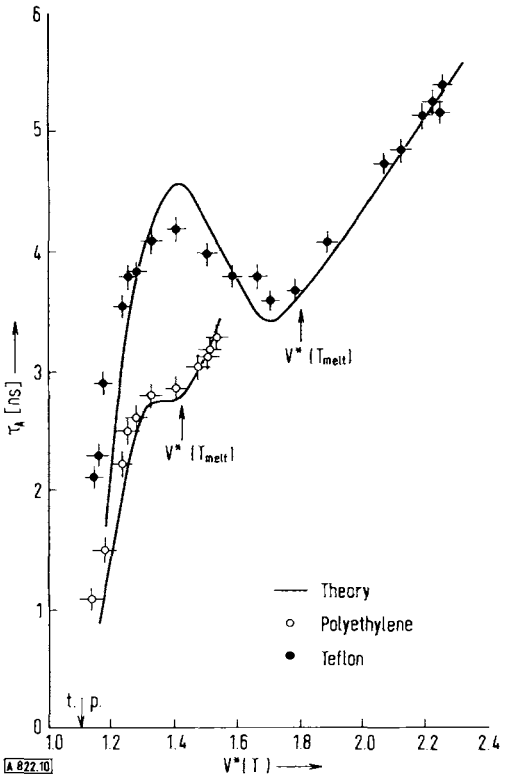


Fig. 10. Lifetime (τ_A) of the long-lived component (*o*-Ps) of the positron annihilation in Teflon and polyethylene as a function of the reduced free cell volume V^* [cf. eq. (14)].

However, it must be pointed out that the free volume model is valid only when no other reactions occur apart from pick-off.

6.2. *ortho-para* Conversion

Under the influence of a magnetic field, such as is produced *e.g.* by the presence of paramagnetic ions in solution, conversion of *o*-Ps into *p*-Ps or *vice versa* can occur.

In its simplest form, the spin conversion can be formulated as a direct spin exchange:

$$\uparrow M + {}^3S_1(\downarrow\uparrow) \rightleftarrows \downarrow M + {}^1S_0(\uparrow\downarrow) \qquad (15)$$

In this case, the *ortho-para* conversion is associated with a reversal of the spin of the paramagnetic particle. However, *Ferrell*[21] was able to show quantum-mechanically that the only condition for such a spin conversion is the encounter of the *o*-Ps or *p*-Ps with an atom or molecule having unpaired electrons; spin flip or electron exchange are not absolutely essential ingredients of the *o-p* or *p-o* conversion of positronium. For example, oxygen molecules in the triplet state can initiate the *o-p* conversion of Ps without themselves undergoing a simultaneous triplet-singlet transition.

$$O_2\uparrow + {}^3S_1(\uparrow\uparrow) \rightarrow O_2\uparrow + {}^1S_0(\downarrow\uparrow) \qquad (16)$$

The result of an *o*-Ps → *p*-Ps conversion is again a decrease in the lifetime of the positron, since it is now in the form of the much shorter-lived *p*-Ps ($\tau_S^0 = 1.25 \times 10^{-10}$ s), which decays with emission of two photons.

The detection of the *ortho-para* conversion can be used as a highly sensitive detection method for the presence of free radicals and other paramagnetic species, particularly in gaseous systems.

Thus on the basis of results in the system Ar—NO, *Goldanskii et al.*[3] were able to show that as little as about 10^{13} radicals or atoms per cm^3 of gas can be detected by this method.

6.3. Chemical Reactions of Positronium

The chemical reactions of the Ps atom will be discussed at length in Sections 8—11. For the present, it is sufficient to point out that they all lead to a decrease in the lifetime of *o*-Ps. The oxidation of *o*-Ps, for example, leads to the formation of a free positron, whose average lifetime in any medium is shorter than that of *o*-Ps in the same medium. This is also true of the lifetimes of the positron or positronium compounds with substrate molecules or fragments; these decompose mainly by two-quantum annihilation (Fig. 8).

7. Experimental Methods for the Observation of the Annihilation of Positrons

As indicated earlier, there are two parameters, *i.e.* the positronium yield (P^0) and the average lifetime of the positron (τ), whose observation can yield information about the interaction of positrons with matter. Three different experimental methods are available.

7.1. Determination of the Probability of Three-Quantum Annihilation

Direct measurement of the probability of three-quantum annihilation is possible with the triple-coincidence arrangement shown in Figure 11[22]. This arrangement ensures that only γ quanta that reach all three detectors simultaneously, as in the emission of photons by three-quantum annihilation, are recorded.

The method can therefore detect the presence of *o*-Ps, but does not enable one *e.g.* to decide which factor (τ_T, the lifetime of *o*-Ps, or P^0, the Ps yield) is responsible for the change in the three-quantum annihilation rate ($R_{3\gamma}$), since these quantities are related as follows:

$$R_{3\gamma} \approx 3/4 P^0 \frac{\tau_T}{\tau_T^0} + \frac{1}{372}(1 - P^0) \qquad (17)$$

This means that experimental data obtained in this way do not show whether a change in $R_{3\gamma}$ is due to reactions of Ps or to inhibited Ps formation.

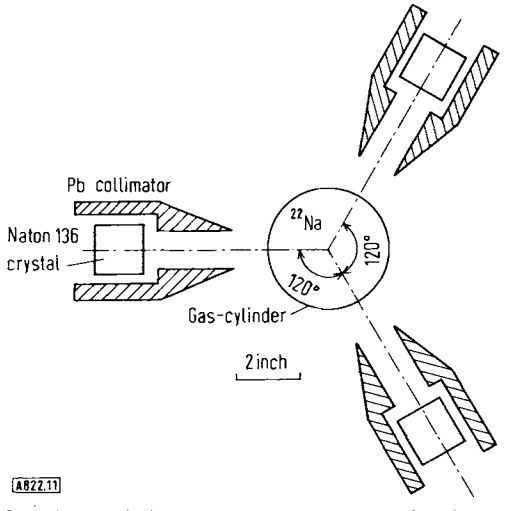


Fig. 11. Typical experimental arrangement for determining the frequency of 3γ coincidences [22].

7.2. Determination of the Angular Distribution in Two-Quantum Annihilation

It can be shown that in two-quantum annihilation the deviation of the angle between the emission directions of the two 0.51 MeV photons from 180° corresponds to

$$\Delta\theta \sim 2\,v/c \qquad (18)$$

where c is the velocity of light and v is the velocity of the center of gravity of the electron and the positron in the system in question[23–25].

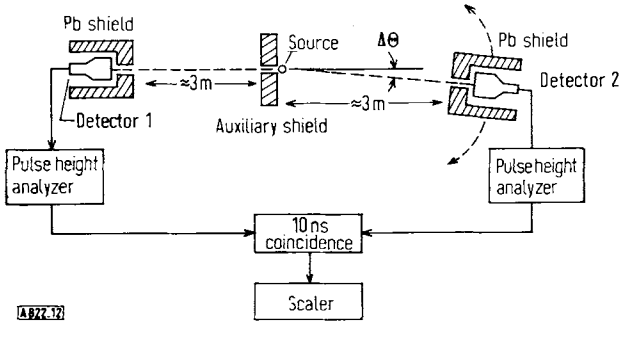


Fig. 12. Typical experimental arrangement for determining the angular distribution (Δθ = deviation from 180°).

The deviation, which is only a few milliradians in all practical cases, can be measured with the aid of the system outlined in Figure 12. The 0.51 MeV photons produced in the same act of annihilation are recorded in this system as a function of Δθ. The form of such angular distribution curves provides a basis for conclusions both regarding the various annihilation mechanisms and regarding the reactions of Ps and its formation.

Free positrons usually still have low kinetic energies when they are annihilated; the angle between the two annihilation quanta therefore differs considerably from 180°, and leads to the "broad" component in the angular distribution curves (Fig. 13). The heavier *para*-positronium, on the other hand, loses most of its kinetic energy very rapidly after its formation, and at the instant of annihilation, it is close to or in thermal equilibrium with its environment; the photons emitted in this case deviate only slightly from 180°, and are responsible for the occurrence of the "narrow" component in the angular distribution curves. Ps formation can therefore be very readily recognized from the presence of the "narrow" component (Fig. 13).

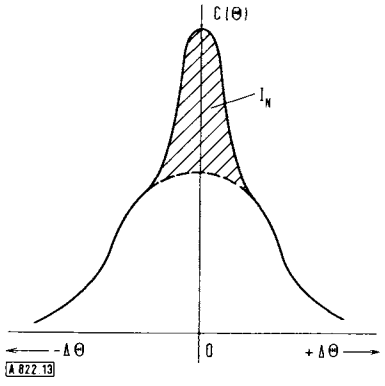


Fig. 13. Angular distribution in two-quantum annihilation: frequency of 2γ coincidences (C(θ)) as a function of Δθ (cf. Fig. 12). The "narrow" component (I_N) is shaded.

However, this method is not confined to the detection of Ps, but can also be used to follow its various reactions. Increased *ortho-para* conversion, for example, causes more positrons to be annihilated in the form of *p*-Ps, and this can be detected by a *relative* increase in the intensity of the narrow component. Oxidation and pick-off of *o*-Ps, on the other hand, cause increased two-quantum annihilation, with a relatively wide angular distribution; the intensity of the "broad" component increases, while that of the "narrow" component does not change. However, if *p*-Ps is also involved in the chemical reaction or in the pick-off (this is generally possible only if these reactions are much faster than the self-annihilation of *p*-Ps), the result is an *absolute* weakening of the "narrow" component instead of a *relative* weakening.

7.3. Determination of the Average Lifetime of the Positron

A direct method that can be used to obtain both the lifetime of the positron or positronium and in most cases the positronium yield P^0 makes use of the "delayed coincidence" technique[26].

The positron source most commonly used for this purpose is ^{22}Na. This decays with a half life of 2.58 years with emission of a positron to give an excited ^{22}Ne nucleus, which passes to the ground state with emission of a 1.28 MeV photon (Fig. 14). Since the excited ^{22}Ne nucleus has an average lifetime of only about 3 ps, it is justifiable, for the purposes of the present investigation, to assume that the two particles are emitted simultaneously. To determine the

lifetime of the positron, one first observes the appearance of the 1.28 MeV photon, and waits until the annihilation of the positron takes place, as indicated by the 0.51 MeV annihilation photons (two-quantum annihilation). The time difference corresponds to the lifetime of the positron. Since the time intervals involved are in the region of a few nanoseconds (ns), the principle of "delayed coincidence" is used for their measurement. A typical arrangement is shown schematically in Figure 15[27].

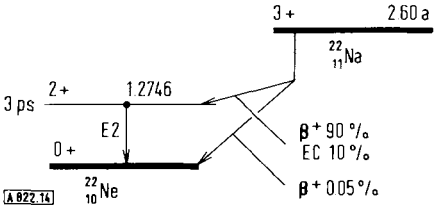


Fig. 14. Decay scheme for ^{22}Na.

The 1.28 MeV photon is observed with a plastic detector (*e.g.* Naton 136). The output signal from the anode of the attached photomultiplier serves as the starting signal for the time-pulse height converter (TPHC). The second similar detector observes one of the two annihilation photons (0.51 MeV). The signal from this detector serves as the stop signal for the TPHC. The amplitude of the output signal of the TPHC is thus proportional to the time difference between the arrival of the start signal and that of the stop signal in the TPHC. The time calibration of the system is effected by a built-in delay unit. The signal from the TPHC passes into a multichannel pulse height analyzer, and is recorded in one of the channels according to its pulse height, provided that the instrument has been activated by a signal from the "slow" coincidence unit (see below).

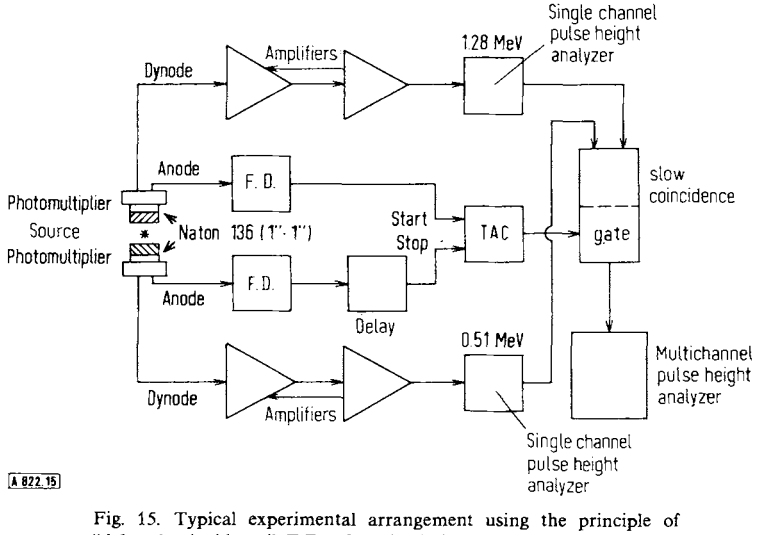


Fig. 15. Typical experimental arrangement using the principle of "delayed coincidence". F.D. = fast discriminator.

To reduce the number of "random coincidences" and to improve the time resolution of the measuring equipment, it is recommended that a second "slow" coincidence circuit be incorporated. For this purpose, a signal from the dynode of the photomultiplier, after passage through a preamplifier and a main amplifier, is led into single-channel pulse height analyzers, one of which passes only signals corresponding to a photon energy of 1.28 MeV, while the other passes only signals corresponding to a photon energy of 0.51 MeV. If two signals filtered in this way by the two single-channel pulse height analyzers enter the "slow" coincidence unit within a specified period (usually 1 μs), they activate the multichannel pulse height analyzer (see above) for a short time and allow the signals arriving from the TPHC during this time to be recorded.

Since the electronic time measurement begins when a positron is formed, the situation is the same as if a large number of positrons was present at a time $t=0$ and decayed with the annihilation constant λ. This is a first order reaction: $T(t)$. The number N of coincidences observed can be plotted logarithmically as a function of time t, and if only one annihilation mechanism is operating, the result should be a straight line whose slope is determined by λ or $1/\tau$ (Fig. 16a). Because of the inadequate time resolution of the measuring arrangement, however, each point on this line is "blurred". The degree of "blurring", and hence the quality of the time measurement, can be found from the "prompt" time spectrum, which can be recorded with the aid of a ^{60}Co source. On radioactive decay, ^{60}Co emits a 1.31 MeV and a 1.17 MeV photon practically simultaneously. The coincidence measurement of these two photons should therefore exhibit no delay, and should give a sharp line at $t=0$. In practice, however, one obtains the spectrum shown in Figure 16b, which exhibits a Gaussian distribution: $P(t)$. The resulting "blurring" of the function $T(t)$ by the measuring arrangement with a resolution function $P(t)$ is finally shown in Figure 16c.

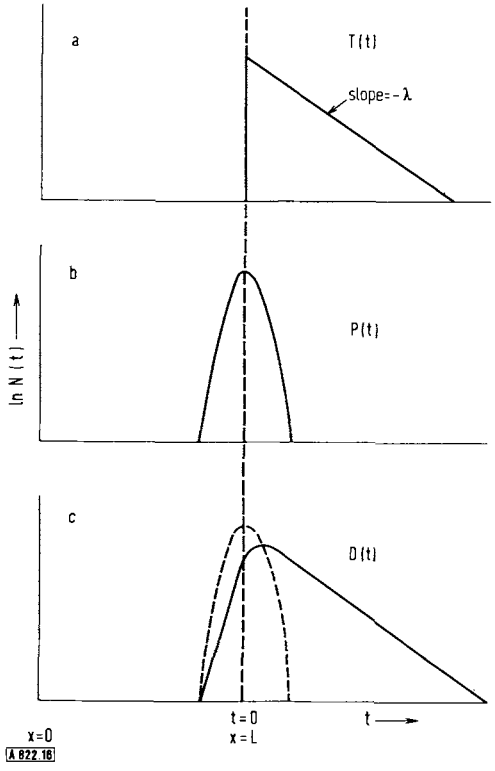


Fig. 16. a) Theoretical $T(t)$ curve for positrons that are annihilated in a first order reaction in the interval between t and $t+dt$; b) "prompt" time spectrum (^{60}Co): $P(t)$ curve; c) "blurring" of the $T(t)$ function in a measuring arrangement with the resolution function $P(t)$: $D(t)$ curve.

A positron lifetime spectrum recorded in this way, which can be resolved into two components, is shown in Figure 17. The number of coincidences (ordinate) is plotted logarithmically as a function of the time that elapses between the start and stop pulses in the TPHC (abscissa). It can be shown mathematically that the right-hand part of the spectrum can be interpreted as a multiexponential function of the form:

$$D(x) = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t} \qquad (19)$$

where λ_1 and λ_2 are the annihilation constants for the various modes of annihilation of the positron or of positronium, and A and B are constants. These quantities can be determined either graphically from the curve or by suitable computer programs. The relative number of positrons or Ps atoms that disappear with one of these annihilation constants is given by the area (I) under the corresponding component in the time spectrum, integrated from $t=0$ to $+\infty$, compared with the total area of the time spectrum.

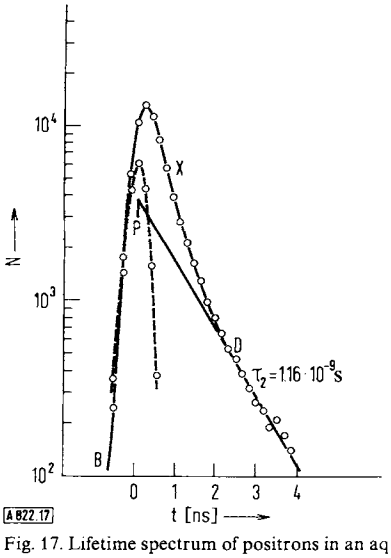


Fig. 17. Lifetime spectrum of positrons in an aqueous $KMnO_4$ solution (0.01 M; pH = 11), resolved into two components. Broken curve: "prompt" spectrum (^{60}Co). N = number of coincidences.

The time $t=0$ is given by the position of the center of the "prompt" spectrum. Details of the evaluation of such a spectrum will be described in the next section.

In most cases, two components can be isolated from the time spectrum. It is usual to attribute the short-lived component to the decomposition of the free positron and the annihilation of *p*-Ps, whereas the long-lived component is attributed to the annihilation of *o*-Ps. This seems justifiable if only a simple pick-off mechanism is involved. If, on the other hand, other reactions of *o*-Ps take part in the process, the relation between τ_2 and λ_2 and the annihilation constants and the *o*-Ps yield is much more complicated, and must be established separately for each individual case (see Section 8).

8. Positronium Chemistry in Aqueous Solutions

The fact that Ps atoms can exist in condensed matter and have proved to be relatively stable in the chemical sense led at an early date to investigations on the reactions of Ps with H_2O molecules and with ions in aqueous solutions.

Since the structure of positronium is very similar to that of the hydrogen atom, its reactivity should also be comparable with that of the H atom. However, as will be shown, there are a number of fundamental differences in the manner in which they react.

Whereas the reaction of Ps in pure water can be best described by a reaction scheme in which the *o*-Ps atoms formed decompose by pick-off annihilation with emission of two photons, other reactions besides the pick-off process can also cause the decomposition of *o*-Ps in aqueous solutions of salts (cf. Fig. 18).

It is admittedly difficult to correlate the many possible reactions and their reaction constants with the quantities obtainable by experiment (P_T^0, the *o*-Ps yield, and τ, the lifetime of the positron or positronium). By careful investigation of these experimental quantities as a function of the

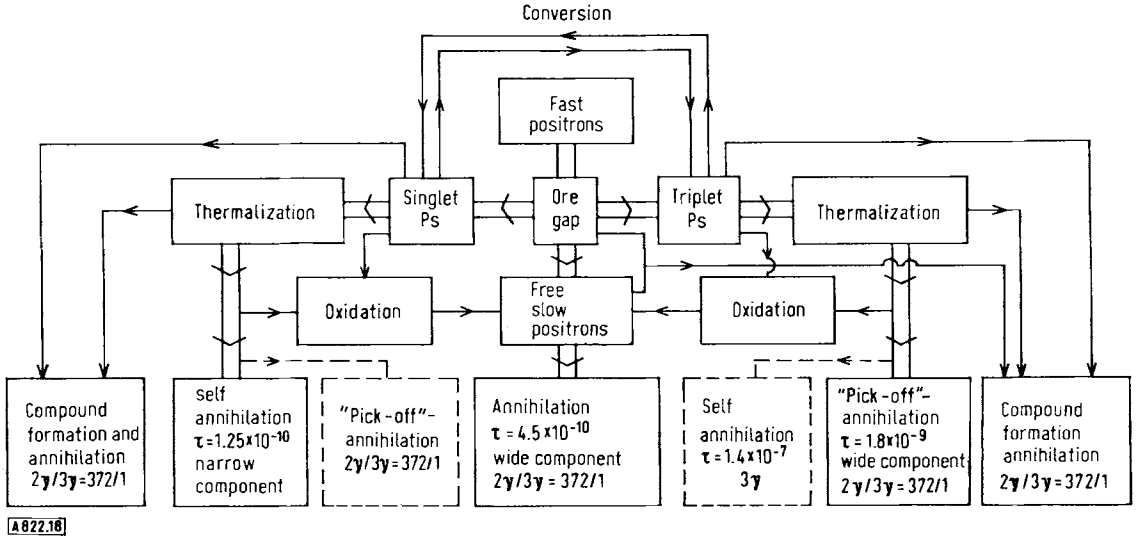


Fig. 18. Flow scheme of the possible reactions of positrons in aqueous solutions.

concentration or of the temperature, however, it is possible in many cases to distinguish the various reaction types and to measure the reaction rate constants.

The evaluation of the results of positron lifetime measurements can be demonstrated by the example of two investigations by *Horstman*[29] and by *Williams* and *Ache*[27].

A relation had been observed in earlier investigations[30] between the chemical oxidation potential of the dissolved compound and the *o*-Ps annihilation constant in the solution. This indicated that the oxidation of Ps should have an activation energy (which should lead to a temperature dependence of the oxidation rate), provided that the observed decomposition of *o*-Ps does in fact proceed by an oxidation mechanism.

The authors therefore investigated the temperature dependence of the *o*-Ps annihilation in aqueous solutions of $HgCl_2$, $SnCl_4$, $SbCl_3$, $PdCl_2$, and $KMnO_4$. These compounds are not paramagnetic; spin conversion is therefore very unlikely, and it was possible to confine the analysis of the results to the pick-off annihilation and to the possible oxidation of *o*-Ps in the solution.

The kinetics will first be considered in general for a solution in which both the annihilation of free positrons and the pick-off annihilation and the oxidation of positronium with regeneration of a free thermal positron are possible[27,29,31]. If the formation of a positron is denoted by $t=0$ and if the probabilities of finding this positron in the various states at a time t are P_S=*p*-Ps, P_T=*o*-Ps, and P_F=free positron, the time dependence of these quantities can be expressed by:

$$dP_S/dt = -(\lambda_S + \lambda_P + \lambda_O)P_S \quad (20)$$

$$dP_T/dt = -(\lambda_T + \lambda_P + \lambda_O)P_T \quad (21)$$

$$dP_F/dt = -\lambda_F P_F + \lambda_O(P_S + P_T) \quad (22)$$

λ_S and λ_T = rate constants for self-annihilation of *p*-Ps and of *o*-Ps respectively;
λ_P = rate constant for pick-off annihilation of Ps;
λ_O = rate constant for oxidation of Ps;
λ_F = rate constant for annihilation of the free positron.

It will be assumed below that λ_O is the only temperature-dependent quantity, and that λ_T may be regarded as negligible. Solution of the above equations then gives:

$$P_S = P_S^0 \exp[-(\lambda_P + \lambda_O + \lambda_S)t] \quad (23)$$

$$P_T = P_T^0 \exp[-(\lambda_P + \lambda_O)t] \quad (24)$$

$$P_F = \left(P_F^0 - P_T^0 \frac{\lambda_O}{\lambda_F-(\lambda_O+\lambda_P)} - P_S^0 \frac{\lambda_O}{\lambda_F-(\lambda_O+\lambda_P)-\lambda_S}\right)\exp[-\lambda_F t] + \frac{P_T^0 \lambda_O}{\lambda_F-(\lambda_P+\lambda_O)}\exp[-(\lambda_P+\lambda_O)t] + \frac{P_S^0 \lambda_O}{\lambda_F-\lambda_S-(\lambda_P+\lambda_O)}\exp[-(\lambda_P+\lambda_O+\lambda_S)t] \quad (25)$$

The coincidences observed in the time spectra, because of the experimental arrangement used, are exclusively the result of two-quantum annihilation. If one disregards the small fraction of free positrons that decay with emission of three photons, the two-quantum annihilation rate $R_{2\gamma}$ is found to be:

$$R_{2\gamma}(t) = \lambda_S P_S + \lambda_F P_F + \lambda_P(P_S + P_T) \quad (26)$$

This is a multiexponential function of the form:

$$R_{2\gamma}(t) = A\exp[-\lambda_F t] + B\exp[-(\lambda_S + \lambda_O + \lambda_P)t] + C\exp[-(\lambda_P + \lambda_O)t] \quad (27)$$

Since in general $\lambda_S \gg \lambda_O + \lambda_P$ and $\lambda_S \simeq \lambda_F$, the first two terms of equation (27) cannot be distinguished experimentally; they will occur together in the short-lived component of the time spectrum, τ_1 (Fig. 17).

On the other hand, the observed rate constant of the second, long-lived component of the time spectrum, λ_2, is determined by the sum of λ_P and λ_O [third term in eq. (27)].

$$1/\lambda_2 = \tau_2 = 1/(\lambda_P + \lambda_O) \quad (28)$$

Separate experiments in pure water, where only pick-off annihilation of Ps occurs, gave $\lambda_P = 0.65\ ns^{-1}$[27,29]. No temperature dependence was observed between 25 and 100 °C, and this value was taken as the pick-off annihilation rate in the dilute solutions investigated here. It was thus possible to determine λ_O from the experimentally observed temperature dependence of τ_2 (for $KMnO_4$; see Table 1), and to find the activation energy for the oxidation from the Arrhenius equation (Table 2). The activation energies found were between 0.05 and 0.2 eV.

P_T^0, the *o*-Ps yield, can be obtained by integration of the part of eq. (26) that contains the exponent $\exp[-(\lambda_P+\lambda_O)t]$ over all times. This leads to the following relation between the intensity of the long-lived component I_2 and P_T^0:

$$I_2 = [1 + \lambda_O/(\lambda_F - \lambda_2)]\,P_T^0 \quad (29)$$

Though I_2 exhibits the temperature dependence shown in Table 1, the *o*-Ps yield calculated in this way remains constant over the entire temperature range investigated (Table 2).

The temperature dependence of the oxidation rate in the solutions investigated indicates that the *o*-Ps atoms, which are formed with kinetic energies of a few eV, are oxidized only after they have reached thermal equilibrium with their environment. This can also be deduced from the linear dependence of $1/\lambda_O$ on the viscosity η of the solution (Fig. 19) and from the low activation energy of the oxidation reactions (0.05—0.2 eV), which differ only slightly from the activation energy for the viscosity in water (0.06 eV). All these findings point to a diffusion-controlled oxidation process in the solutions.

In aqueous $KMnO_4$ solutions, the chemical oxidation potential is a function of the pH. In our investigation[27], however, the oxidation constant λ_O showed no dependence on the pH of the solution, which was varied between 2 and 11 (Table 1). This is in agreement with the results obtained by *Goldanskii*, who carried out angular distribution measurements in the same system and was also unable to find any dependence on the pH.

Table 1. Average lifetime of *o*-Ps in aqueous $KMnO_4$ solutions at various temperatures, concentrations, and pH values [27].

T(°C)		30		45		60		75	
pH	c(mole/l)	τ_2 (ns)	I_2 (%)	τ_2 (ns)	I_2 (%)	τ_2 (ns)	I_2 (%)	τ_2 (ns)	I_2 (%)
2	0.1	0.41±0.02	—	0.40±0.02	—	0.41±0.02	—	0.41±0.02	—
7	0.1	0.42±0.02	—	0.43±0.02	—	0.42±0.02	—	0.42±0.02	—
11	0.1	0.40±0.02	—	0.42±0.02	—	0.41±0.02	—	0.46±0.02	—
2	0.01	1.6 ±0.03	31.1	1.05±0.03	34.1	0.99±0.04	35.1	0.94±0.04	38.4
7	0.01	1.16±0.03	31.9	1.03±0.03	33.2	0.92±0.03	40.0	0.88±0.04	42.5
11	0.01	1.16±0.03	32.1	1.05±0.04	32.8	0.95±0.07	35.0	0.83±0.04	45.0
2	0.001	1.73±0.03	26.6	1.70±0.04	26.1	1.64±0.04	29.1	1.52±0.04	31.4
7	0.001	1.69±0.03	26.0	1.63±0.04	27.9	1.62±0.04	27.7	1.58±0.04	28.6
11	0.001	1.68±0.03	26.7	1.61±0.04	26.7	1.57±0.04	26.7	1.50±0.03	28.9

Table 2. Activation energy and *o*-Ps yield (P_T^0) in various oxidizing solutions [27, 29].

Substrate	pH	c(mole/l)	E (eV)	P_T^0 (%)
$KMnO_4$	2	0.01	0.12	24.4
	7	0.01	0.14	24.1
	11	0.01	0.16	24.6
	2	0.001	0.44	26.3
	7	0.001	0.15	24.4
	11	0.001	0.11	—
$SnCl_4$	—	0.25	0.10	16
$SbCl_3$	—	0.11	0.13	23
$PdCl_2$	—	0.008	0.03	25
		0.018	0.07	16
$HgCl_2$	—	0.015	0.16	34
		0.020	0.16	30
		0.031	0.10	33

Jackson and *McGervey*[32], who investigated the oxidation of Ps in solutions of MnO_4^-, IO_3^-, and Hg^{2+}, pointed out important differences between the chemical oxidation potential and the ability of an ion to oxidize Ps atoms. Both the short lifetime and the low concentration of Ps in solution rule out the establishment of an equilibrium such as occurs in conventional chemical reactions. It follows that

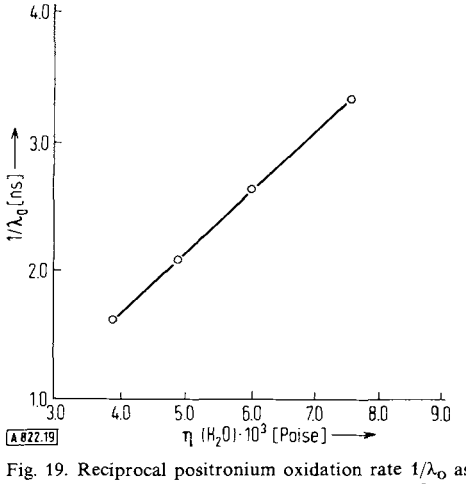


Fig. 19. Reciprocal positronium oxidation rate $1/\lambda_O$ as a function of the viscosity of an aqueous solution (0.01 M $KMnO_4$; pH = 11).

chemical and physical parameters determined by equilibrium measurements can have at most only limited application in positronium chemistry. It is therefore probably more appropriate to regard the oxidation of Ps as a kinetic process, *i.e.* the observed oxidation constants reflect the ability of a single ion to abstract an electron from Ps.

Kinetic equations can be established for spin conversions and other reactions of Ps in solution in the same way as for the oxidation of Ps, and can be used to determine the reaction rate constants for spin conversion *etc.* from the experimental data. A number of ions and compounds that can cause oxidation, spin conversion, or both are listed in Table 3 together with the rate constants for the corresponding reactions[3]. It should be pointed out that λ_O is related to the conventional reaction rate (k) l mol^{-1} s^{-1} by: $\lambda_O = k[s]$ (s = substrate concentration (in mol/l)). It is interesting to note that ions such as U^{4+}, Ti^{3+}, and Ce^{3+}, though paramagnetic, do not appear to cause spin conversion.

Table 3. Reaction rate constants for reactions of positronium in aqueous solutions [3].

Acceptor	K_R (cm^3/s)	Acceptor	K_R (cm^3/s)
Fe^{3+}	2×10^{-11}	$Cr_2O_7^{2-}$	1.5×10^{-10}
Cu^{2+}	8×10^{-12}	CrO_4^{2-}	1.5×10^{-11}
Ti^{4+}	3.3×10^{-12}	MnO_4^-	2.7×10^{-11}
UO_2^{2+}	1.2×10^{-11}	Fe^{2+}	3.5×10^{-12}
Ce^{4+}	2.8×10^{-11}	Mn^{2+}	2.5×10^{-12}
Sn^{4+}	0.9×10^{-11}	Ni^{2+}	2.75×10^{-12}
Cr^{3+}	3.3×10^{-12}	Co^{2+}	3.3×10^{-12}
U^{4+}	$<10^{-14}$	H_2SO_4	$<10^{-14}$
Ti^{3+}	$<10^{-14}$	Na_2SO_4	$<10^{-14}$
Ce^{3+}	$<10^{-14}$	NaCl	$<10^{-14}$
Pb^{2+}	$<10^{-14}$	$Fe(CN)_6^{4-}$	$<10^{-14}$
Nd^{3+}	$\approx 10^{-13}$		

Goldanskii[3] compared the reaction rate constants of the reactions of Ps with Fe^{3+} and Fe^{2+} (see Table 3) with data for the reactions of hydrogen atoms with the same ions in aqueous solution (Fe^{3+}: 1.5×10^{-13} cm^3/s; Fe^{2+}: 3.3×10^{-14} cm^3/s), and found that positronium reacts about one hundred times as fast as the hydrogen atom in both cases.

An explanation for this difference will be largely dependent on whether one assumes that the observed reaction rate constant K_R is controlled by diffusion (diffusion rate constant K_D), *i.e.* by the number of collisions between the solvent cells containing the Ps or the Fe ion, or by the reaction probability per collision of the two reactants (kinetic rate constant K_k) within a solvent cell. Since these quantities are related as follows:

$$1/K_R = 1/K_D + 1/K_k \qquad (30)$$

$K_R \approx K_D$ in the first case, and $K_R \approx K_k$ in the second.

If the highest observed value for K_R from Table 3 ($Cr_2O_7^{2-}$: 1.5×10^{-10} cm^3/s) is taken as the diffusion constant K_D, the "true" kinetic constant of the ($Ps + Fe^{3+}$) reaction is

found to be 2.3×10^{-11} cm^3/s. If it is also assumed that the difference between the kinetic constants for the (Ps+M) and (H+M) reactions (M = Fe^{2+} or Fe^{3+}) is determined only by the difference in the activation energies E, and that the number of collisions of the reactants is the same in both cases, it is found that $E_H - E_{Ps} \approx 3$ kcal/mole, which in *Goldanskii*'s opinion[3] could point to a "tunnel effect" for the Ps reaction. However, if the ratio of the number of collisions in the two systems is given by v_{PsM}/v_{HM} or $\sqrt{m_H/m_{Ps}} \approx 30$, the result would be practically perfect agreement of the activation energies of the reactions of H and Ps with Fe^{2+} or Fe^{3+}. It is not possible at present to decide between these alternatives. In general, however, it can be said that the determination of the true kinetic constants K_k of Ps reactions, *e.g.* by extrapolation to extremely low viscosities ($K_D \gg K_k$), offers interesting possibilities for the study of the reaction mechanisms in conjunction with collisions of solvent cells.

The influence of complex formation and the accompanying spin delocalization or "blurring" of the electron density in the outer sphere of complexes (in solution) on the reactions of positronium was also investigated by *Goldanskii et al.*[33].

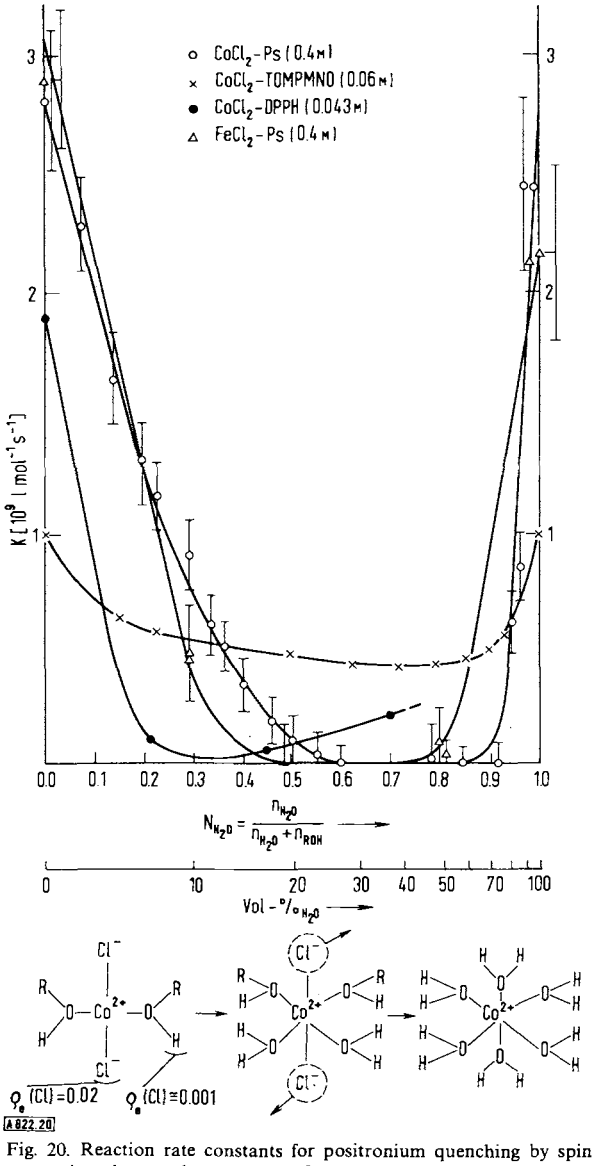


Fig. 20. Reaction rate constants for positronium quenching by spin conversion due to the presence of paramagnetic centers in water-propanol mixtures (0.01 M $CoCl_2$ or $FeCl_2$) as a function of the composition of the solvent; action of tetraoxymethylpentamethylene-nitroxide (TOMPMNO) or diphenylpicrylhydrazyl (DPPH) on the substrate [3]. $K = \lambda_0$/[solute conc. (mole/l)].

These authors determined the reaction rate constants for spin conversions caused by the presence of paramagnetic centers in Co^{2+} or Fe^{2+}-water-propanol mixtures having various compositions. A selection of the results are shown in Fig. 20 as a function of the solvent composition, the complex present in each case being indicated. The authors conclude from these investigations that the unpaired electrons of the paramagnetic central atom are blocked by the coordination sphere, and cannot affect the Ps reaction. The reaction rate constant of the spin conversion is therefore essentially determined by the concentration of the unpaired electrons in the ligands, *e.g.* on chlorine when the solvent is the alcohol, or on oxygen when the solvent is water. As can be seen from Fig. 20, the reaction rate constant reaches a maximum in the pure solvents, whereas the spin conversion is practically suppressed in mixtures containing between 50 and 80% of water. A possible explanation is that in mixtures having the composition mentioned, the electrons, which are concentrated on the oxygen of the solvate groups in this case, are blocked by formation of intermolecular hydrogen bridges with solvent molecules, and can no longer interact with the Ps.

The influence of the delocalization of unpaired electrons on Ps reactions in the system $Co(ClO_4)_2 \cdot 6H_2O$-water-propanol can be explained in a similar manner[3] (Fig. 21). In this case, the reaction rate constant is relatively small even in pure propanol, since, unlike in the case described above, no chlorine atoms function as carriers of unpaired electrons, and the oxygen atoms of the alcohol groups are accessible only with difficulty as sites of unpaired electrons. On replacement of the alcohol groups by water groups, in which access to the oxygen is sterically less hindered, the rate constants increase considerably.

On the other hand, complex formation and spin delocalization appear to have little effect on the oxidation of Ps. *Goldanskii et al.*[34] compared lifetimes and intensities of the long-lived components in time spectra of Fe^{III} compounds, some of which exhibited no complex formation in aqueous solution (*e.g.* perchlorate), while others exhibited partly strong complex formation (sulfates, cyanoferrates); however, they were unable to find any dependence of the oxidation constants on the complex that was present.

Special interest has been shown in recent years in the question of the existence of positronium compounds in aqueous solutions.

Green and *Bell*[35] observed a large decrease in I_2, the intensity of the long-lived component, with increasing ion concentration in the positron time spectra of aqueous nitrite and nitrate solutions, whereas the corresponding lifetime τ_2 was practically unchanged. The explanation given for this effect calls for a mechanism in which the NO_2^- or NO_3^- ions capture positrons, and so compete with the Ps formation. However, it was not very clear why such a capture should be confined to these two ions if other anions showed no effect of this nature. *McGervey* and *Jackson*[32] therefore considered the possibility that the Ps is oxidized by these ions before it has reached thermal energies. In this case, its lifetime would be shortened to such a degree that

it would appear together with the result of the *p*-Ps annihilation and the annihilation of the free positron in the short-lived component of the time spectrum τ_1. The only visible result of this would be a decrease in the number of *o*-Ps atoms that reach thermal energies and then react, which would be seen mainly in a change in I_2 while τ_2 remained constant. The results of angular distribution measurements[36], on the other hand, indicate that some of the positrons annihilated in these solutions decompose *via* a state that is not identical either with that of the free positron or with that of *o*-Ps; this would support the hypothesis of a positronium compound.

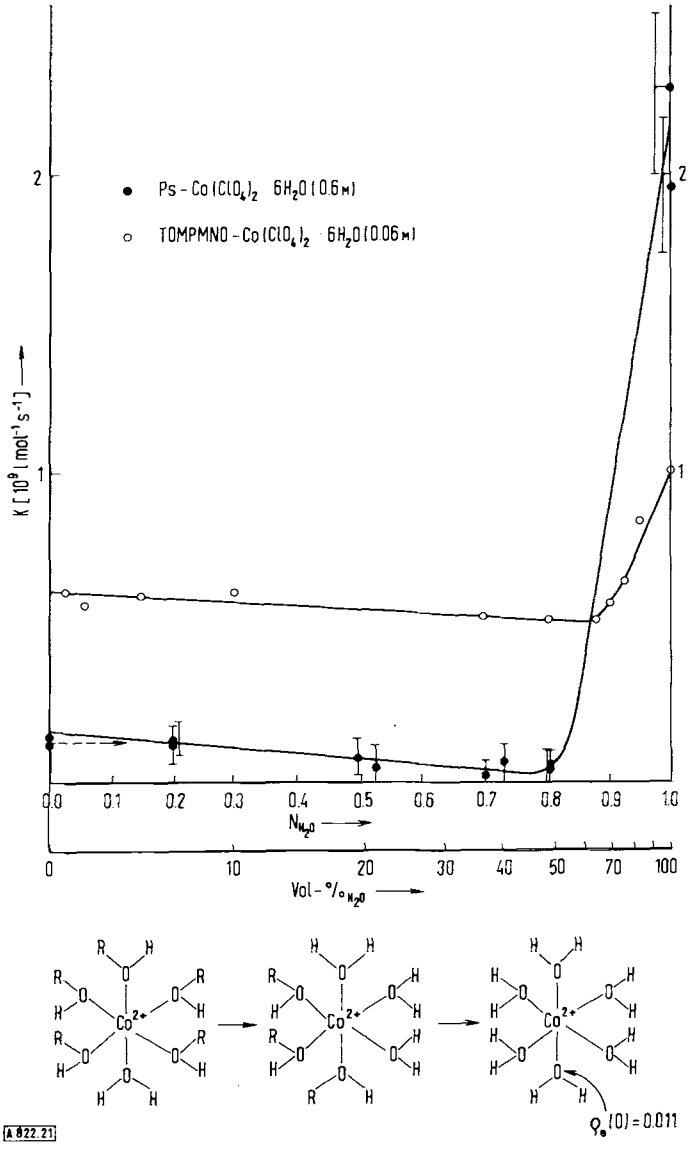


Fig. 21. Reaction rate constants for positronium quenching with $Co(ClO_4)_2 \cdot 6H_2O$ (0.6 M), with and without TOMPMNO, as a function of the composition of the solvent water-propanol [3]. $K = \lambda_0/$[solute conc. (mole/l)].

A similar possibility was suggested by *Tao* and *Green*[37], who recently reinvestigated the problem of Ps compound formation by recording the positron lifetime spectra for a series of oxy acids such as H_3PO_4, H_2SO_4, $HClO_4$, and HNO_3 and for HCl, HF, NH_3 (all in aqueous solution), and H_2O. The observed intensities I_2 for the aqueous oxy acids are shown in Figure 22. They exhibit a pronounced dependence on the acid concentration, whereas the corresponding lifetime τ_2 is practically constant. Linear extrapolation of these curves (to an acid mole fraction of 0) leads in every case to a value of 17% for I_2, which differs considerably from I_2 in pure water. The authors therefore assume a common mechanism for the change in I_2, which is effective at low acid concentrations, *i.e.* the oxidation of "hot" (not thermal) *o*-Ps atoms by H^+ ions *via* simple electron transfer.

$$Ps + H^+(aq.) \rightarrow Ps^+(or\ e^+) + H(aq.) \tag{31}$$

It can also be seen from the same figure that the I_2 values remain approximately constant in the concentration range between $n_{acid} = 0.3$ and 0.7. However, the plateau values which I_2 reaches at this concentration range in the various systems differ markedly. Changes in the "Ore gaps" as a result of the acid addition in these systems could be ruled out as an explanation for this effect, since this could not justify the observed decrease in I_2 in $HClO_4$—H_2O and HNO_3—H_2O. (One would normally expect the presence of an additive to widen the Ore gap, since Ps can then be formed not only in the Ore range of the solvent, in this case H_2O, but also in that of the additive, in this case the acid, with the result that the Ps yield should be increased; cf. also the remarks in Section 9.) The other possibility, *i.e.* that positron capture, as originally postulated by *Green* and *Bell*[35] in the case of NO_3^-, is the reason for the relative position of the I_2 plateaus in the various systems in Figure 22, is opposed by the fact that, by analogy with the corresponding hydrogen compounds, one would then expect the formation or the stability of $e^+ClO_4^-$, $e^+HSO_4^-$, and $e^+H_2PO_4^-$ to be much higher than that of $e^+NO_3^-$, since HNO_3 is much more strongly dissociated than the other acids. The tendency of the I_2 values should thus be the reverse of that shown in Figure 22. *Tao* and *Green* were therefore convinced that the reaction mechanism that occurs in these systems includes the formation of a Ps compound, *e.g.*:

$$Ps + H_2PO_4^- \longrightarrow PsO + H_2PO_3^- \tag{32}$$

For the formation of a stable Ps compound to be possible in a reaction of the type

$$Ps + AB \longrightarrow PsA + B \tag{33}$$

in general, the dissociation energy of the Ps compound (D_{PA}) must be positive. Moreover, the minimum energy that must be supplied by the positronium to enable the reaction to take place is determined by $D_{AB} - D_{PA}$, where D_{AB} is the dissociation energy of the compound AB.

If $D_{AB} - D_{PA} > E_{therm.}$, the reaction cannot take place with thermal Ps atoms. $D_{AB} - D_{PA}$ is thus the lower energy limit for these reactions if the activation energy can be disregarded. In the case $D_{AB} - D_{PA} < 0$, on the other hand, the reaction can also proceed at thermal energies.

The following reaction is found for the intensity of the long-lived component, I_2[32]:

$$I_2 \sim \frac{D_{AB} - D_{PA}}{V} \tag{34}$$

V = ionization potential of AB.

In the present example, values are known for D_{AB} (H_2PO_3—O, *etc.*). D_{PA} for PsO can, in the opinion of the

authors, be estimated by an empirical method. The values for D_{AB} are plotted as a function of I_2 (Fig. 23), I_2 being measured in the constant region of the curves in Fig. 22. According to equation (34), I_2 assumes the value 0 when $D_{AB}=D_{PA}$. D_{PA} can therefore be obtained by extrapolation of the curve in Figure 23 to $I_2=0$. The numerical evaluation

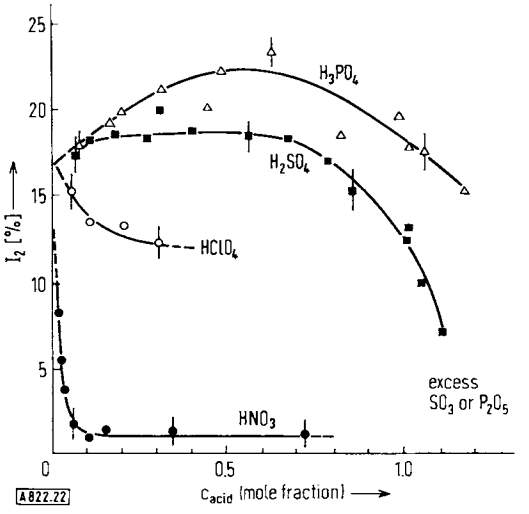


Fig. 22. Intensity I_2 of the long-lived component in positron lifetime spectra of some oxy acid-water systems [37].

gives $D_{PA}=2.2$ eV (dissociation energy of Ps—O) if the activation energy of the reaction is neglected. Since $D_{AB}-D_{PA}>0$, therefore, these compounds should be produced only by reactions of "hot" Ps atoms. The bond energies of a series of other Ps compounds were determined in a similar manner; they are listed in Table 4.

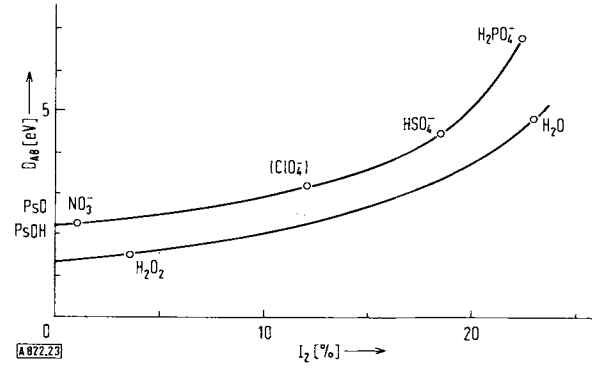


Fig. 23. Empirical relation between the values of D_{AB} and I_2.

Though the theory outlined above certainly corresponds to the experimental findings, it is not clear *e.g.* why the Ps—OH bond should be weaker than the Ps—O bond, since the corresponding hydrogen compounds exhibit the reverse trend (H—OH 5.0 eV; H—O 4.5 eV). There is no doubt that further investigations in this field will be necessary before any final and general explanation of the phenomena observed in aqueous solutions will be possible.

Table 4. Bond energies in positronium compounds [37].

Compound	D_{PA} (eV)
Ps—O	2.2±0.5
Ps—OH	1.3±0.5
Ps—Cl	2.0±0.5
Ps—F	2.9±0.5
Ps—CH_3	≈0.0
Ps—NH_2	≈0.0

9. Positronium Chemistry in the Gas Phase

A number of recent investigations have been carried out on the formation of positron compounds in gases below the "Ore gap".

Positrons whose kinetic energy has fallen below the lower Ore limit can be re-accelerated to the energies of the Ore gap in electric fields. It should theoretically be possible in this way to obtain practically 100% yields of positronium. However, if compound formation occurs below the Ore gap, these positrons are lost from the Ps formation, since they are annihilated rapidly in the bound form. The occurrence of e^+ compound formation can therefore be recognized by a decrease in the Ps yield superimposed on an increase under the influence of an electric field (cf. Fig. 7). The Ps yield was equated here, as in many other cases (not entirely correctly) to the intensity I_2 of the long-lived component in the time spectrum. *Hughes et al.*[39-40] observed that the presence of an electric field leads to the expected increase in I_2 in inert gases (He, Ne, Ar) and in H_2 and N_2, whereas no increase is observed in a number of other gases, such as CO_2, CH_4, C_2H_6, and $C_2Cl_2F_2$. Small quantities of this last group of gases, when added to argon, suppress the increased Ps formation found in pure Ar under the same experimental conditions. The authors explain these findings by compensation, or even over-compensation, of the effect of the electric field (acceleration of the positrons to Ore energies and hence increased Ps formation) by positron capture processes with compound formation in CO_2, CH_4, C_2H_6, and $C_2Cl_2F_2$.

Leung and *Paul*[41] reported interesting observations on argon-propane mixtures in the gaseous and liquid phases. The I_2 values increase considerably on transition from liquid to gaseous, and pass through a maximum at a propane content of 7—10% (Table 5). This would agree with the idea that Ps, if formed in the Ore range, has a greater probability in the liquid phase than in the gas phase of decomposing again in one of the next few collisions or of being destroyed by pick-off. C_3H_8 molecules could stabilize the Ps atoms by energy transfer in inelastic collisions; this effect should be smaller in the gas phase, which would explain the small changes found for I_2 as a function of the C_3H_8 concentration in this case.

Table 5. Positronium yields in gaseous and liquid argon-propane mixtures [41].

Substrate	I_2 (gas phase) (%)	I_2 (liquid phase) (%)
Ar	35.2±3.5	10±1
Ar+ 0.2% C_3H_8	(relative: P=1)	20±2
Ar+ 0.5% C_3H_8	(relative: P=0.96−0.97)	27±2
Ar+ 7 % C_3H_8		64±3
Ar+10 % C_3H_8	52.8±3.7	
Ar+22 % C_3H_8	45.1±5.0	
C_3H_8	43.0±2.7	39±2

Brandt and *Feibus*[42] calculated the influence on the Ps yield of small quantities of an additive whose ionization potential, and hence also its Ore gap, is lower than that of the substrate. They considered the possibility that positrons that have not been captured in the Ore gap of the substrate with Ps formation now produce positronium in the Ore gap of the additive. According to these calculations, even very small quantities of impurities cause considerable changes in the Ps yield. This model also appears to offer a very convincing explanation of the processes found in the argon-propane system.

The positron compounds postulated in the course of these investigations present an interesting phenomenon, not only in the sense that a positron shell would be present in the atom or molecule, but also because entirely new types of interatomic bonds and types of compound could occur. It is to be hoped that further investigations will soon contribute further to their characterization. No theoretical treatment of the positron compounds of the type e^+ He *etc.* will be given here, since this is discussed *e.g.* in[3,4].

10. Positronium Chemistry in the Liquid Phase

In simple hydrocarbons, where the *o*-Ps atoms formed can be annihilated mainly by the pick-off mechanism, a good estimate of the extent of Ps formation in the liquid phase can be obtained from the intensity of the long-lived component I_2 in the time spectra. Though the Ore model was developed especially for gaseous systems, good agreement is found here between the P^0 values calculated by *Ore* and the experimental values for I_2[2].

Table 6. Observed and calculated (after *Hatcher*) *o*-Ps yields in halogenated hydrocarbons [38, 43].

Substrate A-B	V(eV) [a]	D_{A-B} (eV)	I_2 (calculated) (%) [b]	I_2 (observed) (%)
C_6H_5—F	9.19	4.98	21	24±2
C_6H_5—Cl	9.07	3.72	12	14±7
C_6H_5—Br	8.98	3.07	7.4	6±2
C_6H_5—I	8.73	2.47	4.6	4±2
C_3H_7—Cl	10.7	3.4	<0	16±2
C_3H_7—Br	10.29	3.0	<0	10±2
C_3H_7—I	9.41	2.5	<0	4±2

[a] Ionization potential of AB.

[b] $I_2 = \frac{3}{4} \cdot \frac{D_{A-B} - (V - 6.8)}{V}$.

On the other hand, the experimental results differ considerably from the Ore values in alcohols and particularly in halogenated benzene derivatives. *Hatcher*[43] was able to show that better agreement can be achieved in the case of monohalogenated aromatic compounds if the dissociation energy of the weakest bond in the molecule (C-halogen) is taken as the upper limit of the Ore gap instead of the first excitation potential (Table 6). However, on application of this modified Ore model to the monohalogenated propanes, one would expect practically no Ps formation in such systems, whereas the experimental values, as in the case of the monohalogenated aromatic compounds, are found to be $I_2 = 16$—4% (Table 6). This appears to suggest that the probability of Ps formation is a function of the nature of the halogen rather than a property of the molecule as a whole.

Tao and *Green*[38] have systematically investigated the problem of Ps formation in the liquid phase and have concluded that the Ps yield, as required in the original Ore model, is determined by the ionization potential V of the substrate (upper limit) and $[V - 6.8\ \text{eV}]$ (lower limit). They found that a relation exists between the true Ps yield, P^0, and the measured intensity, I_2, this relation being very strongly dependent on the type of reaction undergone by the Ps, such as pick-off, spin conversion, oxidation, compound formation, or reduction. Whereas in simple pick-off, for example, I_2 is proportional to the width of the Ore gap, a dependence in accordance with equation (34) is found for I_2 in the case of Ps-compound formation with subsequent decomposition in accordance with equation (33).

If the reaction between Ps and the monohalogenated hydrocarbons proceeds by compound formation with subsequent decomposition,

$$\text{Ps} + \text{R—Cl} \longrightarrow \text{PsCl} + \text{R}^\bullet \qquad (35)$$

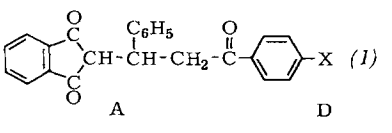
the trend observed in Table 6 is easily explained. The bond energies of the C-halogen and Ps-halogen bonds (Table 4) are predominantly a function of the halogen atom, and it follows that the threshold energy $D_{AB} - D_{PA}$ also depends only on the nature of the halogen. Since V varies only slightly within this series, I_2 is determined by the halogen atom. $D_{AB} - D_{PA}$ assumes positive values in these systems, *i.e.* the reaction should be possible only with "hot" Ps atoms.

An alternative to the above views was proposed by *Hatcher et al.*[44], who attempted to attribute the observed decrease in the I_2 values with increasing dipole character of the substrate molecule to "self-suppression" of the Ps formation by the competing positron capture reaction.

$$\text{R—X} + e^+ \longrightarrow \text{R}^\bullet + e^+\text{X} \qquad (36)$$

This is supported by the fact that this trend for I_2 is not restricted to the halogen derivatives and alcohols since a corresponding variation is found in the xylene system (*o*: 32%, *m*: 25% and *p*: 16%), where the inductive effect of the methyl groups leads in the order $o > m > p$ to a decrease in the negative charge on the substituents.

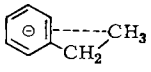
An interesting result in this connection was reported by *Zalukaev et al.*[45]. The anti-vitamin K activity in compounds of the type *(1)* is determined exclusively by the



(1)

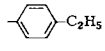
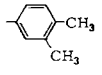
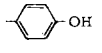
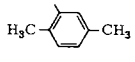
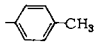
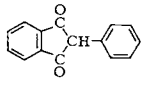
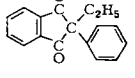
substituent X, which is separated from the indan-1,3-dion-3-yl reaction center by at least two saturated carbon atoms. The influence of the substituent X on the hypocoagulation activity was explained by the existence of an intramolecular charge transfer complex between the indan-

dionyl and the aroyl components of the molecule, the β-diketone part acting as the acceptor (A) and the carbonyl group plus the alkylphenyl component acting as the donor (D). The authors found that in the series of alkylbenzenes and in the series of indanyl derivatives of the type *(1)* that contain the end group $-C_6H_4X$ (X = H, CH_3, C_2H_5, C_3H_7, and C_4H_9), I_2 reaches a minimum at $X = C_2H_5$, which coincides with a maximum in the anticoagulant action or a minimum in the prothrombin index (Table 7). They attribute this to the formation of an additional charge transfer complex between the ring and the ethyl group, which strengthens the electron donor property of the ethylbenzene group:



An interesting relation thus appears to exist between the Ps yield and the electron density distribution in the molecule, and hence also the stability of charge transfer complexes, which ultimately have a decisive influence on the biological activity of certain compounds.

Table 7. Prothrombin index and positron annihilation in indan-1,3-dione derivatives [45].

Aryl in *(1)*	Prothrombin-index	Positron-annihilation I_2 (%)	τ_2 (10^{-10} s)
	8	0	0
	50	0	0
	63	—	—
	71	—	—
	90	19.2 ± 5.8	7.3 ± 2.2
	100	15.2 ± 4.5	6.6 ± 2
	40	0	0
	100	18.8 ± 5.6	4.8 ± 1.4

As was mentioned earlier, a decrease in I_2 with no simultaneous increase in the corresponding lifetime τ_2 can result either from inhibited Ps formation or from chemical reaction of the Ps before it has reached thermal energies.

The question whether inhibited Ps formation or reactions of "hot" Ps atoms are responsible *e.g.* for the drastic decrease in I_2 in benzene on addition of CCl_4 (Fig. 24) was recently answered by *Chuang* and *Tao*[46] by measurement of the time spectra of silica gels on which small quantities of the substrates under investigation were adsorbed.

Brandt and *Paulin*[47] had been able to isolate three components in the time spectra in the investigation of the dependence of positron annihilation on the particle size of solids such as SiO_2, Al_2O_3, and MgO. The first two components, with average lifetimes of $\tau_1 = 0.4$ ns and $\tau_2 = 2$ ns, are due as usual to the annihilation of the free positron and of *p*-Ps (τ_1) and to the annihilation of *o*-Ps (τ_2). The lifetime of the third component, however, is close to the theoretical lifetime of free *o*-Ps, *i.e.* 1.4×10^{-7} s. The intensity of this component (I_3) increases at the expense of I_2 with decreasing particle size of the substrate. These observations were interpreted as resulting from diffusion of the *o*-Ps formed (up to 95% of all Ps atoms) from the solid phase into the cavities of the substrate, where the *o*-Ps is subsequently trapped.

By using this "*o*-Ps source", *Chuang* and *Tao*[46] found that the lifetime (τ_3) and intensity (I_3) of this component are very strongly influenced by the presence of small quantities of iodine (Fig. 25), whereas much greater quantities of CCl_4 must be adsorbed to produce the same effect (Fig. 26).

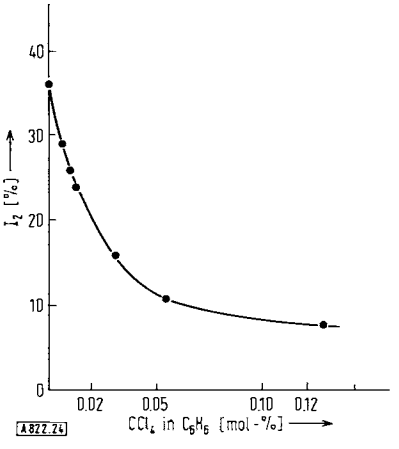


Fig. 24. Inhibition of positronium formation in benzene in the presence of small quantities of carbon tetrachloride [49].

The attraction between an *o*-Ps atom and the pore surface of the adsorbent is mainly due to van der Waals forces. The probability of annihilation of Ps, as in the "free volume"

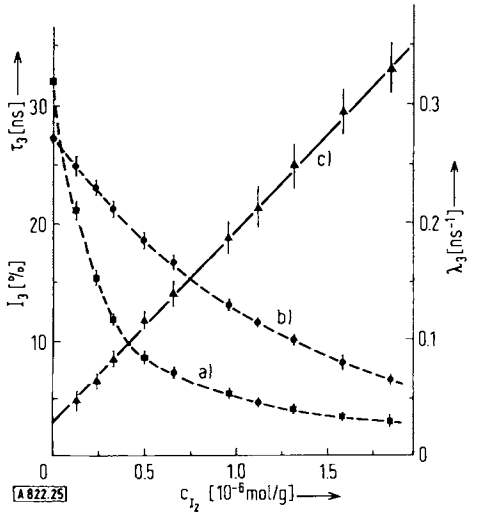


Fig. 25. Lifetime (τ_3) and intensity (I_3) of the third (long-lived) component in positron lifetime spectra of silica gel as a function of the quantity of adsorbed iodine [46]: a) τ_3; b) I_3; c) $\lambda_3 = 1/\tau_3$.

model (cf. Section 6.1), is thus given by the extent of the resulting overlap of the Ps wave function with the electron density function of the molecules on the surface of the SiO_2. If an adsorbate is a species with which positronium can react chemically (compound formation, *etc.*), chemical forces of attraction occur in addition to the van der Waals forces. This leads to an increase in the overlap of the wave functions and an increase in the Ps annihilation constant, as in the case of the adsorption of I_2. On adsorption of

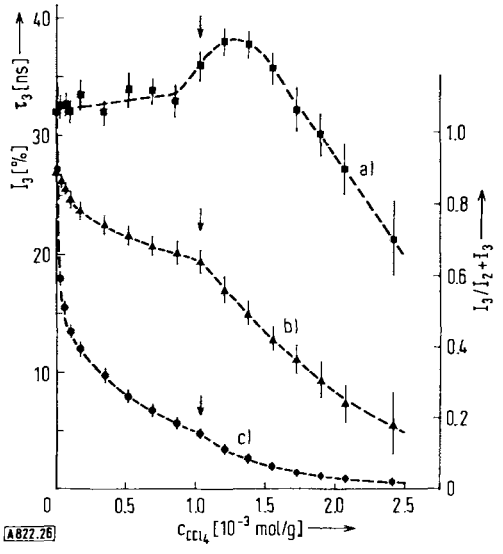


Fig. 26. τ_3 and I_3 in positron lifetime spectra of silica gel as a function of the quantity of carbon tetrachloride adsorbed [46]: a) τ_3; b) I_3; c) I_3/I_2+I_3.

CCl_4, on the other hand, the lifetime of *o*-Ps (τ_3) and the intensity I_3 remain constant, or even increase, over a wide concentration range. It can be concluded from these findings that iodine is very reactive toward positronium, and probably forms Ps-compounds in accordance with

$$Ps + I_2 \rightarrow PsI_2 \text{ or } PsI + I \qquad (37)$$

This is in agreement with investigations[48] on mixtures of hydrocarbons and iodine, in which it was found that iodine seems to react very rapidly with Ps, but only slightly inhibits the Ps formation. The role of CCl_4, whose classical Ore gap is 0, appears on the other hand to consist mainly in the inhibition of Ps formation, though it is not certain whether this is due to positron capture reactions, as suggested by *Ormrod* and *Hogg*[49], or to moderation to energies below the Ore range as a result of energy transfer in inelastic collisions.

11. Positronium Chemistry in the Solid Phase

The discussion of the chemistry of positronium in the solid phase will be confined to three areas.

11.1. Investigation of Radiation-Induced Polymerizations in the Solid Phase by Positron Lifetime Measurements

Tabata et al.[50] used this method to investigate the γ-radiation-induced polymerization of diethyl itaconate (diethyl methylenesuccinate) in the solid phase. The time spectra show that τ_2 remains practically constant over the entire range investigated, while I_2 exhibits the dependence on the radiation dose shown in Figure 27. In these circumstances, two factors should determine the lifetime of the *o*-Ps. These are the number of free radicals and other paramagnetic species produced by the γ radiation, which shorten the *o*-Ps lifetime by spin conversion, and the "free volume" available for the accommodation of *o*-Ps, which undoubtedly changes during the polymerization. However, it is possible that, as appears to be the case in the present example, these two effects balance each other, so that τ_2 remains constant. The change in I_2 during the polymerization can be attributed to the transition from the monomeric to the polymeric phase. The *o*-Ps yield is evidently lower in the monomer (f_M) than in the polymer (f_P). Since I_2 increases linearly with the polymer yield at conversions of more than 10%, the following equation can be given for the *o*-Ps formation

$$f_{total} = cf_P + (1-c)f_M \qquad (38)$$

where c is the polymer content of the system. Numerical evaluation gives $f_M = 0.13$ and $f_P = 0.36$. However, this linear dependence is not found in the initial stage of the polymerization. This interval appears to reflect the time taken for the nucleation process. 10% of polymer is always found experimentally during this period, irrespective of the experimental conditions; this agrees well with the observed linear dependence of I_2 starting at a conversion of 10%. It appears that the polymer is suspended in the crystal during this period, and that no phase separation has occurred.

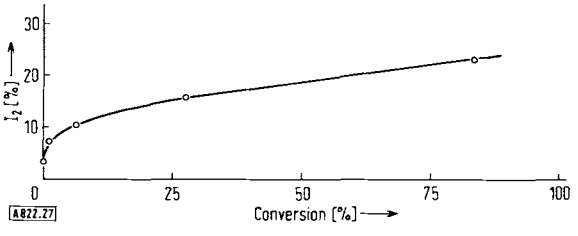


Fig. 27. Relation between I_2 in the positron lifetime spectrum and degree of polymerization (% conversion) in the γ-induced polymerization of diethyl itaconate in the solid phase [50].

Tabata et al. have also used this method to investigate the polymerization of *N*-vinylcarbazole[51, 52]. Unlike in the diethyl itaconate system, the τ_2 values here increase rapidly with the degree of polymerization, whereas I_2 exhibits a characteristic minimum at radiation doses of 12—13 Mrad (Fig. 28). The authors distinguish four regions: I and II are the induction periods, III is the propagation period, and in IV the polymerization has reached its saturation value. In I and II, where τ_2 is practically constant, the lifetime-shortening effect of the free radicals and other active centers is evidently compensated by the effect of the "free volume"; in III, however, the latter effect predominates, and τ_2 increases. In IV, where the "free volume" becomes constant, τ_2 is again shortened by Ps reactions with the free radicals. ESR measurements confirm the linear increase in the free-radical concentrations with the radiation dose. A clue to the cause of the observed minimum of I_2 in the propagation

period III was obtained in experiments in which the substances colored green by the irradiation were bleached by UV light. The same decoloration takes place in III. The intense color under these circumstances is an indication of the presence of ions. *Tabata et al.* therefore conclude that positrons react to form compounds with the ions, which are evidently present in increased quantities during III (as is indicated by the green color), and that the positrons are therefore not available for Ps formation. When most of the ions have disappeared, as in period IV, I_2 again increases.

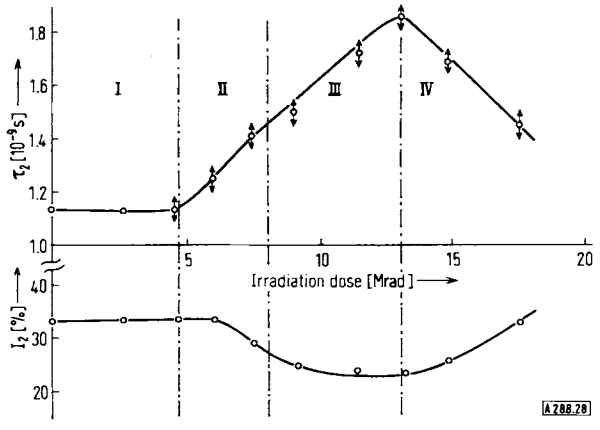


Fig. 28. τ_2 and I_2 of the long-lived component in positron lifetime spectra of solid *N*-vinylcarbazole as a function of the γ radiation dose at 23 °C (7.2×10^6 rad/h) [51].

Post-polymerization has also been investigated by this method[53].

Incomplete as they still are in some respects, such investigations clearly show that this technique offers a possibility of studying the detailed mechanism of polymerization in the solid phase, both the nucleation process and the nature of the active particles in the crystals that initiate and carry on the polymerization.

11.2. Investigation of Phase Transitions by the Positron Annihilation Technique

The dependence of the lifetime of *o*-Ps in solids on the density of the substance can generally be explained very satisfactorily by the "free volume" model[16–18]. However, this model cannot explain the drastic changes in τ_2 that have been observed in many phase transitions.

A particularly interesting example is the liquid crystal system, which was first investigated by *Cole* and *Walker*[54], and which very clearly demonstrates the effect of the intermolecular forces and the internal structural arrangement of the molecules on the lifetime of *o*-Ps. The results, which are summarized in Figure 29, show that a change in τ_2 is found only in transitions that involve a sudden change in the intermolecular dipole-dipole forces; such a change occurs in the transition from the solid to the smectic phase or from the smectic to the nematic phase, but not from the nematic or smectic to the liquid (isotropic) phase. The dipole-dipole interaction is undoubtedly strongest in the solid phase, and this would explain the shortening of τ_2 observed there. From the observation that no *o*-Ps is formed in solid *p*-azoxyanisole, it was concluded that the same effect also leads to inhibition of Ps formation. This is opposed by the observation by *Nicholas* and *Ache*[55] that I_2 changes only slightly in the region of the phase transitions in cholesteryl benzoate and myristate, *i.e.* the Ps yield is

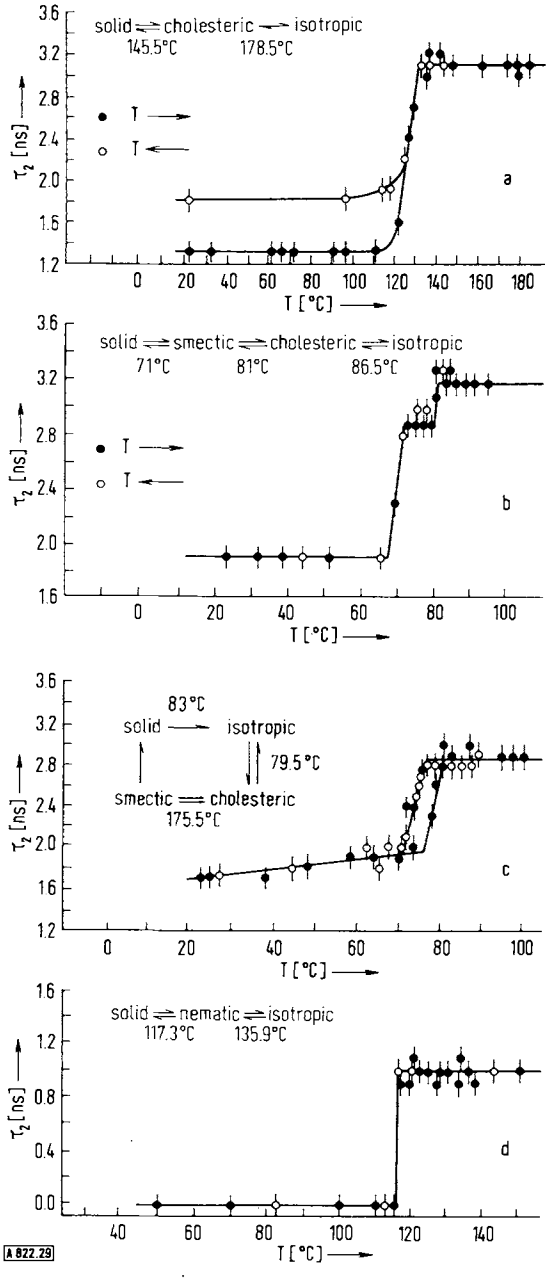


Fig. 29. Temperature dependence of τ_2 for some liquid crystals [54]: a) cholesteryl benzoate; b) cholesteryl myristate; c) cholesteryl stearate; d) *p*-azoxyanisole.

only slightly influenced by the phase transition in these systems. There thus appears to be no obvious connection between the Ps yield and the phase change. Recent angular distribution measurements[56] support the view that *ortho-para* spin conversion processes are responsible for the shortened lifetime of *o*-Ps in the solid phase in such systems.

11.3. Positron Interactions with Crystal Defects (in Ionic Crystals)

Though Ps formation in ionic crystals such as NaCl was ruled out by *Ferrell*[13] on the basis of thermodynamic considerations, the time spectra of the alkali metal halides can be resolved into at least two components[57-61], *i.e.* in addition to the annihilation of the free positron, at least one other annihilation mechanism must be active. *Goldanskii* and *Propokev*[62-64] discuss three positron states through which annihilation could take place, *i.e.* e^+-anion, polaron-e^+, and e^+-crystal defect. *Brandt*[65] developed the view that positrons that are annihilated in cation vacancies could be the reason for the appearance of the long-lived component in the time spectra.

The first indication that crystal defects could influence the lifetime and intensity of the long-lived component was provided by *Williams* and *Ache*[60] as a result of investigations on the dependence of these quantities on the defect concentration in proton-irradiated and γ-irradiated NaCl and NaF crystals. The I_2 values increase considerably on irradiation. However, thermal annealing of the crystals brings I_2 back to the original value for the unirradiated crystals. τ_2 changes only slightly. Since the high proton and γ doses undoubtedly lead to a series of different defects, these results provide no indication of the exact nature of the defects. Recent investigations by *Singru et al.*[66] and particularly by *Brandt*[67], who produced cation vacancies by plastic deformation of the crystals, indicate that such vacancies cause an increase in I_2. This is also indicated by a study on the temperature dependence of τ_2 and I_2[61].

These studies as well as more recent investigations by *Brandt*[68-69] and *Ache*[70] led to the development of a model, in which the positrons are assumed to annihilate either in the bulk of the crystal at a typical rate $\lambda_0 = 1/\tau_0$ or to be captured in crystal-defects, most likely cation-vacancies, at a rate K_1 which is proportional to the number of the defects (n_v). Since in these "positron traps" there is less overlapping between the positron wave function and the wave functions of the electrons of the surrounding atoms, the annihilation process is delayed. The result is an increase in the lifetime of the positron. The kinetic treatment of the various annihilation processes involved results in the following relation between the defect concentration n_v and the experimental quantities τ_1, τ_2 and I_2:

$$K = \text{Const.} \times n_v = I_2 (1/\tau_1 - 1/\tau_2)$$

τ_1 and τ_2 are lifetimes of the short- and long-lived components in the observed positron lifetime spectra; I_2 is the intensity of the long-lived component.

Since the lifetimes of the two components that appear in the time spectra are close to each other and are both very short, considerable difficulties are still often encountered in the evaluation. However, it is to be hoped that an improvement in the resolving power of the instruments will allow more detailed investigation of the individual components in the spectra, so that this technique can be developed into a method for the identification and measurement of crystal defects of types that are little known at present.

A first practical application has been reported by *Kelly* and *Merrigan*[71], who studied the properties of chemically light-sensitized AgCl crystals. Among other things, they found that the degree of light sensitivity of these specially prepared crystals can be correlated to the relative intensity, I_2 of the long-lived component in the time spectra.

12. Summary and Outlook

In this progress report, which is not claimed to be complete, an attempt has been made to discuss the problems of positronium chemistry that have arisen in recent years from the viewpoint of the chemist.

It is clear that the chemical applications of the positron annihilation process are still in their early stages; however, a number of areas already stand out where this new nuclear technique will be able to contribute most to the solution of chemical problems. The most important of these are probably:

1. the detection of free radicals and other paramagnetic species in gases, where this technique, with its high sensitivity, should be superior to most conventional methods;

2. the investigation of spin delocalization in complexes;

3. the determination of the true kinetic parameters of chemical reactions in solution;

4. the study of the physico-chemical processes in phase transitions and the accompanying changes in the nature and strength of the intermolecular forces;

5. the detailed elucidation of the mechanism of polymerization processes in the solid phase (duration and course of the nucleation process, nature and role of free radicals and ions in radiation-induced polymerization);

6. the determination of the effect of parameters such as ionization potentials, dissociation energies, and charge distributions on the additions of positrons (or electrons) with subsequent decomposition of the compound (fundamental processes that occur in radiation chemistry and may determine the radiation-chemical stability of the compound);

7. the identification and measurement of various types of defects in solids.

It seems certain that as this nuclear method becomes increasingly widely used, it will find interesting new applications in chemistry.

Received: October 9, 1970 [A 822 IE]
German version: Angew. Chem. *84*, 234 (1972)
Translated by Express Translation Service, London

[1] This work was supported by the U. S. Atomic Energy Commission.

[2] *J. H. Green* and *J. Lee*: Positronium Chemistry. Academic Press, New York 1966.

[3] *V. I. Goldanskii*, At. Energy Rev. *6*, 3 (1968).

[4] *A. T. Stewart* and *L. O. Roellig*: Positron Annihilation. Academic Press, New York 1967.

[5] *J. A. Merrigan, S. J. Tao,* and *J. H. Green* in *A. Weissberger*: Technique of Organic Chemistry. Interscience, New York, in press.

[6] *F. A. M. Dirac*, Proc. Cambridge Phil. Soc. *26*, 361 (1930).

[7] *S. J. Tao, J. H. Green*, and *G. J. Celitans*, Proc. Phys. Soc. (London) *81*, 1091 (1963).

[8] *S. Mohorovic*, Astron. Nachr. *253*, 94 (1934).

[9] *M. Deutsch*, Phys. Rev. *82*, 455 (1951).

[10] *M. Deutsch*, Phys. Rev. *83*, 866 (1951).

[11] *A. Ore* and *J. L. Powell*, Phys. Rev. *75*, 1696 (1949).

[12] *A. Ore*, Univ. Bergen Arbok Naturvitenskap. Rekke, No. 9 (1949).

[13] *R. A. Ferrell*, Rev. Mod. Phys. *28*, 308 (1956).

[14] *S. J. Tao, J. Bell*, and *J. H. Green*, Proc. Phys. Soc. (London) *83*, 453 (1966).

[15] *W. Brandt, S. Berko*, and *W. Walker*, Phys. Rev. *120*, 1289 (1960).

[16] *P. R. Wallace*, Phys. Rev. *100*, 738 (1955).

[17] *R. L. de Zafra* and *W. T. Joyner*, Phys. Rev. *112*, 19 (1958).

[18] *R. K. Wilson, D. O. Johnson*, and *R. Stump*, Phys. Rev. *129*, 2091 (1963).

[19] *G. A. Henderson* and *W. E. Millett*, Bull. Amer. Phys. Soc. *7*, 120 (1962).

[20] *W. Brandt* and *I. Spirn*, Phys. Rev. *142*, 231 (1966).

[21] *R. A. Ferrell*, Phys. Rev. *110*, 1355 (1958).

[22] *J. McGervey* and *S. de Benedetti*, Phys. Rev. *114*, 495 (1959).

[23] *S. de Benedetti, C. Cowan, W. Konneker*, and *H. Primakoff*, Phys. Rev. *77*, 205 (1950).

[24] *L. G. Lang* and *S. de Benedetti*, Phys. Rev. *108*, 914 (1957).

[25] *P. U. Arifov, V. I. Goldanskii*, and *Yu. S. Sayasov*, Fiz. Tverd. Tela *6*, 3118 (1964).

[26] For positron lifetime measurements cf. [2—5].

[27] *T. L. Williams* and *H. J. Ache*, J. Chem. Phys. *50*, 4493 (1969).

[28] *W. W. Souder*, Ph. D. Thesis, Iowa State University 1969.

[29] *H. Horstman*, J. Inorg. Nucl. Chem. *27*, 1191 (1965).

[30] *J. McGervey* and *S. de Benedetti*, Phys. Rev. *114*, 495 (1959).

[31] *J. D. McGervey* in [4], p. 143.

[32] *J. E. Jackson* and *J. D. McGervey*, J. Chem. Phys. *38*, 300 (1963).

[33] *V. P. Shantarovich, V. I. Goldanskii, Yu. N. Molin, V. P. Perminov*, and *G. I. Skubnevskaya*, Izv. Akad. Nauk SSSR, Ser. Khim. *10*, 2188 (1967).

[34] *V. I. Goldanskii, V. G. Firsov*, and *V. P. Shantarovich*, Kinetika i Kataliz *6*, 564 (1965).

[35] *R. E. Green* and *R. E. Bell*, Can. J. Phys. *35*, 398 (1957).

[36] *R. L. de Zafra*, Phys. Rev. *113*, 1567 (1959).

[37] *S. J. Tao* and *J. H. Green*, J. Phys. Chem. *73*, 882 (1969).

[38] *S. J. Tao* and *J. H. Green*, J. Chem. Soc. *A 1968*, 408.

[39] *S. Marder, V. W. Hughes, C. S. Wu*, and *W. Bennett*, Phys. Rev. *103*, 1258 (1956).

[40] *W. B. Teutsch* and *V. W. Hughes*, Phys. Rev. *103*, 1266 (1956).

[41] *C. Y. Leung* and *D. A. L. Paul* in [4], p. 409.

[42] *W. Brandt* and *H. Feibus*, Phys. Rev. *184*, 277 (1969).

[43] *C. R. Hatcher*, J. Chem. Phys. *35*, 2266 (1961).

[44] *C. R. Hatcher, T. W. Falconer*, and *W. E. Millett*, J. Chem. Phys. *32*, 28 (1960).

[45] *L. P. Zalukaev, B. P. Vikin*, and *L. P. Perfilyev*, Biofizika *11*, 18 (1966).

[46] *S. Y. Chuang* and *S. J. Tao*, J. Chem. Phys. *52*, 749 (1970).

[47] *W. Brandt* and *R. Paulin*, Phys. Rev. Lett. *21*, 193 (1968).

[48] *S. J. Tao*, J. Chem. Phys. *52*, 752 (1970).

[49] *J. H. Ormrod* and *B. G. Hogg*, J. Chem. Phys. *34*, 624 (1961).

[50] *Y. Tabata, T. Miyairi, S. Katsura, Y. Ito*, and *K. Oshima* in: Large Radiation Sources for Industrial Processes. Int. At. Energy Agency, Vienna 1969, p. 233.

[51] *Y. Tabata, Y. Ito*, and *K. Oshima*, Proc. Symp. Org. Solid State Chem., BNL, UST (1968).

[52] *Y. Tabata, Y. Ito*, and *K. Oshima*, Rep. Progr. Polymer Phys. Japan *11*, 417 (1968).

[53] *Y. Ito, Y. Tabata*, and *K. Oshima*, Rep. Progr. Polymer Phys. Japan *12*, 477 (1969).

[54] *G. D. Cole* and *W. W. Walker*, J. Chem. Phys. *42*, 1692 (1965).

[55] *J. B. Nicholas* and *H. J. Ache*, J. Chem. Phys., in press.

[56] *M. Szuszkiewicz*, Acta Phys. Polon. *36*, 365 (1969).

[57] *A. Bisi, A. Fiorentini*, and *L. Zappa*, Phys. Rev. *131*, 1023 (1963).

[58] *A. Bisi, A. Fiorentini*, and *L. Zappa*, Phys. Rev. *134 (A)*, 328 (1964).

[59] *C. Bussolati, A. Dupasquier*, and *L. Zappa*, Nuovo Cimento *B 52*, 529 (1967).

[60] *T. L. Williams* and *H. J. Ache*, J. Chem. Phys. *51*, 3536 (1969).

[61] *M. Bertolaccini* and *A. Dupasquier*, Phys. Rev. *B 1*, 2896 (1970).

[62] *V. I. Goldanskii* and *E. P. Prokopev*, Soviet Phys.—Solid State *6*, 2641 (1965).

[63] *E. P. Prokopev*, Soviet Phys.—Solid State *8*, 368 (1966).

[64] *V. I. Goldanskii* and *E. P. Prokopev*, Soviet Phys.—Solid State *8*, 409 (1966).

[65] *W. Brandt* in [4], p. 155.

[66] *K. P. Singh, R. M. Singru, M. S. Tomar*, and *C. N. R. Rao*, Phys. Lett. *A 32*, 10 (1970).

[67] *W. Brandt, H. F. Waung*, and *P. Levy*, Proc. Int. Symp. Color Centers in Alkali Halides, Rome 1968.

[68] *W. Brandt, H. F. Waung*, and *P. Levy*, Phys. Rev. Lett. *26*, 496 (1971).

[69] *W. Brandt* and *H. F. Waung*, Phys. Rev. B *3*, 3432 (1971).

[70] *C. S. Tumosa, J. B. Nicholas*, and *H. J. Ache*, J. Phys. Chem. *75*, 2030 (1971).

[71] *T. H. Kelly* and *J. A. Merrigan*, private communication.

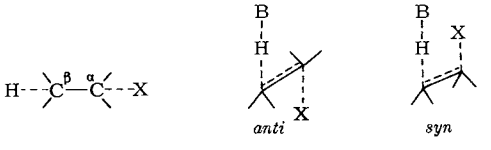
The *syn* and *anti* Steric Course in Bimolecular Olefin-Forming Eliminations

By Jiří Sicher[*]

Earlier evidence led to the view that in bimolecular olefin-forming eliminations the anti steric course is generally preferred over the syn. Recent experiments, however, show that in some common bimolecular elimination reactions, notably those involving onium bases, syn- and anti-eliminations proceed side by side, the former preferentially leading to the trans- and the latter to the cis-olefins.

1. Introductory

One of the features essential for the description of the mechanism of a concerted 1,2-elimination process is the torsion angle about the C^{α}—C^{β} bond in the activated complex. In principle, this angle can posses any value between 0 and 180°. However, it is suggested by theory (*e.g.* the principle of maximum orbital overlap) and supported by experiments on mono- and bicyclic ring systems that arrangements in which the C^{α}—X and the C^{β}—H bond are antiperiplanar (*anti*-elimination, torsion angle 180°) and synperiplanar (*syn*-elimination, torsion angle 0°) will be greatly preferred in the transition state of an HX elimination reaction (Scheme 1)[1-4].



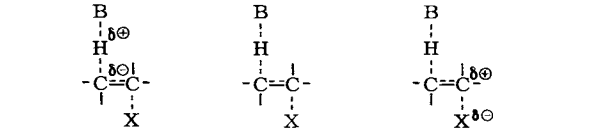
Scheme 1.

Accepting this view one must next ask what the situation is with respect to a possible preference of the one steric mode of elimination over the other[**]. Until recently there seemed to be universal agreement that whenever the molecule was "free to choose" between the 0° and the 180° torsion angle to effect elimination it would definitely prefer the latter.

2. The Case for Preferred *anti*-Elimination

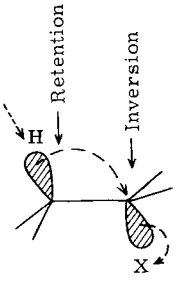
2.1. Theoretical Considerations

Frequently, the problem of the steric course is discussed in terms of eclipsing effects. In *syn*-elimination all three pairs of groups attached to C^{α} and C^{β} are eclipsed or nearly so; by contrast, the transition state for *anti*-elimination, barring cases with highly developed double bond character, permits a staggered arrangement. These conformational differences led to an estimated factor of 10^2 or 10^3 in favor of *anti*-elimination[6]. In the non-synchronous, yet concerted elimination processes [E1-like *(paene-carbonium ion)* or E1cb-like *(paene-carbanion)*[7], cf. Scheme 2] the advantage accruing from maximum orbital overlap is not as great as in the fully synchronous process, and, as a result, the *syn*-elimination transition state need not be fully eclipsed. It was suggested that this feature could lead to a lowered preference of *anti*- over *syn*-elimination[6].



Scheme 2.

An alternative treatment, stressing electronic effects[8-11], is based on a conceptual dissection of the elimination process into two components, *viz.* a "nucleophilic substitution" on C^{α}, through the electrons on C^{β}, and the complementary "electrophilic substitution" on C^{β} by C^{α} (Scheme 3). An S_N2 substitution invariably proceeds with inversion of configuration, and the stereochemistry of S_E2 is generally retention: this combination thus results in overall *anti*-elimination.



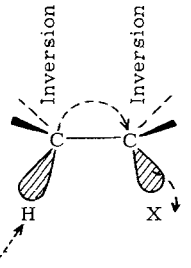
Scheme 3.

In 1962, *Ingold*[11] added the following important reservation. If C^{β}—H bond fission in a concerted elimination were considerably progressed in the transition state (as in an E1cb-like process; Scheme 2), sufficient ionicity could develop on C^{β} for the charge to spread on both sides of this carbon and thus for the S_E2 component to proceed with

[*] Prof. Dr. J. Sicher, deceased September 8, 1970
Institut de Chimie Organique
Université de Lausanne
1005 Lausanne (Switzerland)
Annotated by Priv.-Doz. Dr. Manfred Schlosser
Organisch-Chemisches Institut der Universität
69 Heidelberg, Im Neuenheimer Feld 7 (Germany)
and Institut für experimentelle Krebsforschung am
Deutschen Krebsforschungszentrum, Heidelberg.

[**] This discussion relates only to bimolecular processes; processes in which the leaving group acts as an internal base must be *syn*-eliminations. For a review of these reactions, see ref. [5].

inversion; the elimination could then exhibit *syn*-stereospecificity (Scheme 4).



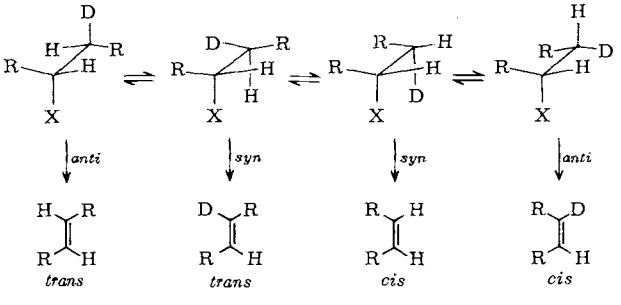
Scheme 4.

Fukui and others[12–14] have provided a quantum mechanical rationale for preferred *anti*-elimination in open-chain systems but a recent qualitative analysis in molecular orbital terms was taken to suggest that either elimination mode may be preferred, depending on the relative timing of the bond changes[15]. Application of the principle of least motion[16] also indicates a general preference for *anti*-elimination.

2.2. Experimental Evidence

2.2.1. Open-Chain Compounds

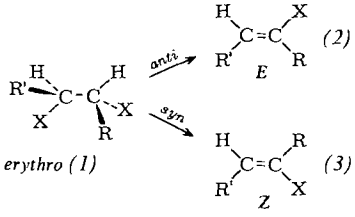
In their pioneering investigations on the steric course of elimination, *Skell* and his co-workers[17,18] made use of the mono-deuterated derivatives of 2-butyl bromide and 2-butyl tosylate (Scheme 5). Starting from the β-deuterated substrates of known configuration, information about the steric course of the elimination can be deduced directly from the deuterium content of the individual olefinic products.



Scheme 5.

It was found that the elimination of both hydrogen bromide and toluenesulfonic acid using potassium ethoxide in ethanol proceeds exclusively by *anti*-elimination[*].

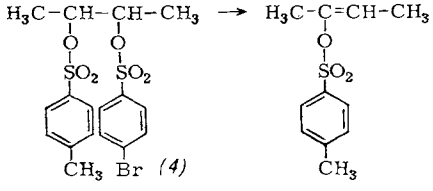
Stereochemical analysis of the course of elimination becomes simpler when the reactant exists as diastereomers without having to be labeled. Thus hydrogen chloride elimination from an *erythro*-dihalide of type *(1a)* (R = R′ = alkyl, X = halogen) can give rise to either *Z*- or *E*-vinyl halide [*(2a)* or *(3a)*], depending on whether the elimination proceeds by an *anti*- or a *syn*-elimination mechanism (Scheme 6).



Scheme 6.

It was reported[19] that the reaction of *erythro*-2,3-dichloropentane *(1b)* (R = CH_3, R′ = C_2H_5, X = Cl) and homologous *erythro* and *meso vic*-dichloroalkanes with potassium hydroxide in *n*-propanol gives exclusively the *E*-vinyl chlorides *(2)*, showing that the elimination proceeds by the *anti* mechanism.

Likewise, the elimination of *p*-bromobenzenesulfonic acid from the two diastereoisomers of 2-brosyloxy-3-tosyloxybutane *(4)* [$N(C_2H_5)_3$/50% aqueous dioxane] leads exclusively to the isomers expected from an *anti*-elimination course[20].

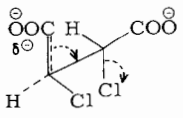


Caution is sometimes required when dealing with earlier results. For example, with the aid of modern analytical instrumentation it has been shown that elimination of HBr from *erythro*-4,5-dibromooctane with piperidine at reflux temperature does not give solely 4-bromo-*cis*-4-octene (*E*-isomer), as previously assumed[21], but also 15% of the *Z*-isomer[22][**].

However, at least two cases have long been on record in which two open-chain diastereoisomers give rise to the same olefin isomer (stereoconvergent elimination). *meso*- and dl-α,α-Dichlorosuccinic acid react with aqueous alkali to give chloromaleic acid. The formation of chloromaleic acid from *meso*-dichlorosuccinic acid was assumed to proceed through a non-synchronous, yet concerted E1cb-like mechanism with approximately *syn*-coplanar geometry. In the transition state the excess charge should reside mainly on the carboxylate group. Consequently, the lone pair that displaces the chlorine atom from its bond to the carbon comes more from the direction of the carboxylate—and elimination is therefore in reality *anti*-coplanar—than from the direction of the leaving hydrogen atom (Scheme 7)[23–25].

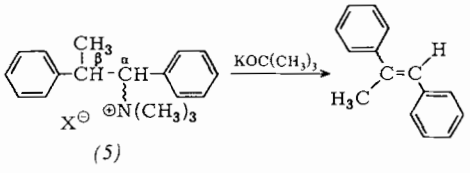
[*] Actually, for the hydrogen bromide elimination the "reverse" argumentation had been employed: *anti*-elimination was assumed as being *given* and the eliminations were run in order to establish the relative configurations of deuterium and bromine in the reactants and also their configurational purity. However, the results are self-consistent to such a degree that the evidence may be considered to have established both aspects.

[**] It appears from unpublished work (*J. Sicher* and *J. L. Schwitzguebel*, Université de Lausanne 1970) that the *Z*-isomer is not actually formed by *syn*-elimination but in a subsequent partial isomerization of the *E*-isomer.



Scheme 7.

Likewise, both the *threo* and the *erythro* isomers of the (1,2-diphenylpropyl)trimethylammonium salt *(5)* react with *tert*-butoxide in *tert*-butanol to give the same olefin isomer, *viz.* α-methyl-*trans*-stilbene[25].



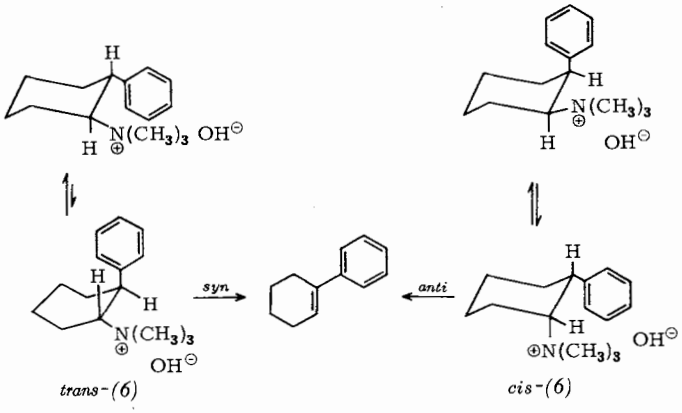
(5)

The two diastereoisomers were found to react at very similar rates and this was taken to indicate that the reaction is an E1cb process, the rate-determining step being deprotonation at C^{β}. An alternative explanation, *i.e.* that the process involves rapid isomerization at C^{α} followed by concerted elimination, was also considered. Subsequent isomerization of the reaction product was ruled out in this (and similar) cases by control experiments: α-Methyl-*cis*-stilbene is stable under the above reaction conditions[26].

Significantly, with ethoxide in ethanol, *threo-(5)* gave α-methyl-*trans*-stilbene, and *erythro-(5)* gave α-methyl-*cis*-stilbene, both processes thus being *anti*-eliminations, and the ratio $k_{threo}/k_{erythro}$ was rather high (*i.e.* 57). The reactions of the corresponding bromides and chlorides *(5)*, Cl or Br instead of $\overset{\oplus}{N}(CH_3)_3$, with a variety of base/solvent combinations were also found to be *anti*-eliminations[26].

2.2.2. Cyclohexyl Compounds

As is well known, bimolecular eliminations take place smoothly in this system only if the two vicinal bonds involved are configurationally *trans*, and, in addition, diaxially disposed; *cis*-placed substituents will not undergo



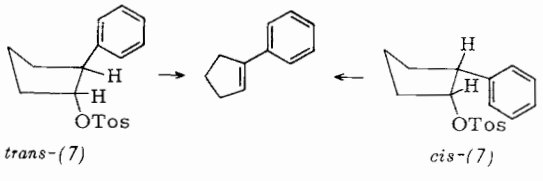
trans-(6) *cis-(6)*

concerted elimination, or will do so only reluctantly. Thus, even though both *trans*-2-phenylcyclohexyltrimethylammonium hydroxide *(6)* and the corresponding *cis*-isomer[30] give 1-phenylcyclohexene[27–29], the reaction is some 140 times slower in the former case.

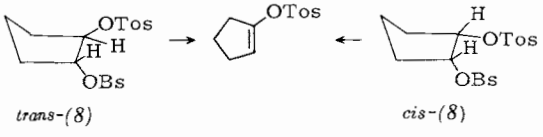
It seems that it was not always appreciated that results such as these are not necessarily relevant to the question of preference of *anti*- over *syn*-elimination. The lower reactivity of *trans-(6)* could be taken to mean that *syn*-elimination is generally less favorable than the *anti* mode. The influence of other important factors on the reaction rate should, however, not be overlooked. While the *trans*-diaxial arrangement in one of the two chair forms of *cis-(6)* corresponds ideally to the geometric requirements of *anti*-elimination, the conditions for *syn*- or near-to-*syn*-elimination cannot be fulfilled in the chair form. Conversion of the chair into the sterically less favorable boat form requires strain energy, even though the energy differences in the case of *trans-(6)*, and in similar systems capable of undergoing *syn*-elimination[31,32], are estimated to be lower than for unsubstituted cyclohexane itself, since the bulky *gauche* groups [*e.g.* C_6H_5 and $\overset{\oplus}{N}(CH_3)_3$ in *trans-(6)*] tend to destabilize the chair conformation relative to the boat[33].

2.2.3. Cyclopentyl, Bicycloheptyl, and Bicyclooctyl Compounds

In the five-membered ring a torsion angle close to zero practically pre-exists for *cis*-placed groups, while for *trans*-placed groups a true *anti*-planar arrangement is hardly attainable[*]. It is therefore not altogether surprising that examples of bimolecular *syn*-eliminations should have been found in this system. Thus, on treatment with *tert*-butoxide in *tert*-butanol and trimethylamine in 50% aqueous dioxane, respectively, the *trans*-isomers *(7)*[34] and *(8)*[20] eliminate *p*-toluenesulfonic acid and *p*-bromobenzenesulfonic acid by what must be a *syn*-elimination. However, the rates of *anti*-elimination from the corresponding *cis*-isomers were found to be higher by factors of 9.1 and 1.3 respectively.



trans-(7) *cis-(7)*



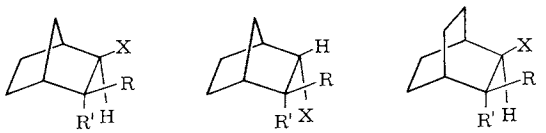
trans-(8) *cis-(8)*

Derivatives of bicyclo[2.2.1]heptane *(9)* and bicyclo[2.2.2]-octane *(10)* possess geometric features which are expected to be especially favorable for *syn*-elimination. Several such compounds have been studied from this point of view (Table 1), and *syn*-elimination has indeed been found to be the preferred reaction mode for the bicyclo[2.2.1]heptyl system provided that the anionic leaving group X occupies

[*] The existence of the *trans*-hydrindan (perhydroindene) system demonstrates, however, that such an arrangement cannot be ruled out entirely.

the *exo* position. The corresponding *endo*-substituted compound [*endo-(9)*] undergoes *anti*-elimination, regardless of the unfavorable torsion angle of 120°. This "lower reactivity" of the *endo*-hydrogen may be a result of steric hindrance to the access of base, or of some other effect.

Several other important conclusions follow from an analysis of the data in Table 1. Thus, the bicyclooctyl system *(10)* exhibits a somewhat greater tendency for *syn*-elimination than the bicycloheptyl system *(9)*. Further, the tendency to react by *syn*-elimination decreases on going from the trimethylammonium to other leaving groups, particularly halogen or tosylate. Finally, the proportion of *syn*-elimination decreases with the polarity of the solvent.



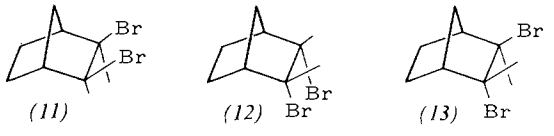
exo-(9) *endo-(9)* *(10)*

Table 1. Steric course of elimination from β-deuterium-labeled bicyclo[2.2.1]heptyl *(9)* and bicyclo[2.2.2]octyl derivatives *(10)*.

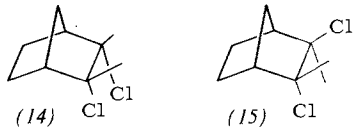
Skeleton and substitution R	R'	X	Base and solvent	*syn*:*anti*	Ref.
exo-(9)					
D	H	$\overset{\oplus}{N}(CH_3)_3$ [a]	$OH^{\ominus}$, "dry" [a]	100: 0	[35]
D	H	$\overset{\oplus}{N}(CH_3)_3$ [a]	$OH^{\ominus}$, "wet" [a]	100: 0	[36]
H	D	Cl	3-methylpentoxide, 3-methylpentanol	98: 2	[37]
D	H	Br	3-methylpentoxide, 3-methylpentanol	98: 2	[36]
H	D	OTos	3-methylpentoxide, *p*-cymene	65: 35	[36]
H	D	OTos	3-methylpentoxide, 3-methylpentanol	18: 72	[36]
endo-(9)					
D	H	Cl	3-methylpentoxide, 3-methylpentanol	0:100	[37, 38]
exo-(10)					
D	H	$\overset{\oplus}{N}(CH_3)_3$ [a]	"dry" [a]	100: 0	[39]
D	H	OTos	*tert*-butoxide, DMF	33: 67	[40]
H	D	OTos	*tert*-butoxide, DMF	87: 13	[40]
D	H	OTos	*tert*-butoxide, benzene	83: 17	[40]
H	D	OTos	*tert*-butoxide, benzene	95: 5	[40]

[a] "Dry" and "wet" refer, respectively, to decomposition at 50°C/10^{-7} torr and *ca.* 110°C/*ca.* 60 torr.

The elimination of hydrogen halide from the 2,3-dihalonorboranes *(11)*—*(15)*[41,42] using 1-pentoxide in 1-pentanol



(11) k_{anti} = 1.0 *(12)* k_{anti} = 2.8 *(13)* k_{syn} = 85.9



(14) k_{anti} = 0.02 *(15)* k_{syn} = 1.6

Scheme 8.

follows the same trends. A further important finding is that the dichlorides show a greater proclivity toward *syn*-elimination than the dibromides. The relative rates of these eliminations are apparent from Scheme 8.

2.3. Conclusions from Studies Prior to 1966

Theoretical considerations largely predicted a general preference of the *anti*-elimination mode, although the possibility of a genuine bimolecular *syn*-elimination was also envisioned. The available experimental evidence appeared to be in full accord with the prevailing view that "any system having the possibility of free choice will prefer the *anti*- over the *syn*-elimination path". The *syn*-elimination mechanism was considered to operate only in more rigid systems in which the torsional arrangement required for *anti*-elimination cannot be attained.

That many of the model compounds studied simply do not permit definite conclusions to be drawn was largely overlooked. Cyclopentyl and bridged bicyclic systems, which favor *syn*-elimination, are counterparts of the cyclohexyl derivatives in which *anti*-elimination is torsionally enforced. Interesting and significant as these results are, neither the one nor the other bears directly on the question of the general preference of the one or the other elimination mode.

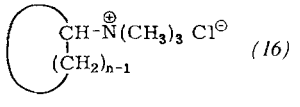
There were, nevertheless, several aspects of E2 reaction data which were difficult to understand on the basis of this simple picture of a sterically homogeneous elimination behavior. One of these was the frequent lack of correlation between the relative stabilities of *cis-trans* olefin pairs and the ratio in which the two isomers were formed in certain elimination reactions[43]. Moreover, reservations could be held against the significance of some of the evidence. This concerns, as we have just seen, some of the ring systems frequently employed. Also, the point could be made that the range of base/solvent systems employed in some of the studies was not sufficient to justify the generalizations made.

3. Recent Investigations: Evidence for *syn*-Elimination as a Frequent Reaction Mode

3.1. Rate Profile Studies on Eliminations from Cycloalkane Derivatives

The study of the variation of rate with ring size of a reaction in a homologous series of ring compounds ("rate profile") can provide useful mechanistic and stereochemical information[44-49]. By relating the "rate profile" of the process under investigation to that of a reaction of known mechanism one may hope to obtain evidence on its course, the argument being that reactions which are similar with respect to their salient geometric features should also be similar as regards rate profile.

In the case of bimolecular eliminations rate profiles were first determined for base-induced degradation of cycloalkyltrimethylammonium compounds[50-53]. Fig. 1 shows an example.



(16)

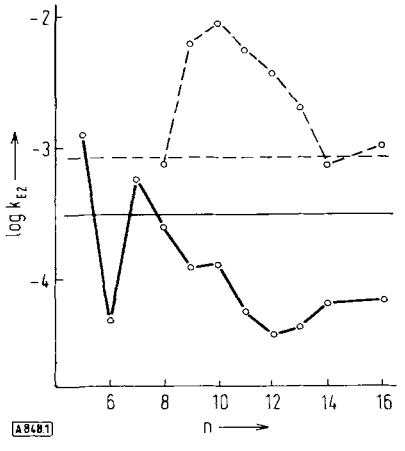
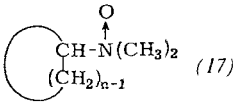


Fig. 1. Effect of ring size n on rates of formation k_{E2} of *cis*- and *trans*-cycloalkenes from cycloalkyltrimethylammonium chlorides *(16)* with potassium *tert*-butoxide in *tert*-butanol at 55 °C [50, 51]. – – –: *trans*-cycloalkenes, ——: *cis*-cycloalkenes.

The immediately obvious feature of these results is the very marked difference in the rate profiles for *cis*- and *trans*-cycloalkene formation. Provided one accepts the tenet that processes possessing similar salient stereochemical features will exhibit rate profiles of similar type[45], one also has to accept the converse of this statement, namely that rate profiles of different types may indicate the operation of stereochemically different mechanisms. Accepting this view, one is forced to conclude that two geometrically distinct mechanisms are operating in the present reaction, the one being mainly, or even exclusively, the route of choice for *trans*-olefin formation, the other for *cis*-olefin formation.

A similar rate profile study for a *bona fide syn*-elimination process, the thermolysis of amine oxides (Cope elimination) (Fig. 2), provides further information.

It is clearly apparent that the rate profiles for *trans*-cycloalkene formation from the onium base elimination and the amine oxide elimination are closely similar, and must therefore both be *syn*-eliminations. By contrast, the rate profiles of *cis*-olefin formation in the two processes are very different, suggesting that *cis*-olefin formation from the onium compounds does not proceed by a *syn* route, and hence must proceed by an *anti*-elimination mechanism[50, 54-57], at least largely, if not exclusively.



(17)

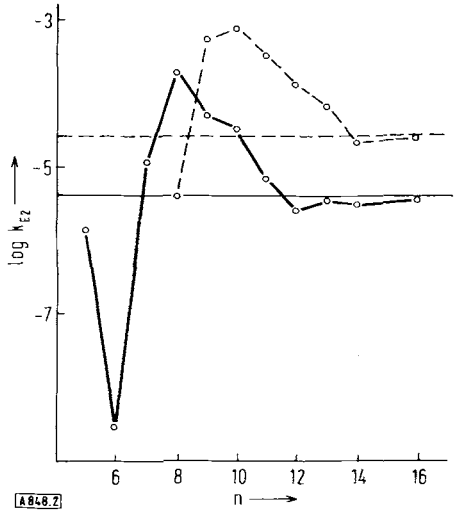


Fig. 2. Effect of ring size n on rates k_1 of *cis*- and *trans*-cycloalkene formation from cycloalkyldimethylamine oxides *(17)* in *tert*-butanol at 20.6 °C [54]. – – –: *trans*-cycloalkenes; ——: *cis*-cycloalkenes.

These studies thus not only revealed the operation of the hitherto stigmatized *syn*-elimination mechanism but they also led to the discovery of an unexpected mechanistic dichotomy. By means of the rate profile approach we cannot decide how rigorous the observed mechanistic stereoselectivity actually is: some *anti*-elimination in *trans*-olefin formation, or, again a certain proportion of *syn*-elimination in *cis*-olefin formation would not necessarily be revealed by this procedure.

This approach was extended to other base/solvent systems. Eleven combinations were investigated and the data obtained led to the same fundamental conclusions. Initial studies on eliminations from cycloalkyldimethylsulfonium salts are consistent with the data for the ammonium compounds[52, 53].

An analogous study on cycloalkyl bromides revealed that in the base/solvent systems *tert*-butoxide/*tert*-butanol and *tert*-butoxide/benzene, *trans*-cycloalkene formation probably also proceeds, either largely or exclusively, by *syn*-elimination (Fig. 3)[58, 59]. By contrast, for the process of *trans*-cycloalkene formation with the base/solvent systems ethoxide/ethanol and *tert*-butoxide/dimethylformamide the rate profiles were found to be quite different from those known to be characteristic for *trans*-olefin formation by *syn*-elimination. In the latter two systems the *syn* → *trans* reaction thus appears to play a subordinate role, if it occurs at all.

In *cis*-cycloalkene formation from cycloalkyl bromides, the *anti*-elimination pathway seems to be obligatory, regardless of the reaction conditions.

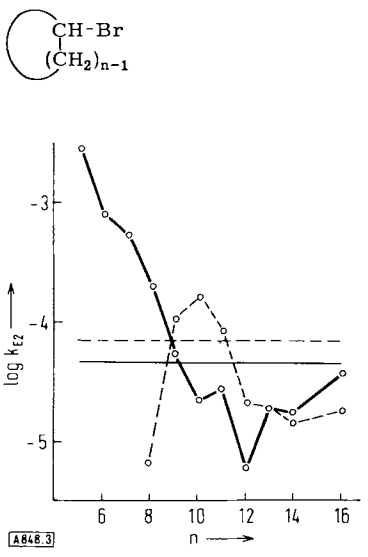
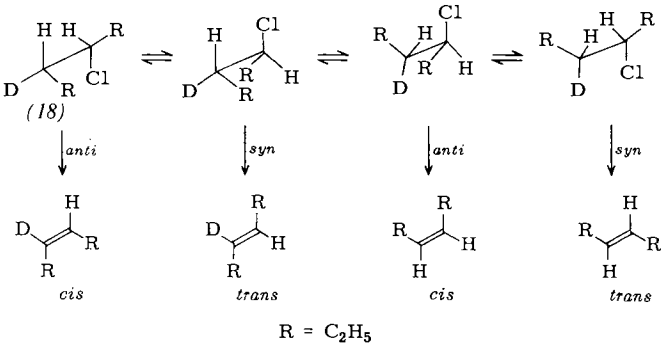


Fig. 3. Plot of log k_{E2} for *cis*- and *trans*-cycloalkene formation from cycloalkyl bromides and potassium *tert*-butoxide in *tert*-butanol at 82.5 °C *versus* the ring size *n*. The horizontal lines indicate the rate of formation of *cis*- and *trans*-4-nonene from 5-bromononane. – – –: *trans*-cycloalkenes; ——: *cis*-cycloalkenes [59].

3.2. Studies Employing Diastereoisomerically β-Deuterium-Labeled Substrates

As already mentioned in Section 2.1.1, deuterium-labeled compounds can be used to determine the relative contributions of the competing *syn* → *cis*, *anti* → *cis*, *syn* → *trans*, and *anti* → *trans* processes to the overall reaction. The procedure entails separate isolation of the two isomeric olefins and determination of their deuterium content[*].

More simply, qualitative or even semiquantitative information concerning the steric course of an elimination may be obtained by comparing the olefin composition obtained from the stereospecifically β-deuterium-labeled reactant with the olefin composition obtained from the non-deuterated "parent" compound. The principle is illustrated in the following example. The reaction of, *e.g.*, [4D]-*threo*-3-hexyl chloride *(18)* to give *trans*-3-hexene by the *syn* route involves rupture of the C—D bond, whereas formation of the same olefin by the *anti* route does not: the formation of *trans*-3-hexene from the *threo*-β-deuterated reactant by the *syn* route is hence slowed down by the operation of a primary deuterium isotope effect, its formation by the *anti* route is not. Consequently, if, relative to the competing formation of *cis*- and *trans*-2-hexene, the proportion of *trans*-3-hexene resulting from the *threo*-β-deuterated reactant is found to be practically the same as that obtained from the parent compound, we must conclude that *trans*-3-hexene formation from *(18)* has taken place by *anti*-elimination. If, on the other hand, the proportion of *trans*-3-hexene from the *threo*-β-deuterated substrate is substantially lower than from the "parent" compound we must conclude that *syn*-elimination is in part, or wholly, responsible for the reaction.



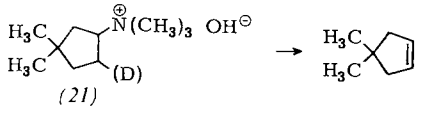
Thus the ratio of the rate constants of the formation of *trans*-3-hexene from non-deuterated and monodeuterated hexyl chloride is available directly from the product composition data. This ratio is an apparent kinetic isotope effect[60][**].

3.2.1. Cycloalkyl Onium Compounds

Degradation of selectively deuterated cyclooctyltrimethylammonium hydroxide *(16a)*, $n = 8$[61, 62], and of selectively deuterated tetramethylcyclodecyltrimethylammonium salts *(19)*[63, 64] confirm the results obtained from rate profile studies (Tables 2 and 3). *trans*-Cyclooctene and 5,5,8,8-tetramethyl-*trans*-cyclodec-1-ene are formed exclusively by *syn*-elimination.

The same technique was used to elucidate the stereochemical course of the formation of *cis*-cycloalkenes having small and medium-sized rings (Table 2). As expected, cyclobutene formation from the cyclobutyl onium hydroxide under "dry" pyrolytic conditions proceeds predominantly by *syn*-elimination[65]. Cyclopentene formation from the onium base using *tert*-butoxide in *tert*-butanol or on "wet" pyrolysis (in steam) at 190 °C is largely an *anti*-elimination reaction[66]; however, "wet" pyrolysis at 110 °C was reported[65] to proceed to approximately equal extents by *syn*- and *anti*-elimination.

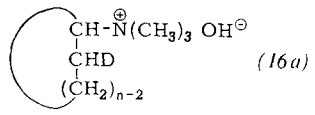
Pyrolysis of 3,3-dimethylcyclopentyltrimethylammonium hydroxide *(21)* to give 4,4-dimethylcyclopentene was found from labeling studies to proceed to the extent of 76% by *syn*-elimination[65]. Since the methyl groups are in a 1,3-relationship to the bulky onium group such a difference seems understandable.



Under pyrolytic conditions, decomposition of cyclohexylammonium hydroxide proceeds to at least 96% by *anti*-elimination[65–67]. In contrast, *cis*-cycloheptene and *cis*-

[*] *Secondary* isotope effects are neglected; this is perfectly legitimate in such cases.

[**] The "apparent" kinetic isotope effect $(k_H/k_D)_{app}$, determined from product composition data will be equivalent to the true deuterium isotope effect k_H/k_D solely when the reaction is exclusively *syn* or exclusively *anti and* this reaction mode requires removal of deuterium. The value of the "true" deuterium isotope effect of the elimination can only be calculated when the deuterium content in the olefinic product is known.



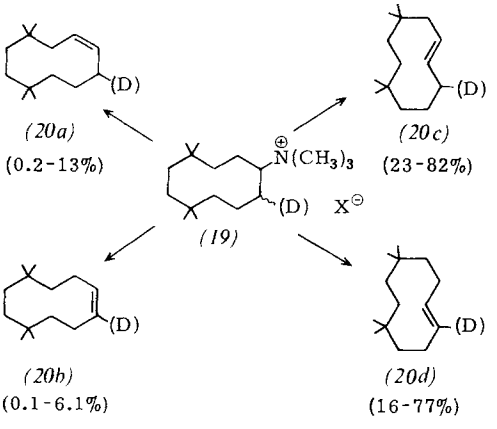
(16a)

No incursion of *syn*-elimination could be detected in the formation of the ten-membered *cis*-olefin *(20b)* from *(19)* using methoxide/methanol[64] (Table 2). Unfortunately, the experiments could not be extended to base/solvent systems which favor *syn*-elimination since the *cis*-olefin *(20b)* is then formed in amounts below 2%. This does, however, indicate that the *syn* → *cis* reaction cannot be of great importance in the cyclodecyl system[*].

Table 2. Steric course of formation of *cis*- and *trans*-cycloalkenes from β-deuterium-labeled cycloalkyltrimethylammonium bases *(16a)*.

(16a) *n* [a]	Reaction conditions [b]	*cis*-Olefin D_1 (%) [c]	*cis*-Olefin *syn*:*anti* [d]	*trans*-Olefin D_1 (%) [c]	*trans*-Olefin *syn*:*anti* [d]	Ref.
4, *cis*	"dry"	69	90: 10	—	—	[65]
5, *cis*	"wet"	86	46: 54	—	—	[65]
5, *cis*	in H_2O, 190°C	98	<10: >90	—	—	[66]
5, *cis*	K *tert*-butoxide in *tert*-butanol, 70°C	95	<15–20: >80–85	—	—	[66]
6, *cis*	"wet"	99	4: 96	—	—	[65]
6, *cis*	in H_2O, 190°C	100	0:100	—	—	[67]
7, *cis*	"dry"	89	37: 63	—	—	[65]
	"wet"	91	31: 69	—	—	[65]
8, *cis*	"dry"	85	51: 49	100	100:1	[61, 62]
8, *trans*	"dry"	89		66		

[a] *trans* and *cis* refer to the positions of $N(CH_3)_3$ and D.
[b] "Dry" and "wet" refer, respectively, to decomposition at 50°C/10^{-7} torr and *ca.* 110°C/*ca.* 60 torr.
[c] Deuterium content as determined by mass spectrometry on isolated individual olefin and corrected for incomplete deuteration in reactant.
[d] Calculated from the deuterium content, assuming $(k_H/k_D)_{syn} = 1.84$.



3.2.2. Cycloalkyl Tosylates

Data are so far available only for ten- and twelve-membered ring systems. The picture for the ten-membered ring derivatives is gratifyingly simple. Both the position isomeric *trans*-cyclodecenes *(23)* and *(24)* appear to be formed by *syn*-elimination almost exclusively, under all the reaction conditions investigated. On the other hand, the *cis*-cyclodecene derivative *(25)* is formed by *anti*-elimination[68].

Table 3. Steric course of formation of *cis*- and *trans*-tetramethylcyclodecenes *(20b)* and *(20c)* from the cyclodecyltrimethylammonium compounds *(19)* [63, 64].

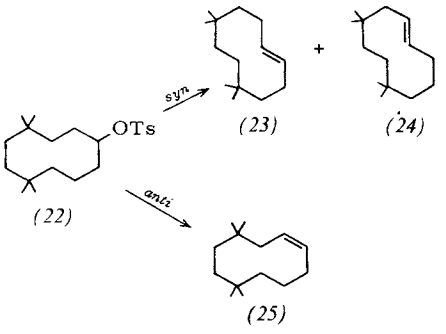
(19) [a]	Reaction conditions	*cis*-Olefin *(20b)* $(k_H/k_D)_{app}$ [b]	D_1 (%) [c]	steric course	*trans*-Olefin *(20c)* $(k_H/k_D)_{app}$ [b]	D_1 (%) [c]	steric course
cis	"dry" [d]	—	—	—	1.3	100	*syn*
trans	"dry" [d]	—	—	—	3.9	0	*syn*
cis	K methoxide in methanol	1.0	—	*anti*	1.1	100	*syn*
trans	K methoxide in methanol	3.6	—	*anti*	2.7	0	*syn*
cis	K *tert*-butoxide in *tert*-butanol	—	—	—	1.2	100	*syn*
trans	K *tert*-butoxide in *tert*-butanol	—	—	—	3.3	0	*syn*
cis	K *tert*-butoxide in DMSO	—	—	—	1.1	100	*syn*
trans	K *tert*-butoxide in DMSO	—	—	—	3.7	0	*syn*

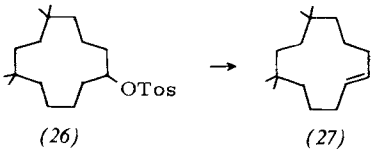
[a] *trans* and *cis* refer to the positions of $N(CH_3)_3$ and D.
[b] Determined by comparison of olefin isomer composition obtained from deuterated and non-deuterated *(19)* [60].
[c] Deuterium content as determined by mass spectrometry on isolated individual olefin and corrected for incomplete deuteration of *(19)*.
[d] Decomposition at 50°C/10^{-7} torr, X = OH.

cyclooctene formation by pyrolysis of the corresponding quaternary onium hydroxides has been found to involve about 34 and 51%, respectively, of *syn*-elimination[65]. Data for the steric course of elimination in homogeneous solution are unfortunately not available.

[*] The following reactivity sequence seems to hold for the ten-membered ring system: *syn* → *trans* ≫ *anti* → *cis* > *syn* → *cis* ≈ *anti* → *trans* (*J. Sicher, G. Jan,* and *M. Schlosser,* Angew. Chem. *83*, 1012 (1971); Angew. Chem. internat. Edit. *10*, 926 (1971)).

For the formation of the *trans*-olefin *(27)*, *syn*-elimination is now no longer the sole reaction path, and the proportion of *syn*- relative to *anti*-elimination using *tert*-butoxide as base falls off sharply on going from the solvent benzene to *tert*-butanol and still more to dimethylformamide[68] (cf. Table 1).





3.2.3. Acyclic Onium Compounds

As already observed in the alicyclic series, acyclic *cis*-olefins of type *(30)* are also formed predominantly or exclusively by *anti*-elimination.

As regards *trans*-olefin formation, however, the situation is distinctly less uniform than in the case of the corresponding alicyclic compounds. *syn*-Elimination does again operate and in many of the cases studied it represents the predominant, if not the sole, route to the *trans*-olefin. However, in other cases it plays only a subordinate role and in one or two instances it appears to be practically absent (Table 4).

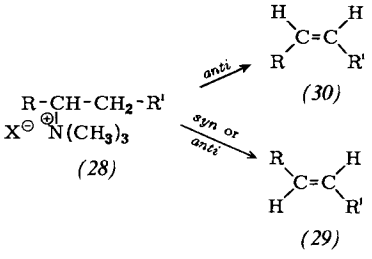


Table 4. Steric course of formation of *trans*-olefins *(29)* and *cis*-olefins *(30)* from ammonium compounds *(28)*.

R	R'	Base and solvent	*trans*:*cis* [a]	*syn*-elimin. (%) *(29)*	*(30)* [b]	Evidence	Ref.
CH_3	CH_3	K ethoxide in DMSO	46:54	0	0	[d]	[69]
CH_3	n-C_3H_7	K *n*-butoxide in *n*-butanol	22:78	0	0	[c]	[70]
CH_3	n-C_3H_7	K *tert*-pentoxide in *tert*-pentanol	30:70	15	0	[d]	[70]
n-C_3H_7	CH_3	NaOH in H_2O	33:67	2	0	[c]	[71]
n-C_3H_7	CH_3	K *n*-butanolate in *n*-butanol	25:75	9	0	[c]	[70]
n-C_3H_7	CH_3	pyrolysis [e]	44:56	44	0	[c]	[71]
n-C_3H_7	CH_3	K *tert*-pentoxide in *tert*-pentanol	49:51	69	0	[c]	[70]
C_2H_5	C_2H_5	NaOH in H_2O	35:65	9	0	[c]	[71]
C_2H_5	C_2H_5	NaOH in 62% DMSO/H_2O	66:34	53	0	[c]	[71]
C_2H_5	C_2H_5	K methoxide in methanol	25:75	20	0	[d]	[70]
C_2H_5	C_2H_5	K *n*-butoxide in *n*-butanol	28:72	16	0	[c]	[71]
C_2H_5	C_2H_5	K *sec*-butoxide in *sec*-butanol	51:49	67	0	[c]	[71]
C_2H_5	C_2H_5	K *tert*-butoxide in *tert*-butanol	67:33	80	0	[d]	[71]
C_2H_5	C_2H_5	pyrolysis [e]	54:46	60	0	[c]	[71]
C_2H_5	C_2H_5	K *tert*-pentoxide in *tert*-pentanol	73:27	83	0	[c]	[70]
n-C_4H_9	n-C_4H_9	K methoxide in methanol	21:79	32	7	[c]	[72]
n-C_4H_9	n-C_4H_9	K *tert*-butoxide in *tert*-butanol	71:29	87	6	[c]	[72]
n-C_4H_9	n-C_4H_9	pyrolysis [e]	71:29	95	5	[c]	[72]
n-C_4H_9	n-C_4H_9	K *tert*-butoxide in DMSO	80:20	91	8	[c]	[72]
n-C_4H_9	n-C_4H_9	K *tert*-butoxide in benzene	91: 9	90	25	[c]	[72]
$(CH_3)_3CCH_2$	n-C_4H_9	K methoxide in methanol	46:54	100	0	[d]	[73]
$(CH_3)_3CCH_2$	n-C_4H_9	K *tert*-butoxide in *tert*-butanol	97: 3	100	0	[d]	[73]
$(CH_3)_3CCH_2$	n-C_4H_9	pyrolysis [e]	94: 6	100	0	[d]	[73]
$(CH_3)_3CCH_2$	n-C_4H_9	K *tert*-butoxide in DMSO	98: 2	100	0	[d]	[73]

[a] Determined in a *cis*-*trans* mixture obtained from unlabeled *(28)*.
[b] Percentage *syn*-elimination (*syn* + *anti* = 100) in formation of *(29)* and *(30)* respectively.
[c] Evaluated from deuterium analyses on products from *threo*- and *erythro*-β-deuterated *(28)* corrected with assumed $(k_H/k_D)_{syn}$ and $(k_H/k_D)_{anti}$; for details see original papers.
[d] Estimated from $(k_H/k_D)_{app}$, the apparent isotope effects, calculated from product proportions.
[e] X = OH.

Two regularities clearly emerge from this picture. The first is the tendency, encountered previously (Table 1), for the *syn* → *trans* route to become appreciably more important than the *anti* → *trans* route as the base becomes stronger (bulkier) and the solvent less dissociating. Thus, in the case of *trans*-3-hexene formation from 2-hexyltrimethylammonium hydroxide, *syn*-elimination accounts for only 9% of the *trans*-olefin formed in aqueous sodium hydroxide; on addition of dimethyl sulfoxide the contribution of *syn*-elimination increases, accounting for 53% of the *trans*-3-

hexene formed when the hydroxide contains 62 mole-% dimethyl sulfoxide[70].

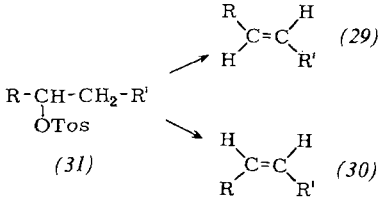
The proportion of *syn*-elimination is only small on reaction of 3-hexyl- and 5-decylammonium salts with primary alkoxide in primary alcohols but definitely becomes the principal reaction mode with tertiary alkoxides in tertiary alcohols or with tertiary alkoxides in an aprotic solvent such as benzene or a polar solvent like dimethyl sulfoxide.

A second remarkable and distinct trend is also apparent from the data in Table 4. It may be seen that the contribution of the *syn* → *trans* reaction increases significantly with the length and degree of branching of the aliphatic chain R, while the choice of steric course is less sensitive to the nature of the group R'. It is informative to compare the formation of *trans*-2-hexene (15 and 69% *syn* route) and *trans*-3-hexene (83% *syn*) from 2- and 3-hexyltrimethylammonium salts [*(28)*, $R=CH_3, R'=C_3H_7$; $R=C_3H_7, R'=CH_3$; $R=R'=C_2H_5$] on treatment with potassium *tert*-pentoxide in *tert*-pentanol.

The case of *trans*-2-butene formation is of particular interest in this context; the evidence is still fragmentary but the available information is consistent with the view that the tendency for *syn*-elimination is very small[69].

3.2.4. Acyclic Alkyl Tosylates

As in the cyclic series, the tendency towards *syn*-elimination is again lower than for the corresponding onium derivatives. The dependence on base/solvent character appears to follow the already familiar pattern. Thus, in DMSO and



3.3. Acyclic Alkyl Halides

As already mentioned (see Section 2.2.1) a direct insight into the stereochemical course of base-induced dehydrohalogenation was provided by studies with selectively deuterated diastereoisomeric alkyl halides[17].

In the meantime, some attempts have also been made to derive qualitative information from less direct evidence. Thus it has been found[76] that the ratio of *trans*- to *cis*-2-pentene obtained in the elimination of 2,2,4,4-tetradeuterio-3-pentyl halides using *tert*-butoxide in *tert*-butanol is significantly lower than that obtained under the same conditions from the "non-deuterated" halide. Since the deuterium isotope effect of *anti*-elimination is now known to be significantly greater for *anti*- than for *syn*-elimination, the observed situation is thus compatible with a dichotomous elimination pattern.

Similarly, it has been suggested that differential contributions by *syn*- and *anti*-elimination could be partly responsible for the characteristic effect of the base/solvent system used upon the *trans/cis* olefin ratios formed in the dehydrohalogenation of 2-hexyl halides[7].

3.4. Eliminations Leading to Trisubstituted Ethylenes: The *syn-anti* and the Hofmann-Saytzeff Dichotomies

Hardly any other aspect of elimination reactions has been discussed as extensively as that of orientation in olefin formation. The discovery that *syn*-elimination is a common reaction mode in the formation of disubstituted olefins places the problem of orientation in a new light. In particular, the question arises whether a relationship exists between the two aspects: steric course and orientation.

That there is indeed such a relationship is suggested by the course of the degradation of *threo*- or *erythro*-(6-methyl-5-decyl)trimethylammonium bromide *(32)* under various conditions[77]. The steric course of formation of the isomeric Saytzeff products *(33)* and *(34)* follows directly from a configurational correlation between reactant and product. Although no direct experimental evidence is available on the steric course of the formation of the disubstituted (Hofmann) ethylenes *(35)* and *(36)*, consideration of earlier findings (Sections 3.1, 3.2.1, 3.2.3) leads to the conclusion that the *trans*-isomer *(35)* arises mainly or exclusively by

Table 5. Steric course of formation of *trans*-olefins *(29)* and *cis*-olefins *(30)* from tosyl compounds *(31)*.

R	R'	Base and solvent	*trans*:*cis* [a]	*syn*-elimin. (%) *(29)*	*(30)* [b]	Ref.
CH_3	CH_3	K ethoxide in ethanol	[c]	0	0	[18]
CH_3	CH_3	K *tert*-butoxide in DMSO	72:28	0	0	[74]
CH_3	CH_3	K ethoxide in DMSO	70:30	0	0	[74]
n-C_4H_9	n-C_4H_9	K *tert*-butoxide in benzene	46:54	33	8	[40]
n-C_4H_9	n-C_4H_9	K *tert*-butoxide in *tert*-butanol	29:71	16	8	[40, 75]
n-C_4H_9	n-C_4H_9	K *tert*-butoxide in DMF	76:24	4.5	8	[40]

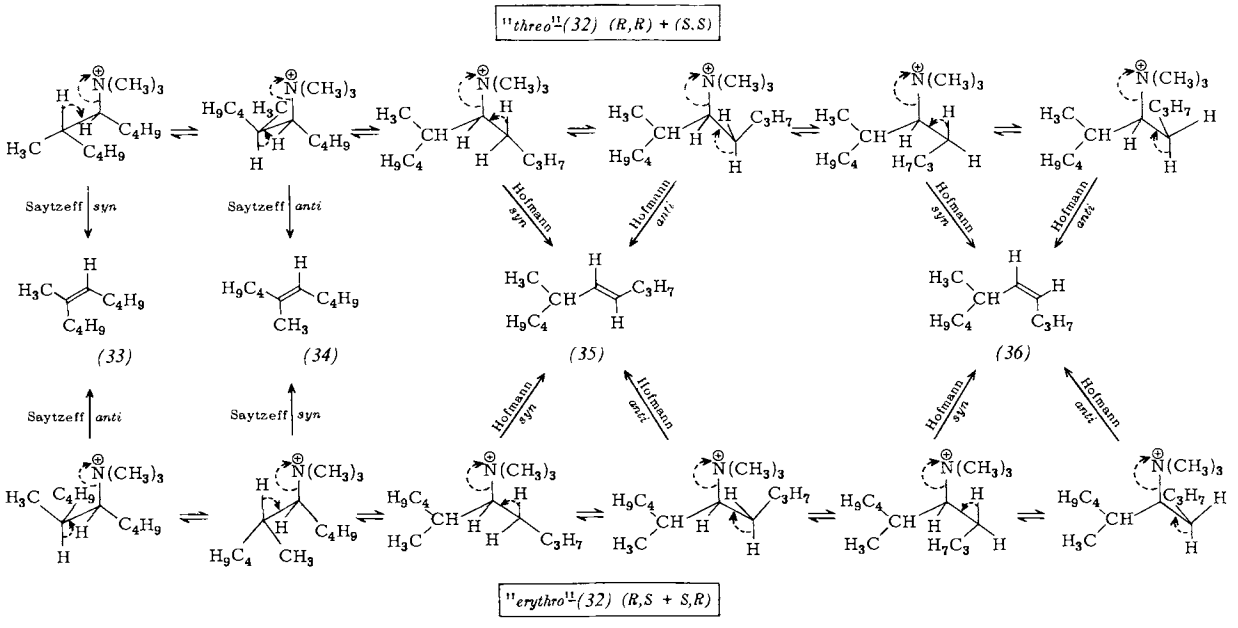
[a] Determined in a *cis-trans* mixture obtained from unlabeled *(31)*.
[b] Percentage *syn*-elimination (*syn* + *anti* = 100) in formation of *(29)* and *(30)* respectively.
[c] Not reported.

when the substrate bears a short, straight-chain substituent *syn*-elimination makes no, or very little, contribution to *trans*-olefin formation. However, *syn* participation increases when the solvent is changed to *tert*-butanol, or even more so in the case of benzene, and also on transition to branched systems (Table 5). Furthermore, *syn*-elimination participates only slightly, if at all, in the formation of the *cis*-olefin.

syn-elimination and the *cis*-olefin *(36)* by *anti*-elimination. It is then possible to draw the following conclusions from the data presented in Table 6: The contribution of *syn*-elimination to the formation of both the disubstituted and the trisubstituted ethylene increases steeply on going from a protic solvent (methanol) to a less protic one (*tert*-butanol), a polar one (dimethyl sulfoxide), or especially to an aprotic, non-polar solvent (benzene). In some cases, this

4. Tentative Rules Regarding the Steric Course of E2 Reactions

The results discussed in the preceding Section have shown that *syn*-elimination is a more frequent reaction mode than has previously been assumed. Both *anti*- and *syn*-elimination should be looked upon as "normal", *i.e.* frequent,



difference is very pronounced, *e.g.* where the Hofmann-Saytzeff dichotomy appears as a reflection of the *syn-anti* dichotomy, the Hofmann olefin, if our analogy is correct, being formed predominantly by *syn*-, and the Saytzeff olefin predominantly by *anti*-elimination. However, such a situation is clearly not general, as a consideration of the elimination using *tert*-butoxide in benzene shows. Here elimination both in the Hofmann as well as in the Saytzeff direction proceeds by *syn*-elimination.

modes in bimolecular reactions, the operation of the one or the other process depending on the structural features of the reactants (substrate and base), as well as on the nature of the solvent. The following incomplete and tentative rules can be given.

Table 6. Formation of the Saytzeff products *(33)* and *(34)* and of the Hofmann products *(35)* and *(36)* from the ammonium compound *(32)*.

(32) Config.	Base and solvent	Rel. yields (%) *(33)*	*(34)*	*(35)*	*(36)*	$\frac{(35)+(36)}{(33)+(34)}$
threo	*tert*-butoxide in benzene	3.16	0.36	96.42	0.06	27.4
erythro	*tert*-butoxide in benzene	0.18	4.51	95.31	0.00	20.3
threo	*tert*-butoxide in *tert*-butanol	0.18	4.43	93.94	1.45	20.7
erythro	*tert*-butoxide in *tert*-butanol	1.82	1.25	95.96	0.97	31.6
threo	*tert*-butoxide in DMSO	0.21	2.28	97.51	0.00	39.2
erythro	*tert*-butoxide in DMSO	0.71	0.40	98.59	0.30	89.1
threo	pyrolysis [a]	0.44	15.68	82.27	1.61	5.20
erythro	pyrolysis [a]	5.05	0.94	92.16	1.85	15.7
threo	methoxide in methanol	0.16	53.30	38.26	8.28	0.87
erythro	methoxide in methanol	42.09	2.25	49.25	6.41	1.25

[a] OH in place of Br.

Reactant structure: Conditions for *syn*-elimination appear to be favorable in bicyclic systems, such as bicyclo[2.2.1]-heptane and bicyclo[2.2.2]octane, and in the monocyclic systems cyclobutane and cyclopentane and then again in

the medium sized rings (8—14 ring members). In open chain alkyl systems, the tendency for H—X elimination to proceed by the *syn* rather than the *anti* pathway is greater when the alkyl groups are long or branched.

The tendency for *syn*-elimination is greater in eliminations leading to 1,2-disubstituted ethylenes than in those yielding trisubstituted ethylenes.

Olefin configuration: *syn*-Elimination is more likely to be encountered, if at all, in the formation of the *trans*-alkene (or *trans*-cycloalkene). The *cis*-alkenes are formed almost exclusively by an *anti* process.

Leaving group: Other factors being equal, *syn*-elimination is more likely to be encountered when the leaving group is an ammonium or sulfonium group. Chlorine, bromine, and tosyloxy leaving groups are more likely to cause *anti*-elimination.

Base: For alkoxide bases, the tendency of the elimination to prefer the *syn*-pathway increases in the order $^{\ominus}OCH_3 < {}^{\ominus}OC_2H_5 < {}^{\ominus}O\text{-}n\text{-}C_4H_9 < {}^{\ominus}O\text{-}sec\text{-}C_4H_9 < {}^{\ominus}O\text{-}tert\text{-}C_4H_9$.

Solvent: Other factors being equal, *syn*-elimination is more likely to be encountered in weakly dissociating solvents, *e.g.* benzene or *tert*-butanol than in solvents such as dimethyl sulfoxide or methanol, which favor *anti*-elimination.

5. Mechanism of *syn*- and *anti*-Elimination

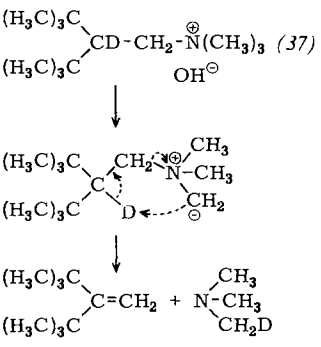
The problem of bimolecular elimination mechanisms has been treated in detail in monographs[78] and several reviews[6, 79–81]. We therefore do not have to survey the problem extensively; nevertheless since all these treatments, except one[81], are based on the view of generally preferred *anti*-elimination it will be useful to discuss here certain new, or novel, aspects which follow from the discovery of the facility of *syn*-elimination.

5.1. Is *syn*-Elimination a One-Step Process?

The strong "prejudice" against bimolecular *syn*-elimination has in the past led some authors to consider alternative, sometimes circuitous, reaction paths for products whose formation could more simply be accounted for by *syn*-elimination, according to the motto "*nicht sein kann, was nicht sein darf*"[82]. One of the questions which, however, it is undoubtedly necessary to consider is whether *syn*-elimination is actually a true single-step process.

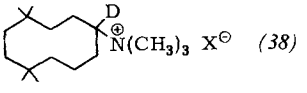
For onium compounds, a two-step *syn*-elimination mechanism is indeed well known[83]. This mechanism, referred to as α′,β-elimination, is normally followed when an organometallic reagent, such as phenyllithium, is employed as base. In such a case, it involves, in the first step, proton removal from a nitrogen-bound methyl group, followed, in a discrete second step, by intramolecular proton transfer from the β position of an ethyl or a longer alkyl group to the carbanion of the intermediate *N*-ylide.

With alkoxides and related bases a substantial contribution of this mechanism has thus far been found for a single instance only[84], namely the pyrolysis of [2D]-2-*tert*-butyl-3,3-dimethylbutyltrimethylammonium hydroxide *(37)*. The replacement of the *tert*-butyl groups by other alkyl groups brings the contribution of the α′,β-mechanism down to zero or a very low percentage at most[85].



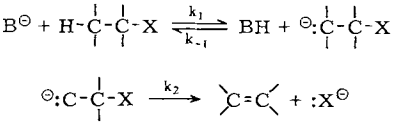
(37)

The α-deuterium labeled ammonium derivative *(38)* was found to give olefins practically without loss of label[64]. No exchange has thus taken place with solvent, and this clearly excludes the α-elimination mechanism, which would pass through a carbene and is very unlikely here anyway.



(38)

The possibility has to be considered that the elimination could be a two-step process of the type E1cb, involving, as the first step, removal of a proton in the β position, followed by release of the leaving group X from C^{α} in a second step (Scheme 9)[86].



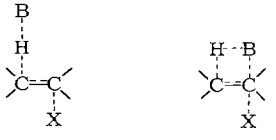
Scheme 9.

Good arguments have been given that substrates of the type considered in this review are unlikely to give rise to a carbanion intermediate which would regenerate the reactant by reaction with external solvent faster, or at a comparable rate, than it gives olefin (reversible E1cb, $k_{-1} \geq k_2$)[81, 87].

On the other hand, the formation of a carbanion intermediate which either does not revert to reactant (irreversible E1cb, $k_{-1} < k_2$) or one that does so in an invisible reaction cannot be rigorously excluded. In the latter case ("E1cb-HBA"[89]) the intermediate could be visualized as a complex between the anion and the alcohol molecule which arose through proton removal[88, 89]. Such a species (a hydrogen bonded anion) would thus revert to reactant without change in configuration and would be suitably set up for *syn*-elimination. As recently pointed out[90], this mechanism would be consistent with the very low deuterium isotope effect found for most *syn*-eliminations ($k_H/k_D \approx 2$). Whether a mechanism of this kind is operating or not is difficult to prove experimentally; it is important to note, however, that the argument given in the sequel for one-step *syn*-elimination would—*mutatis mutandis*—apply to this mechanism also.

5.2. Role of the Base in *anti*-Elimination (E2C and E2H Mechanism)

It was recognized only relatively recently that in bimolecular *anti*-elimination reactions the base could fulfil two functions: in addition to attacking the hydrogen on C^{β}, it could accelerate the reaction by nucleophilically assisting C^{α}—X bond fission (Scheme 10)[83,91].



E2H E2C

Scheme 10.

Simultaneous attack by the base on the C^{α} atom and the β-hydrogen atom is now termed an E2C reaction, and the mechanistic alternative of exclusive interaction between the base and the β-hydrogen atom is denoted E2H.

It may be significant in this context that a reasonably good correlation has been found between the rates of *cis*-cycloalkene formation (presumably largely or entirely by *anti*-elimination) in reactions of homologous series of cycloalkyl onium bases[51] or cycloalkyl bromides[59] and those of an S_N2 reaction on cycloalkyl bromides (Fig. 4).

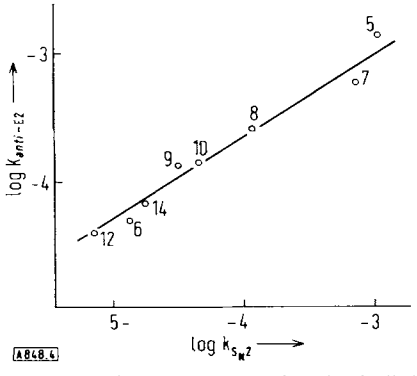
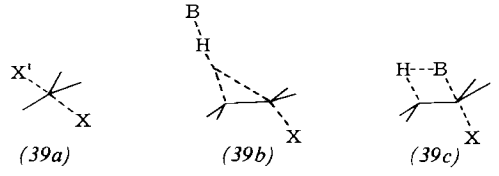


Fig. 4. Plot of log k_{S_N2} of the reaction of cycloalkyl bromides with potassium iodide in acetone, against log $k_{anti-E2}$ of *cis*-cycloalkene formation from cycloalkylammonium chlorides with potassium *tert*-butoxide in *tert*-butanol (numbers in Figure represent ring size).

We have suggested[51,59] that this correlation could be a consequence of a similar geometry around the C^{α} carbon in *anti*-elimination and bimolecular substitution, and thus form evidence for a "double engagement" of the base in the elimination[*].

[*] In private discussions the author accepted a slightly modified concept: The similarity of the rate profiles primarily suggests a comparable electronic environment of the C^{α} atom in the transition state of substitution *(39a)* and in that of *anti*-elimination. However, this would apply



(39a) *(39b)* *(39c)*

just as well to an elimination transition state *(39b)* in which the CH bonding pair has already partly migrated to the α carbon atom, as in the case of the E2C transition state *(39c)*.

Other evidence for the E2C mechanism has been provided by other authors[92-94] in rather different systems. The whole E2C/E2H concept has, however, recently also been criticized[7,95,96].

5.3. Mechanistic Information from the Effects of Variables on the *syn-anti* Ratio in E2 Reactions

5.3.1. The Timing of Bond Changes

A poor leaving group X will favor an E2 transition state in which the process of C^{β}—H bond breaking is considerably progressed while C^{α}—X is largely intact. It has also been assumed that with stronger bases the process of C^{β}—H bond breaking will become more important, but this point of view has recently been challenged[97].

An explanation of the enhancement of *syn*- relative to *anti*-elimination by poor leaving groups and strong (bulky) bases would therefore lie in extensive C^{β}—H bond breaking, assumed to be characteristic of the transition state of a *syn*-elimination. Such an assumption would also account for the notoriously low hydrogen isotope effects, the low Hammett ρ constants[34], and the modest k_{Br}/k_{OTos} ratios[34]. This conclusion would, indeed, be consistent with the concept of a *syn*-elimination mechanism involving an "inversion" on C^{β} (Scheme 4), made possible by the fact that "sufficient ionicity has developed on both sides of this carbon"[11].

According to an alternative view[70,71], the increased tendency for *syn*-elimination with poorer leaving groups and stronger bases results from the fact that in the "more reactant-like transition state" the stereoelectronic constraints towards *anti*-elimination are less pronounced, thus giving the *syn*-mechanism a better chance to compete.

The difference between these two points of view is not merely of a semantic nature. According to the first, the suitable timing of the bond changes actually leads to a lowering of energy for the *syn*-elimination process compared to a (hypothetical) synchronous mechanism; according to the second, *syn*-elimination is not accelerated *absolutely* but merely *relatively* because the usual advantages of *anti*-periplanarity are largely lost.

The entire problem of the timing of the bond changes in elimination reactions may turn out to be even more complex. There is some evidence already that the extent of C^{α}—X and C^{β}—H bond breaking need not necessarily be complementary: thus, there are data which may be interpreted as suggesting that in certain eliminations extensive C^{β}—H bond breaking is accompanied by extensive C^{α}—X bond breaking, a situation referred to as the "E1cb-paradox"[98]. There is also the question whether a spectrum of transition states, analogous to that believed to exist for *anti*-elimination, should not also be considered for *syn*-eliminations[7].

So far in this discussion we have largely stressed the electronic properties of the base and the leaving group. It must be kept in mind that for the alkoxides base "strength" goes parallel with "steric bulk"; similarly, for the departing group X some parallelism may be discerned between "leaving group capacity" and bulk, the onium group being both

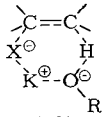
bulkier as well as a "poorer" leaving group than halides or tosylates. We return to this point in Section 5.3.3.

The electronic and steric points of view are, at any rate in this instance, not mutually exclusive: effects of both types could operate and contribute to the observed behavior.

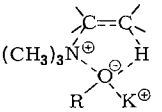
5.3.2. Solvent and Ion-Pair Formation

Solvents such as benzene or *tert*-butanol which favor *syn*-elimination enhance the base strength of the alkoxide ion and this alone could, in the light of the effects discussed above, be responsible for the observed high *syn-anti* ratio. If this were the case, use of the solvents dimethylformamide or dimethyl sulfoxide, in which alkoxide is a very strong base, should further enhance *syn*-elimination. In practice the very opposite is true.

The effect which makes the non-polar solvents favorable for *syn*-elimination may thus be that they support an ion pair association. Such an association will tend to enhance *syn*-elimination since it makes possible a cyclic mechanism. The same feature is clearly unfavorable for *anti*-elimination because it would require separation of charged species.



(40)



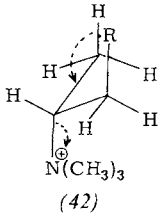
(41)

An analogous formulation is possible for onium base elimination: here one can visualize an association between the ammonium ion and an alkoxide ion. Again, a solvent which would stabilize an ion pair of this type would enhance *syn*-elimination [transition state *(41)*].

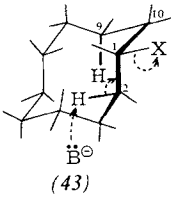
Cyclic multi-center mechanisms were invoked some years ago[99] to explain the occurrence of *syn*-eliminations and recently also of *cis*-eliminations leading to triple bonds[100].

5.3.3. Carbon Skeleton of the Reactant

We have noted (see Section 4) that long-chain and branched alkyl groups promote the *syn* mode. An explanation has been given on the basis of steric hindrance to approach of the base in the *anti* process[70][*].



(42)



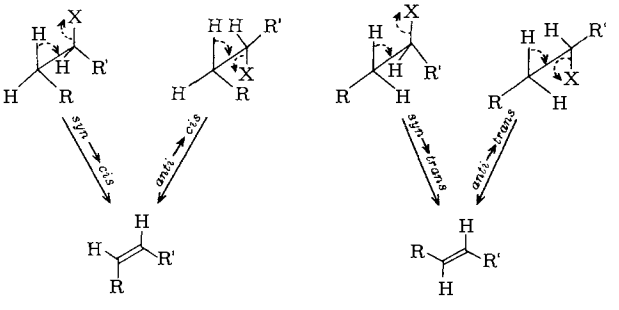
(43)

The argumentation makes use of the reasonable assumption that a *sec*-alkyl-trimethylammonium compound will prefer the conformation *(42)* in which the alkyl group R and the bulky trimethylammonium group are separated by the greatest possible distance. It can then readily be seen that the group R can effectively obstruct attack by the base on the *anti* β hydrogen, and this is why—when R≠H—*anti*-elimination is suppressed and *syn*-elimination gets a chance to compete.

The stereochemical situation is similar in cyclic reactants[71]. Assuming for the ten-membered ring the conformation *(43)* we see that the hydrogen atom *anti* to the leaving group X is in an encumbered 1,3-relationship to the C^9—C^{10} bond and, moreover, in an intraannular position; it is hence not accessible to attack by base. The unusually high ratio of *syn*- to *anti*-elimination in the formation of medium sized *trans*-cycloalkenes[53] thus becomes understandable, although other factors are certainly also involved[57].

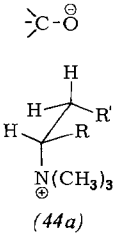
5.4. Speculations on the Cause of the Stereoselectivity in *syn*- and *anti*-Elimination

So far the discussion has been concerned with the distinction between the overall *syn*-elimination process and the overall *anti*-elimination process. We now have to consider in more detail the stereochemical course of those reactions which lead to *cis/trans* isomeric olefins and to distinguish between the four routes possible for a coplanar process, *viz. cis*- and *trans*-olefin forming *syn*-elimination *(syn → cis* and *syn → trans)* and *cis*- and *trans*-olefin forming *anti*-elimination *(anti → cis* and *anti → trans)* (Scheme 11).

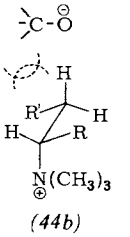


Scheme 11.

It is not difficult to find a simple steric explanation for the tendency of *syn*-elimination to lead preferentially to *trans*-olefins. Since the *syn → cis* route requires an eclipsed or near-to-eclipsed arrangement of two neighboring alkyl groups (R, R') it is clearly at a disadvantage.



(44a)



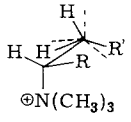
(44b)

It is less simple to give an explanation for the complementary observation, *i.e.* that *anti*-elimination leads preferentially to the *cis*-olefin. An explanation has been proposed based on the model already discussed (see Section 5.3.3)[70]. It is pointed out that (particularly if R is bulky) the hydro-

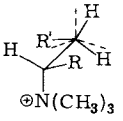
[*] Steric hindrance to solvation of the leaving anion may also play an important role (cf. *J. Sicher, G. Jan,* and *M. Schlosser,* Angew. Chem. *83,* 1012 (1971); Angew. Chem. internat. Edit. *10,* 926 (1971)).

gen on C^{β} is "shielded on both sides" in conformation *(44b)* while in conformation *(44a)* it is "relatively open to attack" on one side. If now "non-linear approach of the base is energetically feasible, *cis*-olefin could form faster than *trans*-olefin, especially with the bulkier bases".

A somewhat modified picture[101] of the transition state may make the above interpretation more readily acceptable. The basic argument is to be found in the assumption that the dihedral angles between vicinal bonds do not necessarily have to be exactly 60° but would, on the contrary, deviate from the idealized staggered arrangement if this were to lead to an overall drop in intramolecular repulsion. Since the dominating *gauche* interaction in the molecule is that between the alkyl group R′ and the trimethylammonio group, the conformers *(44a)* and *(44b)* would adopt the more favorable arrangements *(45a)* and *(45b)*.



(45a)



(45b)

This alteration of the dihedral angle could also apply to the elimination transition state since it probably possesses only very slight double bond character. The base would then encounter the hydrogen to be eliminated in a congested environment in the transition state *(45b)* for *trans*-olefin formation, whereas the hydrogen attacked in *cis*-olefin formation in *(45a)* would be readily accessible.

The above arguments refer specifically to base-induced ammonium salt degradation; however, an analogous situation ($k_{anti \rightarrow cis} > k_{anti \rightarrow trans}$) is encountered in certain tosylate eliminations presumably again under conditions where the transition state has only little double bond character. Thus, 2-butyl tosylate with *tert*-butoxide in *tert*-butanol gives more *cis*- than *trans*-butene[102, 103] although the elimination presumably proceeds largely, or exclusively, through the *anti* process. Following the above arguments, we should have to assume that under these conditions the steric effects are not large enough to suppress *anti*-elimination, yet sufficient to direct *anti*-elimination preferentially into the *anti* → *cis* channel[*].

According to an alternative interpretation of the stereoselectivity of the two elimination modes[104], the observed trend could be rationalized on the grounds that the two hydrogens on C^{β}, being diastereotopic, differ intrinsically in reactivity—in any rotational conformation[**]. Inspection of the four alternative rotameric arrangements depicted in Scheme 11 shows that the rapidly occurring elimination processes *syn* → *trans* and *anti* → *cis* involve removal of the *pro-threo* hydrogen, while the less favorable elimination routes *syn* → *cis* and *anti* → *trans* necessitate removal of the *pro-erythro* hydrogen. This is, of course, a *post hoc* argument and plausible interpretations of the chemical nonequivalence of the hydrogen atoms on C^{β} cannot be given without the postulation of new effects.

Received: April 24, 1970 [A 848 IE]
German version: Angew. Chem. *84*, 177 (1972)

[*] Neither previous arguments to account for preferred *cis*-olefin formation in open-chain tosylate elimination [102, 103] nor the fascinating yet difficult problem of the relationship between *trans-cis* olefin composition in elimination reactions and the relative thermodynamic stabilities of the two isomers, which has recently been treated elsewhere [43], will be discussed here.

[**] This is reminiscent of the differential proton mobilities found for the diastereotopic hydrogen atoms of several sulfoxides ([105], see, however, [106]).

[1] *C. H. DePuy, R. D. Thurn,* and *G. F. Morris,* J. Amer. Chem. Soc. *84*, 1314 (1962).

[2] *M. M. Kreevoy, J. W. Gilje, L. T. Ditsch, W. Batorewicz,* and *M. A. Turner,* J. Org. Chem. *27*, 726 (1962).

[3] *J. Závada, J. Krupička,* and *J. Sicher,* Collect. Czech. Chem. Commun. *28*, 1664 (1963).

[4] *D. V. Banthorpe, E. D. Hughes,* and *C. K. Ingold,* J. Chem. Soc. *1960*, 4054.

[5] *C. H. DePuy* and *R. W. King,* Chem. Rev. *60*, 431 (1960).

[6] *W. S. Saunders* in *S. Patai:* The Chemistry of Alkenes. Interscience, New York 1964.

[7] *R. A. Bartsch* and *J. F. Bunnett,* J. Amer. Chem. Soc. *91*, 1376 (1969).

[8] *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. Cornell University Press, Ithaca 1953.

[9] *M. L. Dhar, E. D. Hughes, C. K. Ingold, K. K. Mandour, G. A. Maw,* and *L. I. Woolf,* J. Chem. Soc. *1948*, 2093.

[10] *E. D. Hughes,* J. Amer. Chem. Soc. *57*, 708 (1935).

[11] *C. K. Ingold,* Proc. Chem. Soc. *1962*, 265.

[12] *K. Fukui,* Tetrahedron Lett. *1965*, 2427; *K. Fukui* and *H. Fujimoto, ibid. 1965*, 4303; Bull. Chem. Soc. Japan *40*, 2018 (1967); *K. Fukui, H. Hao,* and *H. Fujimoto, ibid. 42*, 348 (1969).

[13] *W. T. Dixon,* Chem. Ind. (London) *1967*, 789.

[14] *Nguyen Trong Anh,* Chem. Commun. *1968*, 1089.

[15] Cf. also *E. L. Eliel, N. L. Allinger, S. J. Angyal,* and *G. A. Morrison:* Conformational Analysis. Interscience, New York 1965, p. 483.

[16] *J. Hine,* J. Amer. Chem. Soc. *88*, 5525 (1966).

[17] *P. S. Skell* and *R. G. Allen,* J. Amer. Chem. Soc. *81*, 5383 (1959); *P. S. Skell, R. G. Allen,* and *G. K. Helmkamp, ibid. 82*, 410 (1960).

[18] *P. S. Skell* and *W. L. Hall,* J. Amer. Chem. Soc. *85*, 2851 (1963).

[19] *M. C. Hoff, K. W. Greenlee,* and *C. E. Boord,* J. Amer. Chem. Soc. *73*, 3329 (1951).

[20] *F. C. Bordwell* and *P. S. Landis,* J. Amer. Chem. Soc. *79*, 1593 (1957).

[21] *W. E. Truce* and *J. J. Breiter,* J. Amer. Chem. Soc. *84*, 1623 (1962).

[22] *S. W. Staley* and *R. F. Doherty,* Chem. Commun. *1969*, 288; see Footnote.

[23] *A. Michael* and *G. Tissot,* J. prakt. Chem. *46*, 392 (1892).

[24] *Holmberg,* Ark. Kemi, Min. Geol. *8*, No. 2 (1920).

[25] *E. D. Hughes* and *J. C. Maynard,* J. Chem. Soc. *1960*, 4087.

[26] *D. J. Cram, F. D. Greene,* and *C. H. DePuy,* J. Amer. Chem. Soc. *78*, 790 (1956).

[27] *J. Weinstock* and *F. G. Bordwell,* J. Amer. Chem. Soc. *77*, 6706 (1955).

[28] *G. Ayrey, E. Buncel,* and *A. N. Bourns,* Proc. Chem. Soc. *1961*, 458.

[29] *A. C. Cope, G. A. Berchtold,* and *D. L. Ross,* J. Amer. Chem. Soc. *83*, 3859 (1961).

[30] *S. J. Cristol* and *F. R. Stermitz,* J. Amer. Chem. Soc. *82*, 4692 (1960).

[31] *M. A. Baldwin, D. V. Banthorpe, A. G. Loudon,* and *F. D. Waller,* J. Chem. Soc. *B 1967*, 509.

[32] *J. Levisalles, J. C. N. Ma,* and *J.-P. Pete,* Bull. Soc. Chim. France *1963*, 1126.

[33] a) *R. D. Stolow, T. Groom,* and *D. I. Lewis,* Tetrahedron Lett. *1969*, 913; b) *E. J. Gabe* and *D. F. Grant,* Acta Cryst. *15*, 1074 (1962).

[34] *C. H. DePuy, G. F. Morris, J. S. Smith,* and *R. J. Smat,* J. Amer. Chem. Soc. *87*, 2421 (1965).

[35] *C. W. Bird, R. C. Cookson, J. Hudec,* and *R. O. Williams,* J. Chem. Soc. *1963*, 410; see also *J. L. Coke* and *M. P. Cooke jr.,* J. Amer. Chem. Soc. *89*, 2779 (1967).

[36] *H. Kwart, T. Takeshita,* and *J. L. Nyce,* J. Amer. Chem. Soc. *86*, 2606 (1964).

[37] *J. K. Stille, F. M. Sonnenberg,* and *T. H. Kinstle,* J. Amer. Chem. Soc. *88*, 4922 (1966).

[38] *J. K. Stille* and *F. M. Sonnenberg,* Tetrahedron Lett. *1966*, 4587.

[39] *J. L. Coke* and *M. P. Cooke,* J. Amer. Chem. Soc. *89*, 6701 (1967).

[40] *J. Zavada, M. Pánková,* and *J. Sicher,* Chem. Commun. *1968,* 1145.

[41] *N. A. LeBel, P. D. Beirne, E. R. Karger, J. C. Powers,* and *P. M. Subramanian,* J. Amer. Chem. Soc. *85,* 3199 (1963).

[42] See also *S. J. Cristol* and *E. F. Hoegger,* J. Amer. Chem. Soc. *79,* 3438 (1957); *N. A. LeBel, P. D. Beirne,* and *P. M. Subramanian, ibid. 86,* 4144 (1964).

[43] For details see *J. Sicher,* Rev. Pure Appl. Chem. *25,* 655 (1971).

[44] *J. Sicher* in *P. B. D. de la Mare* and *W. Klyne:* Progress in Stereochemistry. Butterworth, London 1962, Vol. 3.

[45] *R. Heck* and *V. Prelog,* Helv. Chim. Acta *38,* 1541 (1955).

[46] *H. C. Brown* and *G. Ham,* J. Amer. Chem. Soc. *78,* 2735 (1956).

[47] *H. C. Brown* and *K. Ichikawa,* Tetrahedron *1,* 221 (1957).

[48] *R. Huisgen, I. Ugi, M. T. Assemi,* and *J. Witte,* Liebigs Ann. Chem. *602,* 127 (1957).

[49] *C. Rüchardt,* Angew. Chem. *82,* 845 (1970); Angew. Chem. internat. Edit. *9,* 830 (1970).

[50] *J. Sicher, J. Závada,* and *J. Krupička,* Tetrahedron Lett. *1966,* 1619.

[51] *J. Sicher* and *J. Závada,* Collect. Czech. Chem. Commun. *32,* 2122.

[52] *J. Závada* and *J. Sicher,* Collect. Czech. Chem. Commun. *32,* 3701 (1967).

[53] *J. Sicher* and *J. Závada,* Collect. Czech. Chem. Commun. *33,* 1278 (1968).

[54] *M. R. V. Sahyun* and *D. J. Cram,* J. Amer. Chem. Soc. *85,* 1263 (1963).

[55] *A. C. Cope* and *E. R. Trumbull,* Org. Reactions *11,* 317 (1960).

[56] *D. C. Cram* and *J. E. McCarty,* J. Amer. Chem. Soc. *76,* 5740 (1954); *A. C. Cope* and *E. M. Acton, ibid. 80,* 355 (1958).

[57] *J. Závada, J. Krupička,* and *J. Sicher,* Collect. Czech. Chem. Commun. *31,* 4273 (1966).

[58] *J. Závada, J. Krupička,* and *J. Sicher,* Chem. Commun. *1967,* 66.

[59] *J. Závada, J. Krupička,* and *J. Sicher,* Collect. Czech. Chem. Commun. *33,* 1393 (1968).

[60] *M. S. Silver,* J. Amer. Chem. Soc. *83,* 3482 (1961).

[61] *J. L. Coke, M. P. Cooke,* and *M. C. Mourning,* Tetrahedron Lett. *1968,* 2247.

[62] *J. L. Coke* and *M. C. Mourning,* J. Amer. Chem. Soc. *90,* 5561 (1968).

[63] *J. Závada, M. Svoboda,* and *J. Sicher,* Tetrahedron Lett. *1966,* 1627.

[64] *J. Závada, M. Svoboda,* and *J. Sicher,* Collect. Czech. Chem. Commun. *33,* 4027 (1968).

[65] *M. P. Cooke* and *J. L. Coke,* J. Amer. Chem. Soc. *90,* 5556 (1968).

[66] *W. H. Saunders* and *T. A. Ashe,* J. Amer. Chem. Soc. *91,* 4473 (1969); and reference to unpublished work by *K. C. Brown.*

[67] *K. T. Finley* and *W. H. Saunders,* J. Amer. Chem. Soc. *89,* 898 (1967).

[68] *M. Svoboda, J. Závada,* and *J. Sicher,* Collect. Czech. Chem. Commun. *33,* 1415 (1968).

[69] *D. H. Froemsdorf, H. R. Pinnick,* and *S. Meyerson,* Chem. Commun. *1968,* 1600.

[70] *D. S. Bailey* and *W. S. Saunders,* J. Amer. Chem. Soc. *92,* 6904 (1970).

[71] *D. S. Bailey,* Dissertation, University of Rochester 1969; cf. also J. Amer. Chem. Soc. *92,* 6911 (1970).

[72] *M. Pánková, J. Závada,* and *J. Sicher,* Chem. Commun. *1968,* 1142.

[73] *M. Pánková, J. Sicher,* and *J. Závada,* Chem. Commun. *1967,* 394.

[74] *D. H. Froemsdorf, W. Dowd, W. A. Gifford,* and *S. Meyerson,* Chem. Commun. *1966,* 449.

[75] *D. H. Froemsdorf,* personal communication.

[76] *D. L. Griffith* and *B. Singerman,* Chem. Commun. *1968,* 438.

[77] *M. Svoboda, J. Závada,* and *J. Sicher,* unpublished work.

[78] *D. V. Banthorpe:* Elimination Reactions. Elsevier, Amsterdam 1963.

[79] *J. F. Bunnett,* Angew. Chem. *74,* 731 (1962); Angew. Chem. internat. Edit. *1,* 225 (1962).

[80] *D. V. Banthorpe* in *J. H. Ridd:* Studies on Chemical Structure and Reactivity. Methuen, London 1966.

[81] *J. F. Bunnett:* Survey of Progress in Chemistry. Academic Press, New York 1969, Vol. 5.

[82] *Christian Morgenstern,* from "Palmström".

[83] *G. Wittig* and *T. F. Burger,* Liebigs Ann. Chem. *632,* 85 (1960).

[84] *A. C. Cope* and *A. S. Mehta,* J. Amer. Chem. Soc. *85,* 1949 (1963).

[85] *L. Kniežo,* unpublished results.

[86] *D. J. McLennan,* Quart. Rev. *21,* 490 (1967).

[87] *H. M. R. Hoffmann,* Tetrahedron Lett. *1967,* 4393.

[88] *D. J. Cram:* Fundamentals of Carbonion Chemistry. Academic Press, New York 1965, p. 176.

[89] *M. Schlosser* and *V. Ladenberger,* Chem. Ber. *104,* 2873 (1971).

[90] *W. H. Kwok, W. G. Lee,* and *S. I. Miller,* J. Amer. Chem. Soc. *91,* 468 (1969).

[91] *S. Winstein, D. Darwish,* and *N. J. Holness,* J. Amer. Chem. Soc. *78,* 2915 (1956).

[92] *G. M. Fraser* and *H. M. R. Hoffmann,* J. Chem. Soc. *B 1967,* 425.

[93] *A. J. Parker, M. Ruane, G. Biale,* and *S. Winstein,* Tetrahedron Lett. *1968,* 2113.

[94] *D. N. Kevill, G. A. Coppens,* and *N. H. Cromwell,* J. Org. Chem. *28,* 567 (1963).

[95] *D. Eck* and *J. F. Bunnett,* J. Amer. Chem. Soc. *91,* 3099 (1969); *R. J. Anderson, P. Ang, B. D. England, V. H. McCann,* and *D. J. McLennan,* Austral. J. Chem. *22,* 1427 (1969).

[96] *D. J. McLennan* and *R. J. Wong,* Tetrahedron Lett. *1970,* 881.

[97] The volidity of this conclusion has been doubted: *W. H. Saunders, D. G. Bushman,* and *A. F. Cockerill,* J. Amer. Chem. Soc. *90,* 1775 (1968).

[98] *H. M. R. Hoffmann,* Tetrahedron Lett. *1967,* 4393; *G. M. Fraser* and *H. M. R. Hoffmann,* J. Chem. Soc. *B 1967,* 265; however, see also *A. F. Cockerill,* Tetrahedron Lett. *1969,* 4913.

[99] *R. P. Holysz,* J. Amer. Chem. Soc. *75,* 4432 (1953); *R. L. Letsinger* and *E. Bobko, ibid. 75,* 2649 (1953).

[100] *M. Schlosser* and *M. Zimmermann,* Chem. Ber. *104,* 2885 (1971), particularly pp. 2887 and 2888.

[101] *H. Felkin,* personal communication.

[102] *H. C. Brown* and *R. L. Klimisch,* J. Amer. Chem. Soc. *87,* 5517 (1965).

[103] *D. M. Froemsdorf, W. Dowd,* and *K. E. Leimer,* J. Amer. Chem. Soc. *88,* 2345 (1966).

[104] *J. Sicher, J. Závada,* and *M. Pánková,* Chem. Commun. *1968,* 1147; *J. Sicher,* Pure Appl. Chem. *25,* 655 (1971).

[105] *A. Rauk, E. Buncel, R. T. Moir,* and *S. Wolfe,* J. Amer. Chem. Soc. *87,* 5498 (1965); *J. E. Baldwin, R. E. Hackler,* and *R. M. Scott,* Chem. Commun. *1969,* 1415; *B. J. Hutchinson, K. K. Andersen,* and *A. R. Katritzky,* J. Amer. Chem. Soc. *91,* 3839 (1969).

[106] *R. A. Bartsch,* J. Amer. Chem. Soc. *93,* 3683 (1971), particularly p. 3686.

Photooxidation of 3,4-Diethyl-2,5-dimethylpyrrole[1][**]

By *David A. Lightner* and *Gary B. Quistad*[*]

Investigations of the photooxidation of pyrroles have been largely confined to pyrrole itself[2, 3] and to various phenyl-substituted pyrroles[4, 5] which have been studied extensively. Until recently[2, 6] no studies on the photooxidation of alkylpyrroles had been reported. Alkylpyrroles are unstable to air and light[7]; however, only their autooxidation had been examined[8]. We have found the dye-sensitized photooxidation[9] of 3,4-diethyl-2,5-dimethylpyrrole *(1)* in methanol proceeds *via* loss of one or both α-methyl groups to give *(6)* and *(7)*. This novel dealkylation, as well as other reactions leading to *(8)* and *(9)*, have not heretofore been observed.

Synthesis of *(1)* was accomplished from the conveniently obtained pyrrole *(10)*[10] in three steps by treating *(10)* at 230 °C in diethylene glycol/hydrazine/KOH to give 3,4-diethyl-2-methylpyrrole[11] in 67% yield which was converted into 3,4-diethyl-2-formyl-5-methylpyrrole[12] in 83% yield by a Vilsmeier-Haack reaction and then in into *(1)*, in 72% yield, by Wolff-Kishner reduction.

A dilute (0.1—0.2% w/v) methanolic solution of *(1)* containing 0.03‰ Rose Bengal ($^1O_2$ sensitizer) was photolyzed[13] for four hours while bubbling a slow stream of oxygen through the reaction vessel. After evaporation of the methanol *in vacuo* at room temperature, the crude photolyzate was chromatographed on alumina (E. Merck; neutral, Act. V). Ethyl acetate eluted six components (54 weight % of the total photolyzate) which were separated by preparative thin layer chromatography (Silica gel F, M.

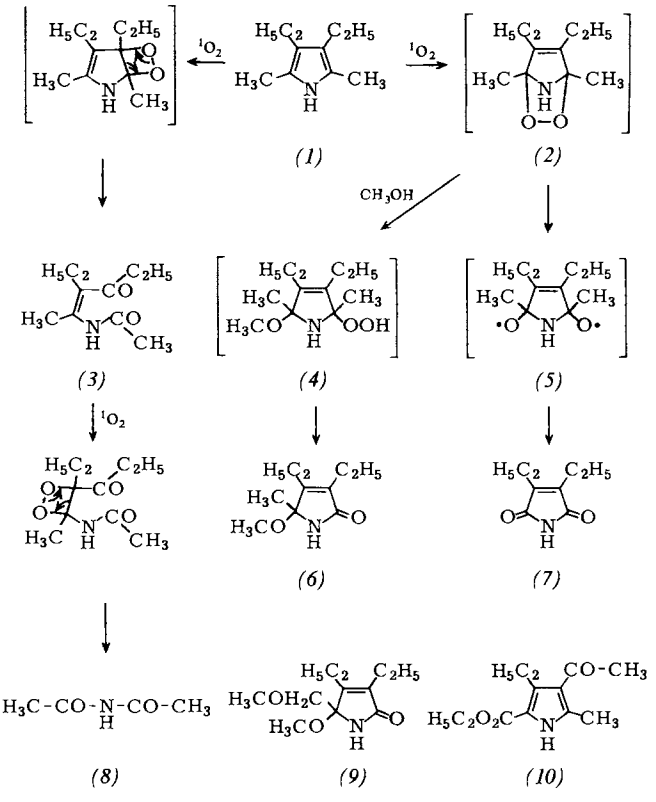


Table. Physical and spectroscopic data for the products of photooxidation of 3,4-diethyl-2,5-dimethylpyrrole.

Compound Yield (%) M. p. (°C)	MS *m/e*	^{1}H–NMR (CCl_4 *vs.* TMS, δ in ppm)	IR (CCl_4, cm^{-1})
(3)	183 (M^+)	0.98 (CH_3/t, J = 8 Hz)	1703 (ν CN—C=C)
9	182.1166 (M – 1)	1.00 (CH_3/t, J = 8 Hz)	
118–119	126.0920	1.48 (=C—CH_3/s)	1670 (ν C—C=C)
	(M – C_2H_5CO)	1.83 (CH_2/q, J = 8 Hz)	
		1.85 (CH_2/q, J = 8 Hz)	
		2.02 ($COCH_3$/s)	
(6)	183.1263 (M^+)	1.03 (CH_3/t, J = 8 Hz)	1700 (ν C=O)
19	152 (M – OCH_3)	1.12 (CH_3/t, J = 8 Hz)	
oil		1.43 (CH_3/s)	
		2.22 (2 CH_2/q, J = 8 Hz)	
		2.91 (OCH_3/s)	
		7.72 (NH/br. s)	
(7)	153 (M^+)	1.17 (2 CH_3/t, J = 7 Hz)	1710 (ν C=O)
17–22		2.44 (2 CH_2/q, J = 7 Hz)	
68–70 [a]			
(8)	101 (M^+)	2.23 (2 CH_3/s)	
5–11			
74–76 [b]			
(9)	213.1360 (M^+)	1.06 (CH_3/t, J = 8 Hz)	1715 (ν C=O)
4	182 (M – OCH_3)	1.09 (CH_3/t, J = 8 Hz)	1130 (ν C—O)
oil	168 (M – CH_2OCH_3)	2.23 (2 CH_2/q, J = 8 Hz)	
		2.99 (OCH_3/s)	
		3.29 (OCH_3/s)	
		3.46 (OCH_2/s)	
		7.20 (NH/br. s)	

[a] See [11], p. 398.
[b] Sadtler Standard Spectra, Sadtler Research Laboratories Inc., Philadelphia, spectrum 26009, 1965.

[*] Prof. Dr. D. A. Lightner and Dipl.-Chem. G. B. Quistad [***]
Chemistry Department, University of California
Los Angeles, California 90024 (USA)

[**] This work was supported by the National Science Foundation and the Petroleum Research Fund of the American Chemical Society.

[***] National Defense Education Act Fellow, 1969—1972.

Woelm Eschwege, 1 mm, ether). The structures of five products were characterized by a combination of spectroscopic methods and also—in the case of *(7)* and *(8)*—by comparison of melting points with those of authentic material.

The formation of *(6)* and *(7)* from *(1)* constitutes the first reported examples of dealkylation by photooxygenation of an heterocycle. Similar dealkylation or dearylation reactions have not been observed for phenyl-substituted pyrroles[4, 5] or for alkylated furans[14–16].

We assume that the products *(3)*, *(6)*, *(7)*, and *(8)* are formed in the manner quoted. The postulated route *(5)*→*(7)* is supported by the decomposition of the *tert*-butoxy radical to acetone and methyl radical[17]. We formulate *(4)* on the basis of the hydroperoxide[16] isolated in the photooxygenation of 2,5-dimethylfuran[15]; however, it has not been reported to demethylate to an analog of *(6)*. *(3)* and *(8)* could be formed in the same way as their analogs in the photooxygenation of 2,3,4,5-tetraphenylpyrrole[4]. We cannot as yet ascribe a simple mechanism to the formation of the rather surprising structure *(9)*. Mechanistic details of these reactions are currently under investigation.

Received: November 5, 1971 [Z 549 IE]
German version: Angew. Chem. *84*, 216 (1972)

[1] Photooxidation of Pyrrole, Part 3.—Part 2 see [6].

[2] *G. B. Quistad* and *D. A. Lightner*, Chem. Commun. *1971*, 1099.

[3] *P. de Mayo* and *S. T. Reid*, Chem. Ind. (London) *1962*, 1576.

[4] *H. H. Wasserman* and *H. Liberles*, J. Amer. Chem. Soc. *82*, 2086 (1960); *H. H. Wasserman* and *A. H. Miller*, Chem. Commun. *1969*, 199; *G. Rio, A. Ranjon, O. Pouchet*, and *M.-J. Scholl*, Bull. Soc. Chim. France, *1969*, 1667.

[5] *R. W. Franck* and *J. Auerbach*, J. Org. Chem. *36*, 31 (1971).

[6] *G. B. Quistad* and *D. A. Lightner*, Tetrahedron Lett. *1971*, 4417.

[7] *W. Metzger* and *H. Fischer*, Liebigs Ann. Chem. *527*, 1 (1937).

[8] *A. R. Katritzky, M. R. Nesbit*, and *E. Höft*, Tetrahedron Lett. *1968*, 2028; *1967*, 3041.

[9] *D. R. Kearns*, Chem. Rev. *71*, 395 (1971).

[10] *H. W. Whitlock* and *R. Hanauer*, J. Org. Chem. *33*, 2169 (1968).

[11] *H. Fischer* and *H. Orth*: Die Chemie des Pyrrols. Akademische Verlagsgesellschaft, Leipzig 1934, Vol. I, p. 57.

[12] See Ref. [11], p. 158.

[13] Colortran tungsten halogen quartz lamp, Berkey-Colortran Inc., 120 V, 1000 W, code B-5-32, run at 50 V.

[14] *S. T. Reid*, Advan. Heterocycl. Chem. *11*, 1 (1970); *K. Gollnick* and *G. O. Schenck* in *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1967, p. 255.

[15] *C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck*, and *K.-H. Schulte-Elte*, Tetrahedron *23*, 2583 (1967).

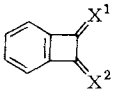
[16] Direct irradiation of 2,5-dimethylfuran *endo*-peroxide in methanol gives 5-methoxy-5-methyl-2,5-dihydrofuran-2-one; *C. S. Foote* and *H. Kane*, unpublished information.

[17] *R. Hiatt*, Intra-Sci. Chem. Rep. *5*, 163 (1971).

The Photochemistry of Dimethyl 1,2-Dihydrocyclobutabenzene-1,2-diylidenediacetate[**]

By *Richard J. Spangler* and *J. Curtis Sutton*[*]

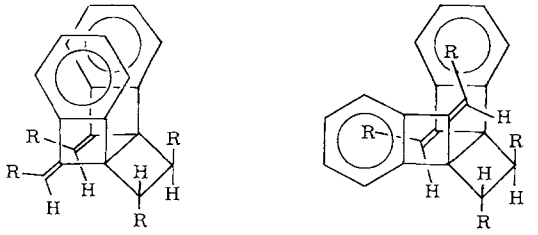
The interesting photochemistry of compounds *(1)* and *(2)* has already been described[1, 2]. We have now obtained a crystalline mixture of two photodimers in 25% yield by ultraviolet irradiation of a dilute methanol solution of dimethyl 1,2-dihydrocyclobutabenzene-1,2-diylidenediacetate *(3)*[3, 4] for 40—50 hours. Separation by preparative thick layer chromatography on alumina and eluting with chloroform yielded the two pure dimers, melting at 260 to



(1), $X^1 = X^2 = O$
(2), $X^1 = CH\text{-}CO_2CH_3$, $X^2 = O$
(3), $X^1 = X^2 = CH\text{-}CO_2CH_3$

265 °C and 304—305 °C. Based on considerations of the spectral data and the likely mechanistic pathways[5–8] we have assigned structures *(4)* and *(5)* to the photodimers.

The parent peak in the 70-eV mass spectra of both photodimers at *m/e* 488 and the close resemblance of the mass spectra below *m/e* 244 to that of the monomer *(3)* indicate that there has been no rearrangement during the photo-



(4) R = CO_2CH_3 *(5)*

dimerization. Furthermore, a small but significant peak at *m/e* 344 ($M-CH_3OCOCH{=}CHCO_2CH_3$) in the mass spectra of both dimers is consistent with the head-to-head arrangements *(4)* and *(5)* but would not be expected from a head-to-tail photodimer.

The 100-MHz NMR spectrum of the higher melting dimer *(5)* indicates a symmetrical structure: the two methine protons ($\delta = 4.26$), the methyl protons of the two saturated ester groups ($\delta = 3.52$), the two α,β-unsaturated ester groups ($\delta = 3.78$), and the two vinyl protons ($\delta = 6.15$) each give only one signal. In contrast, the NMR spectrum of the lower melting compound *(4)* shows two separate methine signals (an apparent AB quartet centered at $\delta = 4.21$ in which only the middle two peaks of the quartet are visible), a separate signal for each of the four methyl ester groups ($\delta = 3.46, 3.61, 3.76, 3.80$), and two signals in the vinyl region ($\delta = 5.91$ and 6.05). The aromatic protons of *(4)* and *(5)* give signals at $\delta \approx 7.31$ and $\delta \approx 7.75$ (6:2). Two deshielded aromatic protons indicate that the stereochemistry about the double bonds in *(4)* and *(5)* is *anti*, as it is in the monomer *(3)*[4]. IR and UV spectra are also in accord with the proposed structure assignments.

These results indicate that the photochemistry of *(3)* is markedly different from that of the analogous compounds *(1)* and *(2)*. The latter compounds both suffer cleavage of the four-membered ring first[1, 2], while in the case of *(3)*, $[2_\pi + 2_\pi]$ photodimerization, not ring cleavage, is the observed reaction pathway. To the best of our knowledge this represents the first example of a dihydrocyclobutabenzene whose photochemistry has not been dominated by ring opening. This process finds analogy with the recently

[*] Prof. Dr. R. J. Spangler and Dr. J. C. Sutton
Department of Chemistry, University of Idaho
Moscow, Idaho 83843 (USA)

[**] This work was supported by the donors of The Petroleum Research Fund, administered by the American Chemical Society.

reported photochemical behavior of diethyl *trans,trans-o*-phenylenediacrylate[5], *trans,trans-o*-distyrylbenzene[6], and *trans,trans*-1,8-distyrylnaphthalene[7].

Received: November 8, 1971 [Z 550 IE]
German version: Angew. Chem. *84*, 206 (1972)

[1] *R. J. Spangler* and *J. C. Sutton*, unpublished.

[2] *H. A. Staab* and *J. Ipaktschi*, Chem. Ber. *101*, 1457 (1968).

[3] Prepared by the method of *M. P. Cava* and *R. J. Pohl*, J. Amer. Chem. Soc. *82*, 5242 (1960).

[4] The stereochemistry about the double bonds of *(3)* has been determined to be *anti,anti*: *R. J. Spangler* and *J. C. Sutton*, unpublished results.

[5] *D. F. Tavares* and *W. H. Plodder*, Tetrahedron Lett. *1970*, 1567.

[6] *E. Müller, H. Meier*, and *M. Sauerbier*, Chem. Ber. *103*, 1356 (1970).

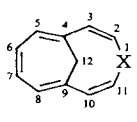
[7] *J. Meinwald* and *J. W. Young*, J. Amer. Chem. Soc. *93*, 725 (1971).

[8] *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry. Verlag Chemie GmbH, Weinheim/Bergstr. 1970, pp. 73, 74.

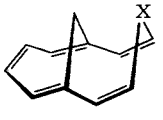
Bridged Hetero[11]annulenes[1]

By *Emanuel Vogel, Rainer Feldmann, Helmut Düwel, Hans-Dieter Cremer*, and *Harald Günther*[*]

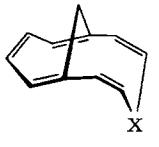
Advances in annulene chemistry have recently encouraged a number of research teams to take up the study of heteroannulenes having medium and large rings, especially the homologs of furan, pyrrole, and thiophene[2]. Since the members of homologous heteroannulene series, like the simple annulenes, differ considerably in conformation and mobility of the ring skeleton, attempts to establish correlations between physical and chemical properties of the respective compounds meet with difficulties. In the case of heteroannulenes having medium-sized rings, a planar skeleton desirable for comparative studies seems attainable only by introduction of bridges or triple bonds.



(1a), (1b)
a: X = S
b: X = O



(2a), (2b)
syn

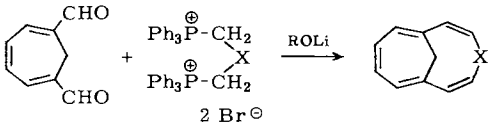


(3a), (3b)
anti

The present communication describes the bridged hetero[11]annulenes 4,9-methanothia[11]annulene *(1a)* and -oxa[11]annulene *(1b)*, which can be regarded as potential 12π-electron systems. These compounds can adopt conformations with an approximately planar heteroannulene ring while incurring only a moderate degree of ring strain; however, owing to lack of resonance stabilization they are likely to prefer the almost strain-free conformations with the hetero atom *syn* or *anti* to the bridge [*(2a)* and *(2b)*; *(3a)* and *(3b)*].

4,9-Methanothia[11]annulene *(1a)* was synthesized by a Wittig reaction: Cycloheptatriene-1,6-dialdehyde *(4)*[3] in dimethylformamide was allowed to react for 24 h at room temperature with thiodimethylenebis(triphenylphosphonium bromide) *(5a)* and lithium methoxide as a base (added in methanol to the reaction mixture). Compound *(1a)*, isolated in 30% yield as red crystals (m. p. 27—28 °C, from ethanol), underwent a fairly rapid change above 50 °C, partly decomposing to 1,6-methano[10]annulene *(8)* and sulfur[4] and partly polymerizing.

4,9-Methanooxa[11]annulene *(1b)* could be obtained similarly to *(1a)*, albeit in only 2% yield, by reaction of *(4)* with *(5b)*; the oxa compound is an air-sensitive yellow liquid (b. p. ≈70 °C/0.1 torr) best kept in an argon atmosphere.



(4) *(5a), (5b)* *(1a), (1b)*
a: X = S
b: X = O

The hetero[11]annulene structures *(1a)* and *(1b)* of the two compounds were proved by their NMR spectra, which also provided evidence favoring the *syn* conformations *(2a)* and *(2b)*[5].

The NMR spectrum of *(1a)* (in CCl_4) (Fig. 1a) shows an AA'XX' system at $\tau = 3.46$ (H-6, H-7) and 3.91 (H-5, H-8) for the heteroannulene protons of the cycloheptatriene part of the molecule, an AX system at $\tau = 3.55$ (H-3, H-10) and 5.22 (H-2, H-11) with $J = 9.6$ Hz[6] for those in the vicinity of the sulfur atom, and an AX system at $\tau = 3.72$ (H-12b) and 8.76 (H-12a) with $J = -11.5$ Hz for the bridge protons. The A part of the bridge-proton AX system, which is superposed on the absorption of the heteroannulene protons (see Fig. 1a), was located by double resonance. The possibility of *(1a)* being in rapid equilibrium with a significant quantity of its 1,6-methano[10]annulene 3,4-episulfide valence tautomer *(7)* can be ruled out since a) the NMR spectrum shows no temperature dependence and b) the heteroannulene protons of the cycloheptatriene part exhibit practically the same chemical shifts and coupling constants ($J_{5,6} = 5.78$, $J_{6,7} = 10.38$, $J_{5,7} = 0.30$, $J_{5,8} = 1.29$ Hz) as the corresponding protons of the hydrocarbon bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene *(6)*[3,7] (Fig. 1c). From the remarkable agreement in chemical shifts shown by the protons of the cycloheptatriene parts of *(1a)* and *(6)* it follows that *(1a)* does not sustain a significant paramagnetic ring current. The resonance of the bridge proton H-12b at exceptionally low field—difference in chemical shifts between H-12b and H-12a = 5 ppm!—is only in apparent discord with the above observations and is readily explained by the combined effects of the diamagnetic anisotropy of the S—C bonds[8], the field effect of the sulfur atom[9], and possibly also a steric compression[10] of the sulfur atom and the bridge proton H-12b, assuming that the molecule adopts the *syn* conformation *(2a)*.

The UV spectrum of *(1a)* with maxima at 233 ($\varepsilon = 31\,200$), 284 (27000), and 395 nm (427) (in cyclohexane) differs markedly from that of the hydrocarbon *(6)*, thus indicating that the sulfur atom electronically interacts with the double bond system in spite of the clearly non-planar arrangement of the heteroannulene ring.

In its NMR spectrum (CCl_4) (Fig. 1b), and specifically with regard to the bridge-proton absorption, 4,9-methanooxa[11]annulene *(1b)* occupies an intermediate position between *(1a)* and *(6)*. The spectrum of the oxa compound

[*] Prof. Dr. E. Vogel, Dr. R. Feldmann, Dr. H. Düwel, Dipl.-Chem. H.-D. Cremer, and Prof. Dr. H. Günther
Institut für Organische Chemie der Universität
5 Köln 1, Zülpicher Strasse 47 (Germany)

contains an AA'XX' system at $\tau = 3.33$ (H-6, H-7) and 3.85 (H-5, H-8) ($J_{5,6} = 5.96$, $J_{6,7} = 10.54$, $J_{5,7} = 0.08$, $J_{5,8} = 1.51$ Hz), an AX system at $\tau = 4.29$ (H-3, H-10) and 4.52 (H-2, H-11) with $J = 6.2$ Hz, as well as another AX system at $\tau = 5.48$ (H-12b) and 9.37 (H-12a) with $J = -10.4$ Hz. Remarkably,

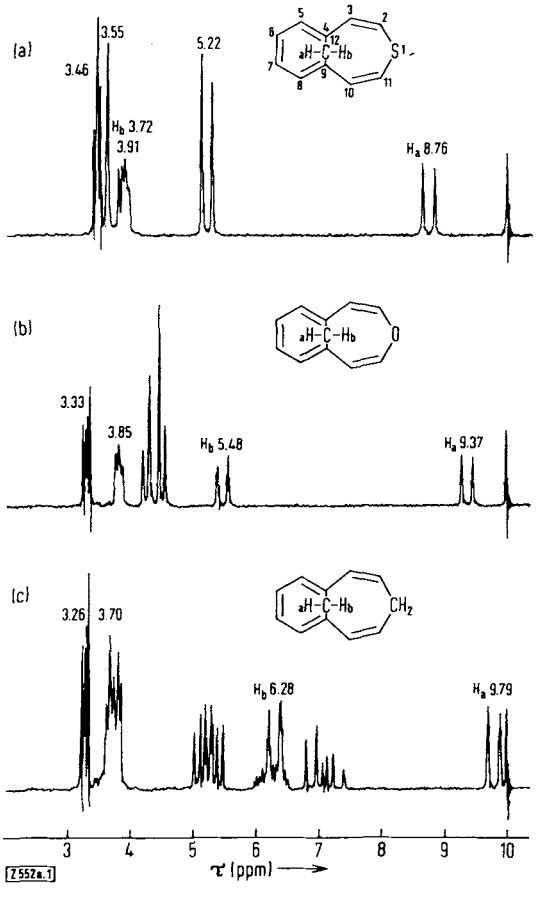
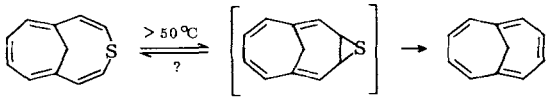


Fig. 1. NMR spectra of a) 4,9-methanothia[11]annulene *(1a)*, b) 4,9-methanooxa[11]annulene *(1b)*, and c) bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene *(6)* in CCl_4 (60 MHz; TMS as internal standard).

the difference between the chemical shifts of the bridge protons decreases by 1.2 ppm on going from *(1a)* to *(1b)*. From analogies with comparable compounds[11] the magnitude of this decrease suggests that *(1a)* and *(1b)* have similar conformations[12].

The UV spectrum of *(1b)*, which exhibits maxima at 248 ($\varepsilon = 39200$) and 328 nm (2450) (in cyclohexane), is almost superimposable with that of the hydrocarbon *(6)*. It therefore follows that *(1b)* and *(6)* definitely belong to the same



(1a) *(7)* *(8)*

conformational type and, furthermore, that the oxygen function in *(1b)*—as in oxonin[2a]—does not transmit cyclic conjugation.

Elimination of sulfur from *(1a)*[4] above 50 °C most probably proceeds *via* the hitherto undetected 1,6-methano-[10]annulene 3,4-episulfide *(7)* formed by a symmetry allowed electrocyclic process. Attempts to trap *(7)* with dienophiles were unsuccessful[13].

Received: November 15, 1971 [Z 552a IE]
German version: Angew. Chem. *84*, 207 (1972)

[1] Based on a lecture by *E. Vogel* at the XXIII IUPAC Congress, Boston, Mass., July 1971.

[2] a) Hetero[9]annulenes: *A. G. Anastassiou, S. W. Eachus, R. P. Cellura*, and *J. H. Gebrian*, Chem. Commun. *1970*, 1133, and further literature cited therein pertaining to the work of this research group; *S. Masamune, S. Takada*, and *R. T. Seidner*, J. Amer. Chem. Soc. *91*, 7769 (1969); *S. Masamune, K. Hojo*, and *S. Takada*, Chem. Commun. *1969*, 1204; b) fused or alkylated thia[11]- and thia[13]annulenes: *A. B. Holmes* and *F. Sondheimer*, J. Amer. Chem. Soc. *92*, 5284 (1970); Chem. Commun., in press; c) hetero[17]annulenes: *G. Schröder, G. Heil, R. Neuberg, G. Plinke*, and *J. F. M. Oth*: lecture by *G. Schröder* at the XXIII IUPAC Congress, Boston, Mass., July 1971.

[3] *E. Vogel, R. Feldmann*, and *H. Düwel*, Tetrahedron Lett. *1970*, 1941.

[4] This reaction corresponds to the elimination of sulfur from thiepines; *J. M. Hoffman jr.* and *R. H. Schlessinger*, J. Amer. Chem. Soc. *92*, 5263 (1970), and further literature cited therein.

[5] Further studies designed to settle the question of the conformations of *(1a)*, *(1b)*, and *(6)* are still in progress.

[6] In contrast to the situation in α,β-unsaturated thioethers, the protones α, α' to the sulfur atom in *(1a)* absorb at higher field.

[7] For the NMR analysis of *(6)* see *K. Müllen*, Dissertation, Universität Basel 1971; cf. *W. Grimme, J. Reisdorff, W. Jünemann*, and *E. Vogel*, J. Amer. Chem. Soc. *92*, 6335 (1970), footnote 13. Regarding the coupling constants of the olefinic protons in 1,3-cyclohexadienes and cycloheptatrienes, see *H. Günther* and *H. H. Hinrichs*, Liebigs Ann. Chem. *706*, 1 (1967).

[8] For examples, see *M. Tomoeda, M. Inuzuka*, and *T. Furuta*, Tetrahedron Lett. *1964*, 1233.

[9] *A. D. Buckingham*, Can. J. Chem. *38*, 300 (1960).

[10] *S. Winstein, P. Carter, F. A. L. Anet*, and *A. J. R. Bourn*, J. Amer. Chem. Soc. *87*, 5247 (1965).

[11] *C. R. Johnson* and *D. C. Vegh*, Chem. Commun. *1969*, 557; *P. T. Lansbury*, Accounts Chem. Res. *2*, 210 (1969).

[12] The large difference in the resonances of the bridge protons, which is also observed in the NMR spectrum of *(6)*, appears unusual. A discussion of the spectrum will appear elsewhere.

[13] After completion of the present manuscript, Dipl.-Chem. *M. Mann* succeeded in synthesizing 1,6-methano[12]annulene, an orange-red compound of m. p. 30—31 °C that is isoelectronic with *(1a)* and *(1b)*. The NMR spectrum (CCl_4) of the hydrocarbon shows an AA'XX' system at $\tau = 3.85$ and 4.29 as well as a narrow multiplet at $\tau = 4.52$ for the annulene protons and an AX system at $\tau = 3.00$ and 7.72 with $J = -11.4$ Hz for the bridge protons.

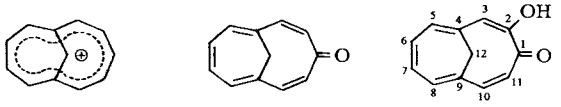
2-Hydroxy-4,9-methano[11]annulenone, a 10 π-Electron Analog of Tropolone[1]

By *Josef Reisdorff* and *Emanuel Vogel*[*]

Identification of the 1,6-methano[11]annulenium ion *(1)*[2] as an aromatic 10π-electron analog of the tropylium ion suggested the interesting possibility that keto- and ketohydroxy derivatives of *(1)* might exhibit physical and chemical properties similar to those of tropone and tropolone, respectively. As recently reported, this expectation was impressively confirmed for the keto derivatives of *(1)* (five structural isomers in all) by the synthesis of 4,9-methano[11]annulenone *(2)*[3] and of the isomeric 3,8- and 2,7-methano[11]annulenones[1]. We now wish to describe the preparation of 2-hydroxy-4,9-methano[11]annulenone *(3)*, one of 36 possible isomers, whose properties justify its being regarded as a 10π-electron analog of tropolone.

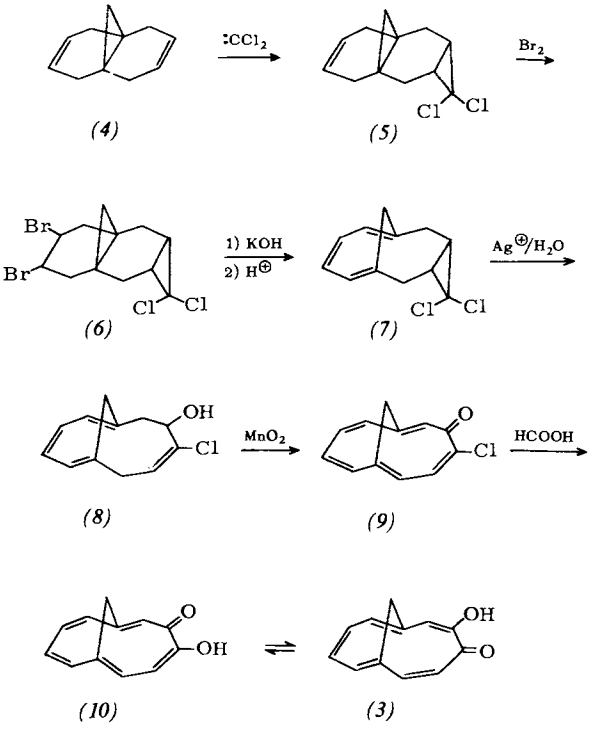
[*] Dr. J. Reisdorff and Prof. Dr. E. Vogel
Institut für Organische Chemie der Universität
5 Köln 1, Zülpicher Strasse 47 (Germany)

The starting point of the route to *(3)* was the readily accessible tricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene *(4)*, an intermediate of the synthesis of 1,6-methano[10]annulene[4]. On reaction with a slight excess of chloroform and potassium *tert*-butoxide the hydrocarbon affords a uniform monoadduct of m.p. 45—46 °C (yield 37%; 78% based on reacted diene) which most probably has the *anti* configuration *(5)*. Treatment of *(5)* with bromine in the cold readily gives the dibromide *(6)* (yield 93%; m.p. 140 °C after repeated recrystallization from ethyl acetate). Heating of *(6)* with potassium hydroxide in methanol/dioxane followed by treatment of the resulting crude dehydrobromination product with dilute perchloric acid in dioxane/water



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

furnished an 88% yield of a compound having m.p. 98 °C which was unequivocally shown to be the cycloheptatriene derivative *(7)* by its NMR spectrum. Subsequent hydrolysis of *(7)*, preferably with silver nitrate in a boiling mixture of water and 1,2-dimethoxyethane in the presence of a small amount of pyridine, effected the desired disrotatory opening of the cyclopropane ring, with formation of the rather unstable alcohol *(8)* (yield 76%; m.p. 92—93 °C after repeated recrystallization from hexane/ethyl acetate). According to the NMR spectrum, that alcohol isomer appears to be formed in which the OH group is *syn* to the CH_2 bridge. Treatment of *(8)* with activated manganese dioxide in boiling 1,2-dimethoxyethane led not only to the

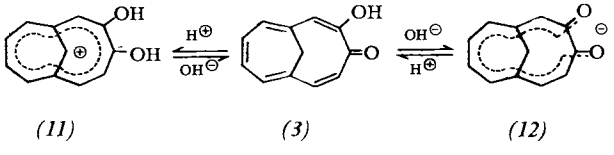


(4) *(5)* *(6)* *(7)* *(8)* *(9)* *(10)* *(3)*

expected conversion of the allylic hydroxyl into a carbonyl group but also to dehydrogenation; as a result 11-chloro-3,8-methano[11]annulenone *(9)* was obtained as orange-red prisms of m.p. 133—134 °C (yield 25—30%). Substitution of the chlorine atom in *(9)* by hydroxyl was best accomplished by heating *(9)* to 145—150 °C in anhydrous formic acid in the presence of sodium formate. There resulted a TLC-homogeneous, stable ketohydroxy compound (yield 60%) which crystallizes as orange prisms of m.p. 99 °C (from diisopropyl ether) and is either compound *(10)* or the tautomer *(3)*—or (in solution) an equilibrium mixture of the two forms.

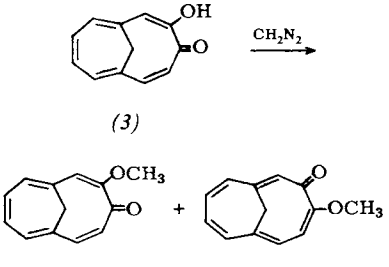
The 60-MHz NMR spectrum (in CCl_4) of the compound, which displays no temperature dependence, contains: an AB system at $\tau = 2.59$ (H-10) and 3.21 (H-11) with $J = 11.5$ Hz, a weakly resolved triplet at 2.65 (H-3), and a multiplet at 2.5—3.2 (H-5 to H-8) for the olefinic protons; an AB system at $\tau = 9.13$ (*anti*-H-12)[5] and 9.83 (*syn*-H-12) with $J = -10.9$ Hz for the bridge protons; and a broad singlet at $\tau = 1.44$ for the hydroxyl proton. This spectrum, and in particular with regard to the chemical shift of the bridge protons, closely resembles those of 4,9-methano[11]-annulenone *(2)* and the methyl ether *(13)* derived from *(3)*, but differs pronouncedly from those of 3,8-methano-[11]annulenone and the methyl ether *(14)*[6]. In parallel herewith the UV spectrum of the compound with maxima (in cyclohexane) at 247 ($\varepsilon = 11\,700$, shoulder), 270 (14900, sh), 304 (40500), 330 (10100, sh), 381 (5980), and 430 nm (3500, sh), is of the same type as the spectra of *(2)* and *(3)*; no marked resemblance is seen, however, to the spectra of 3,8-methano[11]annulenone and the methyl ether *(14)*[6]. The IR spectrum [characteristic absorptions (in KBr): 3290 (OH), 1577, 1558, 1536, 1518 cm^{-1} (C=O and C=C)] does not appear suitable as a basis for distinguishing between *(3)* and *(10)*.

The above comparisons between the NMR and UV spectra permit the assumption that the ketohydroxy compound exists predominately, if not exclusively, as the tautomer *(3)*. This conclusion is in full accord with the prediction made on the basis of the pK_a values[7] of -0.6 ± 0.1 and $+0.5 \pm 0.1$ found for *(2)* and 3,8-methano[11]annulenone. Since 3,8-methano[11]annulenone exceeds the isomer *(2)* by 1.1 pK_a units in its basicity, *(3)* should definitely be the preferred form in the equilibrium between the two keto-hydroxy tautomers.



(11) *(3)* *(12)*

The most important chemical feature of *(3)* is its tropolone-like ability to form salts both with acids and with bases. As readily demonstrated by spectroscopy, *(3)* is protonated by acids to the 8,9-dihydroxy-1,6-methano[11]annulenium ion *(11)*. In the NMR spectrum (in CF_3COOH) the transition from *(3)* to *(11)* is manifested in a considerable down-



(3) *(13)* *(14)*

field shift of the resonances of the olefinic protons (multiplet at $\tau = 1.2$—2.0) and a concomitant upfield shift of the bridge-proton AB system ($\tau = 9.87$ and 11.05 with $J = -10.7$ Hz). The UV spectrum of *(3)* recorded in ethanolic perchloric acid, like that of protonated *(2)*, exhibits excellent agreement with the spectrum of the ion *(1)*[8]. As an acid *(3)* reacts with alkali metal hydroxides to give salts *(12)* that afford dark red aqueous solutions. A pK_a value of 8.25 is measured for *(3)* by potentiometric titration in water. *(3)* is thus not quite as strong an acid as α-tropolone (7.00)[9] but is more acidic than benzo[*d*]-tropolone (10.2)[10].

The acidity of *(3)* permits methylation of the compound with diazomethane in the absence of a catalyst, the ethers *(13)* (m. p. 122 °C) and *(14)* (m. p. 143 °C) being formed in the ratio 6:1 (total yield 64%). Since *(14)* can be synthesized independently by reaction of *(9)* with sodium methoxide, the structural assignments of both ethers are proved beyond doubt. Diazomethane methylation of *(3)* probably proceeds *via* an intimate ion pair[11] formed from the methyl diazonium ion and *(12)*, thus precluding any assessment of the equilibrium mixture of *(3)* and *(10)* from the ratio of *(13)* and *(14)*.

Received: November 29, 1971 [Z 552b IE]
German version: Angew. Chem. *84*, 208 (1972)

[1] Presented in part by *E. Vogel* at the XXIII IUPAC Congress, Boston, Mass., July 1971.

[2] *W. Grimme, H. Hoffmann*, and *E. Vogel*, Angew. Chem. *77*, 348 (1965); Angew. Chem. internat. Edit. *4*, 354 (1965); *E. Vogel, R. Feldmann*, and *H. Düwel*, Tetrahedron Lett. *1970*, 1941.

[3] *W. Grimme, J. Reisdorff, W. Jünemann*, and *E. Vogel*, J. Amer. Chem. Soc. *92*, 6335 (1970).

[4] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964).

[5] The terms *syn* and *anti* refer to the position of the bridge protons relative to the cycloheptatriene structural unit.

[6] *J. Reisdorff*, Dissertation, Universität Köln 1970.

[7] The pK_a values were determined spectrophotometrically in aqueous sulfuric acid utilizing Hammett H_0 values: cf. *H. Hoffmann*, Dissertation, Universität Köln 1967.

[8] *W. Grimme, E. Heilbronner, G. Hohlneicher, E. Vogel*, and *J.-P. Weber*, Helv. Chim. Acta *51*, 225 (1968).

[9] *J. W. Cook, A. R. Gibb, R. A. Raphael*, and *A. R. Somerville*, J. Chem. Soc. *1951*, 503.

[10] *B. E. Bryant* and *W. C. Fernelius*, J. Amer. Chem. Soc. *76*, 3783 (1954).

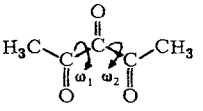
[11] *J. S. Pyrek* and *O. Achmatowicz jr.*, Tetrahedron Lett. *1970*, 2651.

Geometry and n-Ionization Energies of Alkyl-Substituted Triketones[**]

By *Jürgen Kroner* and *Walter Strack*[*]

The dimethyl derivative (pentanetrione) *(1)* was selected as a model compound for the study of the hitherto unknown molecular geometry and the photoelectron (PE) spectra of open-chain triketones.

A MINDO/2 minimization[1] as a function of the torsional angles ω_1 and ω_2 about the CC axes reveals the most stable form to be a non-planar conformation *(2)* (cf. Fig. 1) with an equal and opposite deviation of the two acetyl groups from the C—CO—C plane ($\omega_1, \omega_2 \approx \pm 90°$); the difference in energy between the conformations *(1)* and *(2)* is calculated as 21.8 kcal/mol, the staggered arrangement of methyl groups appearing only marginally more favorable (≈0.4 kcal/mol) than the eclipsed one. Kerr effect measurements[2] and electronic spectra[3] indicate deviations from planarity in biacetyl and triketones, respectively; according to these results the torsional angles in dimethyltriketone should be $\omega_1, \omega_2 \approx 0°, 90°$. Further evidence for a possible non-planar arrangement of the three carbonyl groups in *(1)* is provided by CNDO CI calculations of excitation energies; MINDO/2 (1.95 D) and CNDO/2 dipole moments (1.67 D)[4] are in good agreement with the experimental value of 1.93 D.



(1)

Assuming the validity of the MINDO/2 model in which the acetyl groups protrude in opposite directions from the C—CO—C plane we found a preference for a helix conformation in tri- and tetraketones[5] (Fig. 1).

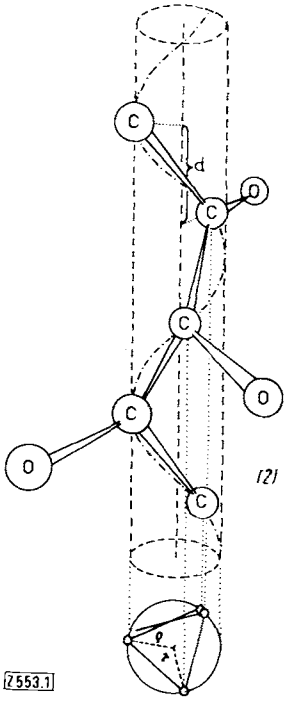


Fig. 1. Helix model of dialkyl-substituted triketones [6].

According to *Shimanouchi* and *Mizushima*[7] the spatial arrangement of the carbon centers can be described in terms of the angle of rotation (τ) about the helical axis, the distance (ρ) from the axis, and the chain lengthening *(d)* per CC segment (Fig. 1). Values of $\tau = 107°$, $\rho = 0.62$ Å, and $d = 1.08$ Å are obtained for dimethyltriketone with $\omega_1, \omega_2 = \pm 90°$. Dimethyltriketone thus proves to have a significantly larger helix radius than, *e.g.*, polyethylene ($\omega = 0°$, $\rho = 0.45$ Å) and polytetrafluoroethylene ($\omega = 18°$, $\rho = 0.45$ Å)[7, 8]. An increase in the torsional angle along the series dimethyl-, diisopropyl-, di-*tert*-butyltriketone, owing to competitive steric interactions of the alkyl groups with each other and with the central carbonyl oxygen, should lead to an increase in the helix radius (ρ) with a concomitant compression of the helix cylinder (*d*).

[*] Dr. J. Kroner and Dipl.-Chem. W. Strack
Institut für Anorganische Chemie der Universität
8 München 2, Meiserstrasse 1 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

The n-ionization energies[9] of alkyl-substituted triketones, as determined by photoelectron spectroscopy, can also be discussed on the basis of the calculated geometry of dimethyltriketone.

The considerable energy difference between orbitals of "nonbonding" (n)-electron pairs in α-diketones[10-12] and α,β-triketones[12] has its origin in their through-bond interaction[13] by way of the σ skeleton. The first bands in the PE spectrum of the simplest open-chain triketone *(1)* are found at 9.52, 10.97, and 12.30 eV; they can be assigned to ionization from "nonbonding" orbitals (n_1, n_2, n_3).

Combination of the orbitals $n_1(-)$, $n_2(+)$, and $n_3(-)$[14], which are threefold degenerate under conditions of slight through-space interaction[10], with lower lying asymmetric and symmetric CCC σ orbitals having the correct symmetry properties yields the highest occupied energy levels which, for C_{2v} symmetry, correspond to the irreducible representations b_1, a_1, and b_1 (Fig. 2). These n-splittings will be discussed with the aid of the simpler planar model.

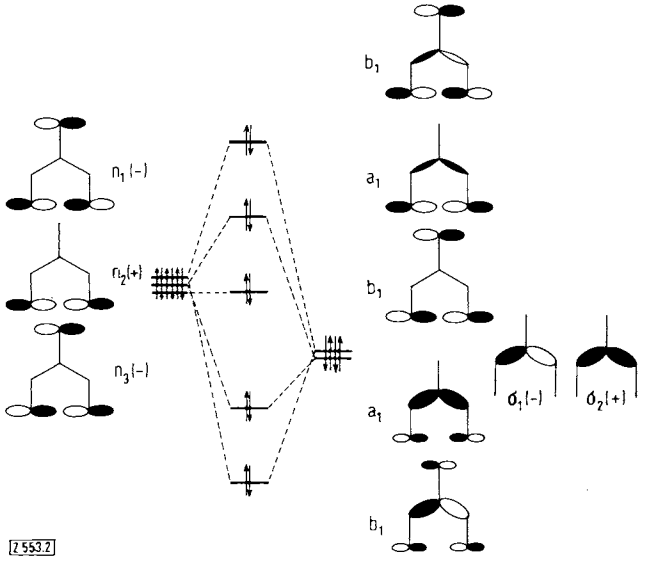


Fig. 2. Qualitative representation of the n-orbital interactions in planar triketones.

The orbital sequence results from the differing number of antibonding and bonding n/σ interactions. According to model calculations no significant admixture of antibonding CCC σ* contributions is to be expected in the range of highest occupied energy levels considered in the present case. The MOs corresponding to the first three ionizations do show a preference for n-components but they also undergo strong delocalization over the σ skeleton.

Table. Vertical ionization energies IE_v (eV), calculated n-orbital energies (eV) and n-splitting of dimethyltriketone.

Orbital type Symmetry [a]	n_1 b_1	n_2 a_1	n_3 b_1	$\lvert\Delta(n_1-n_3)\rvert$
IE_v	9.52	10.97	12.30	2.78
MINDO/2 [b]	−9.25	−11.27	−12.14	2.89
CNDO/2 [b, c]	−9.22	−11.45	−12.30	3.08
MINDO/2 [d]	−9.58	−11.00	−12.24	2.66
CNDO/2 [c, d]	−9.29	−11.03	−12.66	3.37

[a] Based on (planar) C_{2v}-geometry; [b] ω_1, $\omega_2 = 0°$ [16]; [c] energy zero at 1 eV; [d] ω_1, $\omega_2 = \pm 90°$ [16].

Assuming the validity of Koopmans theorem[15] the vertical ionization energies of dimethyltriketone, as measured by PE spectroscopy, are compared with the orbital energies calculated for $\omega_{1,2} = 0°$ and $\pm 90°$ by the MINDO/2 and modified CNDO/2 methods (Table).

As in diketones[10-12], the energies of the n-orbitals and their splitting in triketones proves to be only slightly dependent upon the torsional angle, thus offering some justification for a discussion on the basis of the planar model.

In contrast to dimethyltriketone, Δn is found by experiment to be 2.78 eV ($n_1 = 9.04$, $n_2 = 10.48$, $n_3 = 11.82$ eV) for diisopropyltriketone, and 2.59 eV ($n_1 = 9.00$, $n_2 = 10.28$, $n_3 = 11.59$ eV) for di-*tert*-butyltriketone. A decrease in the splitting would correspond to an increase in the torsional angle and an enlargement of the helix radius along the series $R = CH_3 \approx CH(CH_3)_2 < C(CH_3)_3$ if the differing electronic effects of the alkyl groups on n_1 and n_3 are neglected. The observed splittings are also in good agreement with theoretical predictions (2.72 eV)[10] for a hypothetical cyclopropanetrione. Increasing n-splitting is observed within the series of di-, tri-, and tetraketones[5].

Received: June 23, 1971; revised: September 13, 1971 [Z 553 IE]
German version: Angew. Chem. *84*, 210 (1972)

[1] *M. J. S. Dewar* and *E. Haselbach*, J. Amer. Chem. Soc. *92*, 590 (1970); *N. Bodor, M. J. S. Dewar, A. Harget*, and *E. Haselbach, ibid. 92*, 3854 (1970); *N. Bodor* and *M. J. S. Dewar, ibid. 92*, 4270 (1970); *N. Bodor, M. J. S. Dewar*, and *S. D. Worley, ibid. 92*, 19 (1970).

[2] *J. E. LuValle* and *V. Schomaker*, J. Amer. Chem. Soc. *61*, 3520 (1939); *P. H. Cureton, C. G. LeFèvre*, and *R. J. W. LeFèvre*, J. Chem. Soc. *1961*, 4447.

[3] *M. Calvin* and *C. L. Wood*, J. Amer. Chem. Soc. *62*, 3152 (1940); *L. Horner* and *F. Maurer*, Chem. Ber. *101*, 1783 (1968).

[4] *J. Del Bene* and *H. H. Jaffé*, J. Chem. Phys. *48*, 1807, 4050 (1968); *49*, 1221 (1968); *50*, 563, 1126 (1969). The Ohno two center γ-relationship was used instead of the Pariser-Parr relationship (cf. *K. Ohno*, Theor. Chim. Acta *2*, 219 (1964)).

[5] *J. Kroner* and *W. Strack*, to be published.

[6] The protons of the methyl groups were neglected in the Figure.

[7] *T. Shimanouchi* and *S.-I. Mizushima*, J. Chem. Phys. *23*, 707 (1955).

[8] *K. Morokuma*, J. Chem. Phys. *54*, 962 (1971).

[9] The photoelectron spectra were recorded with a Perkin-Elmer PS 16 spectrometer (He I lamp, electrostatic sector field 127°).

[10] *J. R. Swenson* and *R. Hoffmann*, Helv. Chim. Acta *53*, 2331 (1970).

[11] *D. O. Cowan, R. Gleiter, J. A. Hashmall, E. Heilbronner*, and *V. Hornung*, Angew. Chem. *83*, 405 (1971); Angew. Chem. internat. Edit. *10*, 401 (1971).

[12] *J. Kroner, W. Strack*, and *D. Proch*, to be published.

[13] *R. Hoffmann, A. Imamura*, and *W. J. Hehre*, J. Amer. Chem. Soc. *90*, 1499 (1968).

[14] Signs refer to the C_{2v} symmetry operation of rotation about the central CO bond.

[15] *T. Koopmans*, Physica *1*, 104 (1933).

[16] Distances: CO = 1.20, CC = 1.47, C—CH_3 = 1.54, CH = 1.09 Å; angles: CCO = 123, OC—CH_3 = 122.5, CCH = 109.5° (cf. [2, 3]).

The Equivalent Orbital Method of Interpreting Photoelectron (PE) Spectra: Neopentane[1]

By *Werner Schmidt* and *Bernard T. Wilkins*[*]

While the analysis of the electronic structure of molecules containing π bonds or lone pairs is already quite far advanced, the study of saturated organic compounds by

[*] Dr. W. Schmidt and B. T. Wilkins, B. A.
School of Molecular Sciences, The University of Sussex
Brighton BN1 9QJ (England)

PE spectroscopy is still in its infancy[2]. The reason for this state of affairs is to be found in the fact that the orbitals localized in CC and CH bonds are strongly bonding and have similar energies; in molecules of low symmetry they consequently undergo extensive mixing. Even in the case of medium sized molecules, such as *n*-pentane, ionization therefore leads to a multitude of broad, contourless, strongly overlapping bands whose identification runs into considerable difficulties.

The PE spectrum of neopentane should be free from such complications. The MOs of a molecule of the point group T_d are largely dictated by symmetry and can be deduced without the need for explicit calculations. An EO model[3] is admirably suited for this purpose since it takes full account of the specific requirements of PE spectroscopy: It can readily be parametrized with the aid of PE data for compounds having known orbital sequences and facilitates the analysis of the spectra of molecules whose orbital sequence is still unknown. Alkanes are particularly attractive objects of investigation since they contain only two kinds of chemically nonequivalent bonds (CC and CH)[4].

The starting point for neopentane is provided by the four equal-energy CC EOs and the twelve mutually degenerate but more stable CH EOs (Fig. 1, far left and far right respectively). The first-named orbitals form the basis for a representation Γ_{CC} which can be broken down into the following irreducible representations: $\Gamma_{CC}=a_1+t_2$. The CH EOs also provide the basis for another representation Γ_{CH} which can be reduced as follows: $\Gamma_{CH}=a_1+e+t_1+2t_2$.

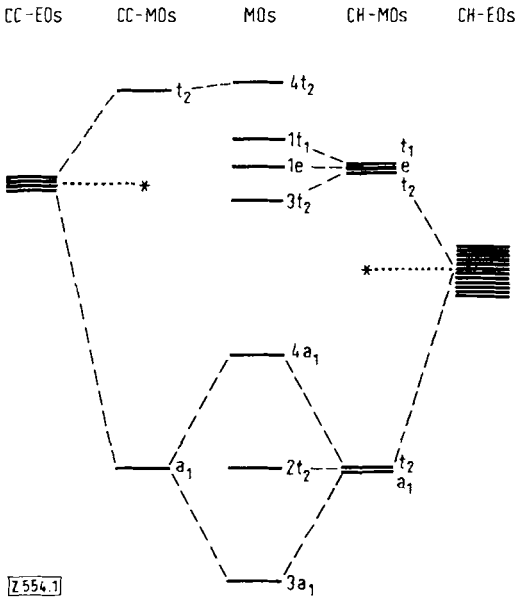


Fig. 1. Qualitative energy level scheme for neopentane (point group T_d). The localized, two-center EOs are seen on the far left and far right, the completely delocalized MOs in the middle, and the semilocalized CC and CH MOs in between.

In order to obtain MOs of correct symmetry that are localized in the CC and CH bonds the CC and CH EOs must each be allowed to interact separately. Since the s and p AOs of the central C atom have different transformation properties and differ in energy the t_2 CC MO is raised and the a_1 CC MO lowered while retaining the mean energy of the system (Fig. 1, left); the splitting probably amounts to about 9 eV, as in methane[5]. Similar arguments lead to the splitting pattern shown on the right-hand side of Figure 1 for the CH EOs.

The semilocalized MOs obtained in this way are still not the "true", completely delocalized MOs since some of them belong to the same irreducible representation and can therefore mix with each other. The extent of this interaction is very sensitive to the choice of parameters; however, it is probably not very large and results only in a lifting of the degeneracy of the (t_1, e) and t_2 CH EOs. The through-space interaction of the methyl groups has to be accounted for by a parameter η which is estimated at about -0.6 eV on the basis of the PE data for propane and *n*-butane[4]. A glance at a group table will reveal that $3t_2$ is stabilized by 2η while $1t_1$ is destabilized by the same amount. In contrast, the 1e MO exhibits the remarkable property of being completely devoid of interaction; its energy, as determined by PE spectroscopy, would therefore represent (within the limitations of Koopmans' theorem) an ideal standard for a strictly localized "CH_3" orbital comprising only C 2p and H 1s AOs.

The PE spectrum reproduced in Figure 2 fulfilled our expectations. It shows four clearly separated bands[6], of which the first (centered at about 11.3 eV[7]) is assignable to ionization from the $4t_2$ MO which is primarily involved in CC bonding. The facts that the splitting pattern of the three CH-bonding MOs $1t_1$, 1e, and $3t_2$ is completely symmetrical and that the centroid of the three bands (*ca.* 14.1 eV) has exactly the same value as we have found for other hydrocarbons[4] indicate a very slight interaction between the CC and CH MOs.

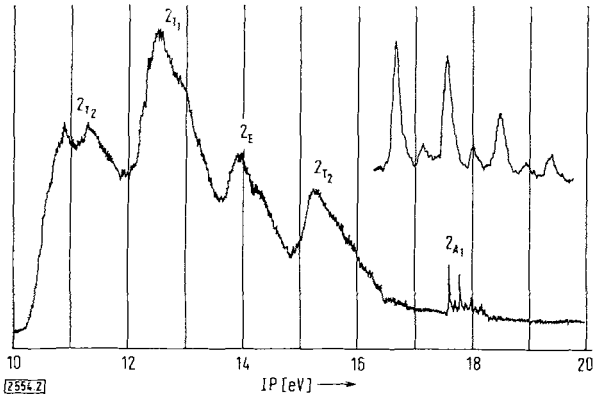


Fig. 2. High-resolution He I-PE spectrum of neopentane (Perkin-Elmer PS 16 spectrometer). Above right: Expanded recording of the band starting at 17.56 eV.

Further justification for this conclusion is also provided by the observation that only the $^2T_2$ ground state of the ion shows a pronounced Jahn-Teller (JT) instability. A comparable JT instability in all $^2T_2$ states would have indicated extensive mixing of the CC and CH MOs. The separation between the two intense JT components of the first band (*ca.* 0.4 eV; the third component can be seen at *ca.* 11.7 eV on an expanded scale) is smaller than that found in the first band of methane (*ca.* 0.7 eV[5]). This is probably due to the smaller degree of repulsion between neighboring CC EOs in neopentane.

The first vertical ionization potential of neopentane is higher than that of *n*-pentane; thus branching does not necessarily lower the ionization potential[8]. This finding is in accord with the present EO study (and also with our *ab initio* calculations) but contradicts current concepts of organic chemistry.

The EO method also readily explains the origin of the band exhibiting fine structure which starts at 17.56 eV: its low intensity, the exceptional sharpness of the vibrational components, and the dominance of the O—O transition leave no doubt that it is to be correlated with the totally symmetric partner of the t_2 CC MO which, for reasons of orthogonality, is largely localized in the 2s AO of the central C atom and is only weakly bonding. The fact that it is mainly the CH_3 deformation mode that is excited (frequency in ion *ca.* 1310 cm^{-1}, in the neutral molecule[9] 1368 cm^{-1}) on ionization while the likewise totally symmetric CC stretching frequency (ion *ca.* 650 cm^{-1}, molecule[9] 734 cm^{-1}) is less intense is presumably attributable to the strong internal strain of the molecule which also manifests itself in the unexpectedly high value of the parameter $\eta = -0.7$ eV. This interpretation is in agreement with the excitation of the SiC stretching mode on ionization from the a_1 SiC MO in tetramethylsilane where these steric problems have largely been solved. It cannot, however, be ruled out that the a_1 CC MO undergoes extensive mixing with the CH MO of the same symmetry (the *ab initio* calculations support this view; cf. also Fig. 1). A further possibility is that both progressions belong to the CC stretching frequency and that the alternation of intensities is due to an accidental equality of the equilibrium geometries of the ion and the neutral molecule. We hope to be able to solve this question by combined use of He I and He II spectroscopy with the perdeuterated compound.

Received: October 11, 1971 [Z 554 IE]
German version: Angew. Chem. *84*, 168 (1972)

[1] This work was supported by the Science Research Council *(B. T. W)* and the Deutsche Forschungsgemeinschaft *(W.S.)*. We are indebted to Prof. *J. N. Murrell* for discussions on the EO method and Prof. *M. F. Lappert* for permission to use the PE spectrometer.

[2] *S. D. Worley*, Chem. Rev. *1971*, 295.

[3] *J. E. Lennard-Jones* and *G. G. Hall*, Trans. Faraday Soc. *48*, 581 (1952).

[4] *W. Schmidt*, Tetrahedron, in press.

[5] *A. D. Baker*, *C. Baker*, *C. R. Brundle*, and *D. W. Turner*, Int. J. Mass Spectr. Ion Phys. *1*, 285 (1968); *W. C. Price* in: Molecular Spectroscopy. The Institute of Petroleum, London 1968.

[6] The bands corresponding to the three CH MOs t_1, e, and t_2 in tetramethylsilane overlap because of diminished through-space interactions between the methyl groups: *M. C. Green*, *M. F. Lappert*, *J. B. Pedley*, *W. Schmidt*, and *B. T. Wilkins*, J. Organometal. Chem. *31*, C 55 (1971).

[7] Adiabatic ionization potential 10.35 eV: *K. Watanabe*, J. Chem. Phys. *26*, 542 (1959).

[8] See also: *H. Bock* and *W. Ensslin*, Angew. Chem. *83*, 435 (1971); Angew. Chem. internat. Edit. *10*, 404 (1971).

[9] *R. G. Snyder* and *J. H. Schachtschneider*, Spectrochim. Acta *21*, 169 (1965).

Structure of the 2:1 Cycloaddition Product of Diazomethane and 1,1,1-Trifluoro-2-trifluoromethyl-3-aza-2,4-*trans*-hexadiene

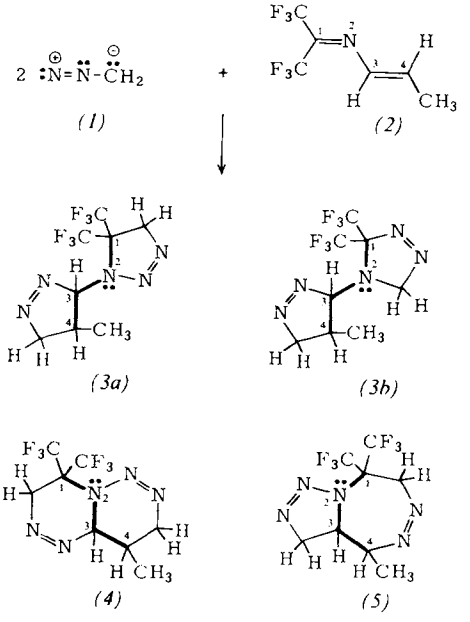
By *Alfred Gieren*[*] together with *Klaus Burger* and *Josef Fehn*[**]

Reaction of diazomethane *(1)* with 1,1,1-trifluoro-2-trifluoromethyl-3-aza-2,4-*trans*-hexadiene[1] *(2)* gives both a 1:1 cycloaddition product[2] and a 2:1 adduct.

[*] Dr. A. Gieren
Abteilung für Röntgenstrukturforschung am
Max-Planck-Institut für Eiweiss- und Lederforschung
8 München 15, Schillerstrasse 46 (Germany)

[**] Dr. K. Burger and Dipl.-Chem. J. Fehn
Organisch-chemisches Institut der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

In the latter case the addition must, in principle, have followed one of three alternative routes giving (i) two linked five-membered rings *(3)* [1,2; 3,4-addition], (ii) two condensed six-membered rings *(4)* ["criss-cross" addition, 1,3; 2,4-addition], or (iii) a 5,7-bicyclic system *(5)* [1,4; 2,3-addition]—the numerals refer to the 2-aza-1,3-*trans*-butadiene skeleton present in *(2)*; see formula scheme). Each addition mode could give four structural isomers depending upon the position at which the 1- and 3-positions of the 1,3-dipole diazomethane add to the dipolarophile. IR and NMR measurements reduced the number of possibilities from twelve to three, *viz.* *(3a)*, *(3b)*, *(4)*. An X-ray structure analysis was performed to decide between these three possibilities and to determine the configuration and conformation of the compound.



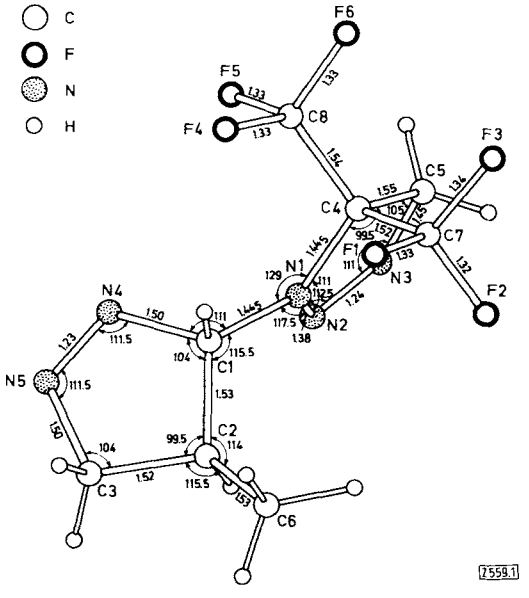
The three-dimensional X-ray structure analysis was carried out with orthorhombic crystals obtained from diethyl ether. Crystallographic data: $a = 19.83_9$, $b = 12.98_5$, $c = 8.82_6$ Å; $d_{exp} = 1.69_5$ g cm^{-3}; space group Pbca. The asymmetric unit contains one molecule $C_8H_9N_5F_6$ ($d_{calc} = 1.68_9$ g cm^{-3}). 2154 reflections (254 not observed, $I < 2\sigma_I$; $\vartheta \leq 70°$, $\vartheta/2\vartheta$ scan; 5 point measurement) were measured with $Cu_{K\alpha}$ radiation on a Siemens diffractometer.

The signs of 294 structure factors could be determined by direct methods[3]. All atoms except the hydrogen atoms were visible in an *E*-Fourier synthesis. The identities of the N and C atoms followed unequivocally, partly from the *E*-Fourier synthesis and partly after the first cycles of refinement on the basis of the bond lengths. Least-squares refinement (full matrix), initially with isotropic and then with anisotropic temperature factors, was carried out until an *R* factor of 9.1% was reached. The nine greatest maxima of a difference Fourier synthesis calculated at this stage indicated the proton positions. Refinement was then pursued including the H atoms (H atoms isotropic, all other atoms anisotropic); the *R* factor has now been reduced to 6.7%. The structure of the molecule is shown in the Figure; it corresponds to that of *(3a)*, 5,5-bis(trifluoromethyl)-1-(4-methylpyrazol-1-in-3-yl)-1,2,3-triazol-2-ine.

The short N1—N2 single bond length in the triazoline ring (1.38 Å) and the angle at N1 indicate rehybridization at N1 from sp^3 to sp^2. The lone pair on N1 undergoes reso-

nance with the N=N double bond. In agreement with the rehybridization at N1, the C—N single bonds emanating from this atom are shortened from 1.47[4] to 1.44$_5$ Å (sp^3—sp^2) and are thus of the same length as the isotypic bond C5—N3. In contrast, the sp^3—sp^2 single bonds (C1—N4, C3—N5) in the pyrazoline ring are lengthened to 1.50 Å. The N=N double bonds (1.24 Å) and C—C (1.53 Å) and RF_2C—F single bonds (1.33 Å) correspond to the expected values.

Both five-membered ring systems are in the "envelope" conformation, the "flap" being provided in both cases by the C atoms lying opposite the N=N double bond. Rehybridization of N1 leads to a significant flattening of the triazoline ring. While C2 protrudes from the plane of the rest of the pyrazoline ring by 0.49 Å, C4 projects from the triazoline ring by only 0.11 Å. The best planes through all five atoms of the two rings enclose an angle of 86°.



Angles (°):

F1–C7–F2: 107.5	F4–C8–F5: 107
F2–C7–F3: 106.5	F5–C8–F6: 107.5
F3–C7–F1: 106.5	F6–C8–F4: 107
C4–C7–F1: 113.5	C4–C8–F4: 113.5
C4–C7–F2: 111.0	C4–C8–F5: 109.5
C4–C7–F3: 111.5	C4–C8–F6: 112
C7–C4–N1: 110.5	C8–C4–N1: 112.5
C7–C4–C5: 112	C8–C4–C5: 110.5
C7–C4–C8: 111.5	

Fig. Molecular structure of 5,5-bis(trifluoromethyl)-1-(4-methylpyrazol-1-in-3-yl)-1,2,3-triazol-2-ine *(3a)*.
The bond lengths are given to the nearest 0.01 Å and the angles to the nearest 0.5°; the mean standard deviations for these quantities are 0.005 Å and 0.3°, respectively.

The adjacent substituents on the pyrazoline ring—triazolinyl and methyl—are *trans*-dipseudoequatorial. The pyrazoline ring also occupies a pseudoequatorial position as a substituent on the triazoline ring. The marked asymmetry of the external angle at the bridge atoms N1 and C1 (129 against 117.5°; 115.5 against 111°) relieves the conformative strain between the two ring systems. The conformation is largely determined by the steric interactions in the molecule.

The angles in the CF_3 groups indicate a distortion of the tetrahedra that appears to be typical for these groups.

Received: November 4, 1971 [Z 559 IE]
German version: Angew. Chem. *84*, 212 (1972)

[1] *K. Burger, G. Dirnsteiner,* and *J. Fehn,* Liebigs Ann. Chem. *747*, 45 (1971).

[2] *K. Burger, J. Fehn,* and *A. Gieren,* Liebigs Ann. Chem., in press.

[3] Program written by *K. Zechmeister; W. Hoppe, J. Gassmann,* and *K. Zechmeister* in *F. R. Ahmed:* Crystallographic Computing. Munksgaard, Copenhagen 1970, p. 26.

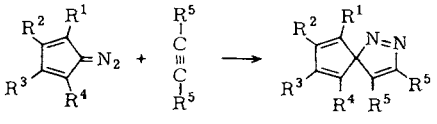
[4] Tables of Interatomic Distances and Configuration in Molecules and Ions. The Chemical Society, London 1965, p. 19s.

Photofragmentation of Spiropyrazoles.—Stable Norcaradienes and Spiroheptatrienes[**]

By *Heinz Dürr, René Sergio,* and *Willy Gombler*[*]

1,3-Dipolar addition of diazocyclopentadienes *(1)* to alkynes *(2)* affords spiropyrazoles *(3)*[1]. Substituted spiropyrazoles *(3)* undergo photochemical fragmentation to give benzocyclopropenes in excellent yields[2]. We have now found that dibenzo derivatives of *(3)* react in a completely different way.

The cycloaddition of diazofluorene *(1a)* to the highly reactive hexafluorobutyne *(2a)* (at −30°C) and dicyanoacetylene *(2b)* (at 20°C) readily affords the spiropyrazoles *(3a)* and *(3b)*[1], respectively, in 91 and 85% yield. The ^{19}F-NMR spectrum of *(3a)* contains two quartets at 57.6 and 62.1 ppm ($CFCl_3$ as internal standard) with $^5J_{FF}$ = 6.8 Hz. In the IR spectrum the stretching vibrations of the CF_3 groups are observed at 1325 and 1365 cm^{-1}, along with the peaks due to the spiro skeleton.



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

(a), R^1–R^2 = R^3–R^4 = benzo, R^5 = CF_3
(b), R^1–R^2 = R^3–R^4 = benzo, R^5 = CN

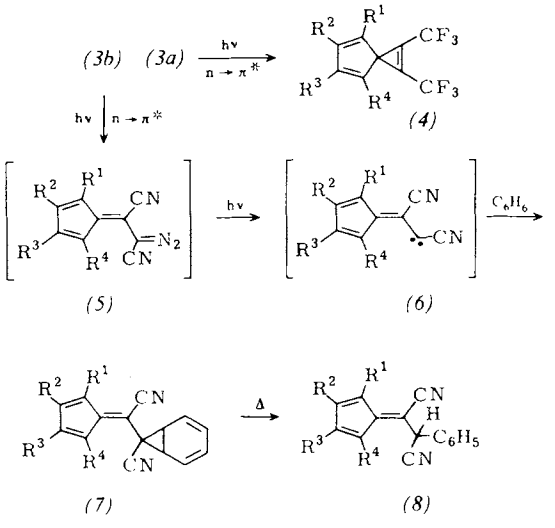
Photolysis (Hg high pressure lamp) of *(3a)* in benzene (Pyrex filter) leads to spiro[2.4]heptatriene *(4)* in 86% yield. The IR spectrum of *(4)* exhibits the typical cyclopropene band at 1900 cm^{-1}, as well as the bands due to the trifluoromethyl groups as 1325 and 1365 cm^{-1}. The only signal in the ^{19}F-NMR spectrum is a singlet at 59.0 ppm which is typical for the highly symmetrical structure of *(4)* (C_{2v} symmetry). Some mono- and dialkoxycarbonyl derivatives of *(3)* react similarly[2–4].

Photolysis of *(3b)* in benzene follows a completely different route. Under the conditions used above for *(3a)*, reaction of *(3b)* furnished an 85% yield of the fulvenylnorcaradiene

[*] Prof. Dr. H. Dürr and Dipl.-Chem. R. Sergio
Institut für organische Chemie der Universität
66 Saarbrücken (Germany)
Chem.-Ing. W. Gombler
Institut für anorganische Chemie der Universität
66 Saarbrücken (Germany)

[**] Photochemistry of small rings, Part 26.—Part 25: *H. Dürr, P. Heitkämper,* and *P. Herbst,* Synthesis, in press.

(7), the *first representative of this type of compound*. In the presence of ether *(3b)* gives a mixture of insertion products. The structure of *(7)* follows from the spectroscopic data. CN stretching vibrations appear at 2200 and 2230 cm^{-1} in the IR spectrum. Further unambiguous evidence for a norcaradiene structure is provided by the ^{1}H-NMR spectrum: $\tau(CDCl_3)=2.2$—2.8 (m), 3.70 (m, vinyl H), and 6.95 (br. s, cyclopropane H) in the ratio 8:4:2.



(7) definitely exists as the norcaradiene; even at 110 °C it is not converted into the cycloheptatriene valence isomer (NMR) but instead rearranges to the phenylfulvene *(8)* (m. p. 183—184 °C; correct elemental analysis; see ref. [5]). The synthesis of the first fulvenylnorcaradiene *(7)* proceeds *via* the diazofulvene *(5)* to the fulvenylcarbene *(6)* which gives *(7)* in an intermolecular cycloaddition. This course has also been established for the photolysis of 5-cyano-3*H*-pyrazoles[6].

7-Cyano-7-(6-cyanodibenzofulvenyl)norcaradiene (7)

A solution of *(3b)* (1.00 g, 3.73 mmol) in anhydrous benzene (200 ml) is irradiated under N_2 with a Philips HPK 125-W lamp for 15 min. After removal of the benzene *in vacuo*, the yellow residue was treated with chloroform to give 1.00 g (85%) of yellow crystalline *(7)*.

Received: December 3, 1971 [Z 560a IE]
German version: Angew. Chem. *84*, 215 (1972)

Spiroheptatrienes by [1+2]-Cycloaddition[1]

By *Heinz Dürr* and *Bernd Ruge*[*]

Spiro[2.4]heptatrienes of type *(1)*[2] are of interest for two main reasons:

1. The spiro bracket introduces additional ring strain into the highly strained (Baeyer strain) cyclopropene group, which should endow these compounds with a relatively low stability or a high reactivity.

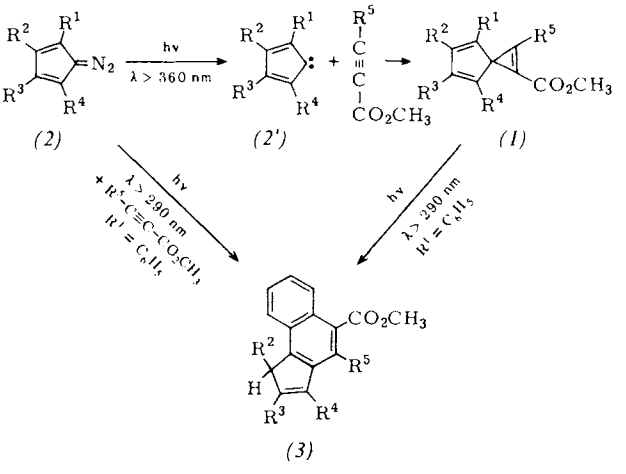
2. Because of their mutually perpendicular π systems, the spiroheptatrienes *(1)* lend themselves for a critical examination of the concept of "spiro conjugation"[3].

The synthesis of these compounds has so far been accomplished in isolated cases only[2,4]. In the present communication we report a general synthesis:

The method involves photolysis of diazocyclopentadienes *(2)* (Hg high pressure lamp) in alkynes such as dimethyl acetylenedicarboxylate or methyl propiolate. Long-wave UV light must be used (GW_v filter: $\lambda > 360$ nm) in the case of phenyl-substituted diazocyclopentadienes in order to avoid possible photorearrangement of *(1)* to benzindenes *(3)*[5].

After removal of the alkyne, chromatography of the photolyzate on silica gel gave medium yields of spiro[2.4]heptatrienes *(1)* (see Table).

Photolysis of the diazocyclopentadiene leads initially to a carbene *(2')* which undergoes [1+2]-cycloaddition with the alkyne to give *(1)*.



	R^1	R^2	R^3	R^4	R^5	Yield (%) *(1)*	Yield (%) *(3)*	IR (cm^{-1}) [a]
(a)	Cl	Cl	Cl	Cl	CO_2CH_3	22	—	1895
(b)	Cl	Cl	Cl	Cl	H	25	—	1795
(c)	C_6H_5	C_6H_5	benzo		CO_2CH_3	26	9	1855
(d)	C_6H_5	C_6H_5	benzo		H	29	—	1775
(e)	C_6H_5	C_6H_5	C_6H_5	C_6H_5	H	9	12	1778
(f)	C_6H_5	C_6H_5	C_6H_5	C_6H_5	CO_2CH_3	40 [5]	—	1865

[a] Cyclopropene band of *(1)*.

The structure of the spiro[2.4]heptatrienes follows from elemental analysis and spectroscopic data. Being very simple, the NMR spectra support the symmetrical structure given. Thus the NMR spectrum of *(1d)* contains a singlet

[1] *H. Dürr* and *L. Schrader*, Z. Naturforsch. *24b*, 536 (1969); and further literature cited therein.

[2] *H. Dürr* and *L. Schrader*, Chem. Ber. *103*, 1334 (1970).

[3] *G. Ege*, Tetrahedron Lett. *1963*, 1667.

[4] *H. Reimlinger*, Chem. Ber. *100*, 397 (1967).

[5] *E. Ciganek*, J. Amer. Chem. Soc. *87*, 652 (1965).

[6] *M. Franck-Neumann* and *C. Buchecker*, Angew. Chem. *82*, 549 (1970); Angew. Chem. internat. Edit. *9*, 526 (1970).

[*] Prof. Dr. H. Dürr and Dipl.-Chem. B. Ruge
Institut für organische Chemie der Universität
66 Saarbrücken (Germany)

at $\tau = 6.19$ ppm for the methoxycarbonyl group, a singlet at $\tau = 1.83$ for the vinyl proton, and a multiplet at $\tau = 2.45$ to 3.13 ppm for the aromatic protons. The signal areas are in the ratio 3:1:14. The characteristic IR spectra of *(1)* exhibit the C=C stretching mode for 1,2-disubstituted cyclopropenes at 1850—1900 cm^{-1} and for 1-substituted cyclopropenes at 1750—1800 cm^{-1} (see Table).

When $R^1 = C_6H_5$, small amounts of benz[*e*]indenes *(3)* are also formed. Use of high-energy UV light ($\lambda > 290$ nm) for the photolysis of *(2c)*—*(2e)* in alkynes leads exclusively to benz[*e*]indenes[5] which are formed from *(1)*. For example, the photolysis of *(1c)* (Hg high pressure lamp, Pyrex filter: $\lambda > 290$ nm) gave an 80% yield of *(3c)* *via* a 1,7 sigmatropic shift and subsequent rearomatization (cf. also ref. [5]), *i.e.* under these conditions *(1)* underwent direct rearrangement to *(3)*.

An attempt was made to deduce information about ring strain in *(1)* from the $^1J_{^{13}C-H}$ coupling constant of *(1b)*. A 49.6% s component of the cyclopropene C—H bond was calculated from $^1J_{^{13}C-H} = 248$ Hz[6, 7]. Studies on the effect of spiro conjugation in *(1)* are currently in progress.

3-Methoxycarbonyl-2',3'-diphenylspiro[cyclopropene-1,1'-indene] (1d)

Compound *(2d)* (2.50 g, 8.5 mmol) is irradiated in methyl propiolate (155 ml) for 2.5 h with the light from a Philips HPK 125-W lamp (GW_v filter: $\lambda > 360$ nm). 85% of the calculated amount of N_2 were evolved within this time. The propiolate was then distilled off at 40 °C/30 torr and the residue chromatographed on silica gel. Elution with benzene/$CHCl_3$ (19:1) gave 1.70 g of a brown oil, from which 0.87 g [29% yield based on reacted *(2d)*] of *(1d)* crystallized on using ether as a solvent; m.p. 118—119 °C after recrystallization from ether; IR: νC=C (cyclopropene) = 1775; νC=O = 1705; νC—H (cyclopropene) = 3110 cm^{-1}.

Received: November 3, 1971 [Z 560b IE]
German version: Angew. Chem. *84*, 215 (1972)

[1] Cycloalkene carbenes, Part 1.

[2] *H. Dürr* and *L. Schrader*, Angew. Chem. *81*, 426 (1969); Angew. Chem. internat. Edit. *8*, 446 (1969).

[3] *H. E. Simmons* and *T. Fukunaga*, J. Amer. Chem. Soc. *89*, 5208 (1967); *R. Hoffmann*, *A. Imamura*, and *G. D. Zeiss*, *ibid. 89*, 5215 (1967).

[4] *E. T. MacBee*, *G. W. Calundann*, and *T. Hodgins*, J. Org. Chem. *31*, 4260 (1966); *G. Ege*, Tetrahedron Lett. *1963*, 1667.

[5] *H. Dürr*, *L. Schrader*, and *H. Seidl*, Chem. Ber. *104*, 391 (1971).

[6] *G. L. Closs*, Advan. Alicycl. Chem. *1*, 76 (1966).

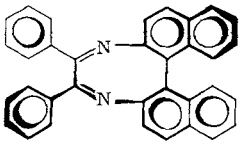
[7] *K. Mislow*, Tetrahedron Lett. *1964*, 1415.

Infrared Rotatory Dispersion (IRD)[**]

By *Bernhard Schrader* and *Ernst-Heiner Korte*[*]

According to the theory of rotatory dispersion[1] it is to be expected that anomalous optical rotation can occur in the infrared owing to molecular vibrations. The amplitude of the anomalies is inversely proportional to the mass of the particles participating in the transition. Effects are therefore predicted that are about four orders of magnitude smaller than those recorded for electronic transitions. Moreover, the components of an IR spectral polarimeter (Nernst glower, polarizer, thermocouple) have less favorable properties than the corresponding components of a UV instrument. The search for anomalies has hitherto been unsuccessful[2].

Previous measurements of the rotatory disperison of molecules covered only the near infrared down to 2500 cm^{-1}. However, the greatest and most informative effects are to be expected in the range of skeletal vibrations. Our studies in this spectral region with a single beam spectral polarimeter[3] having a sensitivity of 0.01° (at 1000 cm^{-1}, 2 cm^{-1} slit width, and 60% absorption) on both antipodes of carvone *(1)*, α-pinene *(2)*, phenylethylamine *(3)*, and 2,3-diphenyldinaphtho[2,1-*e*;1,2-*g*]-[1,4]-diazocine[4] *(4)* show no measurable anomalies apart from the normal drop in rotation with the wave number.



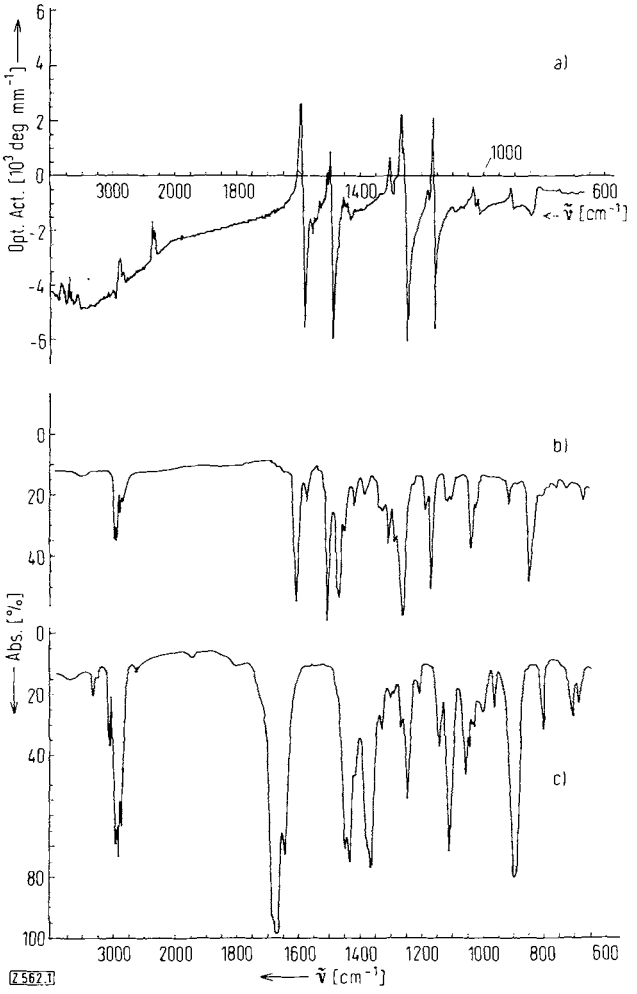


Fig. 1. a) IRD curve of 2 mol-% d-carvone *(1)* in Licristal® *(5)*, layer thickness 13 μm, NaCl windows; b) IR absorption spectrum corresponding to a); c) IR absorption spectrum of d-carvone *(1)*, layer thickness 50 μm.

[*] Prof. Dr. B. Schrader
Abteilung Theoretische Organische Chemie der Universität
46 Dortmund-Hombruch, Postfach 500 (Germany)
Dipl.-Phys. E. H. Korte
Institut für Spektrochemie und angewandte Spektroskopie
46 Dortmund, Postfach 778 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft. We also wish to thank Dr. *E. Steigner*, Frankfurt, for the preparation of the antipodes of *(4)*.

Anomalies do occur, however, when the molecules *(1)* to *(4)* are dissolved in a nematic liquid crystal. This optically inactive mesophase is transformed into the optically active cholesteric phase by addition of small amounts of chiral molecules[5]. We have found that a solution of 2 mol-% d-carvone in Licristal® *(5)* (eutectic mixture of the isomeric *N*-oxides of *p*-methoxy-*p'*-*n*-butylazobenzene) as a 13-μm layer between NaCl windows gives the rotatory dispersion curve reproduced in Figure 1a with anomalies having an unexpectedly large amplitude of *ca.* 7000 deg/mm. A corresponding curve of opposite polarity is recorded for a solution of l-carvone. Solutions of *(2)*, *(3)*, and *(4)* in *(5)* give curves having anomalies at the same frequencies but of different magnitudes and forms. Solutions of *(1)* to *(4)* in a mixture of *N*-(*p*-methoxybenzylidene)- and *N*-(*p*-ethoxybenzylidene)-*p'*-butylaniline *(6)* produce similar curves. The frequencies at which rotational anomalies are observed agree with the IR absorption bands of the *host* molecules—*(5)* and *(6)*—while vibrations of the *guest* molecules—*(1)* to *(4)*—are not seen in anomalies of the dispersion curves (see Fig. 1).

We assume that the steric form of the chiral molecules determines the pitch of the cholesteric phase. Anomalies of the rotatory dispersion are to be expected when the effective wavelength in the cholesteric phase λ_{eff} (vacuum wavelength λ_{opt} divided by the refractive index n) is equal to the pitch. The appearance of several anomalies in the IRD curve can be explained by the fact that $\lambda_{eff} = \lambda_{opt}/n$ is equal to the pitch for various values of λ_{opt} since n is subject to wide variations in absorption bands.

Studies are in progress to determine in how far the sign and degree of helicity of molecules can be ascertained with the aid of this new effect.

Received: November 29, 1971 [Z 562 IE]
German version: Angew. Chem. *84*, 218 (1972)

[1] *L. Rosenfeld*, Z. Physik *52*, 161 (1928); *W. Kuhn* and *K. Freudenberg*: Drehung der Polarisationsebene des Lichts. Akad. Verlagsgesellschaft, Leipzig 1932; *E. U. Condon*, Rev. Mod. Phys. *9*, 432 (1937).

[2] *T. M. Lowry* and *C. P. Snow*, Proc. Roy. Soc. (London) *A 127*, 271 (1930); *H. S. Gutowsky*, J. Chem. Phys. *19*, 438 (1951); *L. R. Ingersoll*, Phys. Rev. *9*, 257 (1917); *H. J. Hediger* and *Hs. H. Günthard*, Helv. Chim. Acta *37*, 1125 (1954); *H. R. Wyss* and *Hs. H. Günthard*, J. Opt. Soc. *56*, 888 (1966).

[3] *E. H. Korte* and *B. Schrader*, to be published.

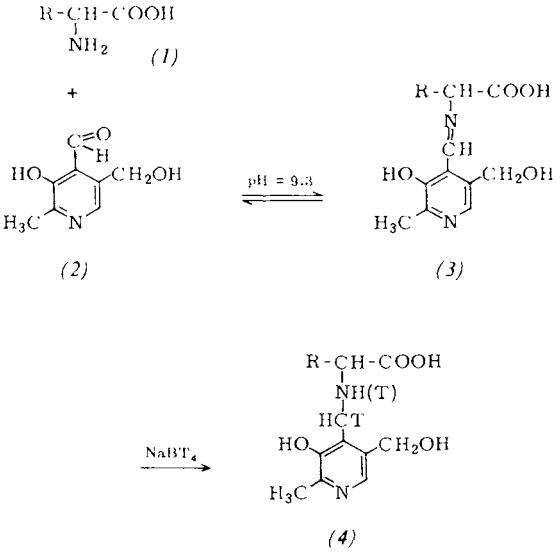
[4] *R. Kuhn* and *P. Goldfinger*, Liebigs Ann. Chem. *470*, 183 (1929).

[5] *G. Friedel*, Ann. Phys. (Paris) *18*, 273 (1922); *A. D. Buckingham*, *G. P. Ceasar*, and *M. B. Dunn*, Chem. Phys. Lett. *3*, 540 (1969); *H. Stegemeyer* and *K. J. Mainusch*, *ibid. 6*, 5 (1970); *H. Stegemeyer*, *K. J. Mainusch*, and *E. Steigner*, *ibid. 8*, 425 (1971).

Amino Acid Analysis on the Picomole Scale[**][1]

By *Norbert Lustenberger*, *Hans-Walter Lange*, and *Klaus Hempel*[*]

In an alkaline medium, amino acids *(1)* and pyridoxal *(2)* undergo condensation to Schiff bases *(3)* which can be converted into pyridoxyl amino acids of type *(4)* by catalytic reduction[2, 3] or by reduction with sodium tetrahydroborate. We have found that pyridoxyl amino acids can be detected extremely readily. After separation by column chromatography, approx. 2×10^{-8} mol of an individual pyridoxyl amino acid can be detected by spectrophotometry and approx. 5×10^{-10} mol by fluorometric methods. Reduction with radioactive $NaBT_4$ offers particular advantages since the tritiated pyridoxyl amino acids *(4)* can be quantitatively determined on a picomole scale (1×10^{-12} mol).



In order to ascertain the sensitivity of this amino acid analysis we have examined: a) the chemical reaction; b) the isotope effect of the $NaBT_4$-reduction of the Schiff bases *(3)*; c) the separation of the pyridoxyl amino acids by column chromatography; as well as d) the possible methods of determination.

a) The yields (Table) were determined by reaction of 25-μmol portions of ^{14}C-labeled amino acids of known specific activity followed by column-chromatographic separation from the pyridoxyl ^{14}C-amino acid. The highest yields were obtained with 0.2 M solutions of pyridoxal in phosphate buffer (pH = 9.3). To the best of our knowledge pyridoxylcysteic acid, -glutamine, -proline, and -hydroxyproline have not previously been described.

The formation of pyridoxylprolines was unexpected since the intermediacy of a Schiff base *(3)* can be ruled out in this case. We suspect that the reaction proceeds *via* a keto enimine intermediate[4, 5]. Cysteine and histidine do not give pyridoxyl amino acids of type *(4)* since the Schiff bases of these compounds undergo spontaneous cyclization to products that cannot be reduced[2]. Use of radioactive pyridoxal recommends itself in this case; investigations are in progress.

b) Considerable isotope effects have been recorded[6] in reactions with mixtures of hydrogen isotopes. For a given series of pyridoxyl amino acids *(4)* we therefore determined the yield and the ^3H activity after reduction of the Schiff bases *(3)* with $NaBT_4$ (spec. activity 10 mCi/mg-atom) and calculated the specific ^3H activities (Table) from these results. Deviations from the value expected with no isotope effect (10 mCi/mmol) lie within the limits of experimental accuracy. The fact that no isotope effect was detected could possibly have something to do with our using $NaBT_4$ diluted with $NaBD_4$.

[*] Dr. N. Lustenberger, Dr. H.-W. Lange, and Priv.-Doz. Dr. Dr. K. Hempel
Institut für Medizinische Strahlenkunde der Universität
87 Würzburg, Versbacher Landstrasse 5 (Germany)

[**] We are grateful to the Deutsche Forschungsgemeinschaft for their support of this work and for a Grant to *N.L.*

Table. Synthesis and optical detection of pyridoxyl amino acids of type *(4)*; for reaction conditions see experimental section. Extinction measured at the absorption maximum (328 nm); fluorescence measurements at E_{max} 332 nm/F_{max} 400 nm; given as relative fluorescence units based on quinine sulfate (1×10^{-6} g/ml; $E_{350\,nm}/F_{450\,nm}$ equal to 1.0). All the optical data refer to 0.35 N sodium citrate buffer solutions (pH 5.28).

Amino acid	Product	Yield (%)	Spec. ^3H activity [e, f] (mCi/mmol)	Mol. ext. coeff. (mmol × cm^{-2})	Mol. fluorescence ($\times 10^{-3}$)	Ref. to synth. of *(4)*
Ala	*(4)*	91	10.3	8400	180	[2, 3]
β-Ala	*(4)*	99	10.1	7500	160	[2]
Arg	*(4)*	94	9.7	8400	220	[3]
Asp	*(4)*	87	10.4	8100	200	[2, 3]
Asn	*(4)*	87	—	7000	160	[2]
Cys-SO_3H	*(4)*	75	—	—	—	—
Glu	[a]	88	9.9	2700	20	[2, 3]
Gln	[a]	82	—	2700	20	—
Gly	*(4)*	90	9.7	7800	180	[2]
His	[b]	99	—	12900	70 [g]	[2]
Hypro	*(4)*	25 [c]	—	—	—	—
Ile	*(4)*	93	10.7	8500	190	[2]
Leu	*(4)*	95	10.0	7600	180	[2]
Lys	[d]	95	20.1	16000	300	[2, 7]
Met	*(4)*	91	9.7	7700	65	[2]
Phe	*(4)*	95	9.9	7800	210	[2]
Pro	*(4)*	24 [c]	7.9	10800	230	—
Ser	*(4)*	90	11.0	7200	170	[2, 3]
Thr	*(4)*	93	10.0	7300	180	[2]
Trp	*(4)*	98	10.0	—	—	[2, 3]
Tyr	*(4)*	96	10.0	4800	35	[2, 3, 8]
Val	*(4)*	99	9.8	8200	170	[2]
Pyridoxine group						
Pyridoxamine				6600	135	
Pyridoxine				3300	50	
Pyridoxal				7000	50	

[a] Pyridoxyloxopyrrolidinecarboxylic acid.
[b] Schiff base *(3)* cyclizes to an imidazopyridine derivative that cannot be hydrogenated [2].
[c] More than 70% of the amino acid resists reaction; yields increased by repeated treatment with pyridoxal and $NaBH_4$.
[d] Dipyridoxyllysine.
[e] Reduction of *(3)* with a $NaBT_4/NaBD_4$ mixture of spec. activity 10 mCi/mg-atom; produced by dilution of $NaBT_4$ (spec. activity 900 mCi/mg-atom) with $NaBD_4$.
[f] Mean value calculated from three to six individual determinations.
[g] Dissolved in 0.2 N NaOH; fluorescence measurements at E_{max} 306 nm/F_{max} 370 nm.

c) We were able to separate the pyridoxyl derivatives of synthetic mixtures of all biologically important amino acids on ion-exchange resins. The Figure illustrates the analysis of an amino acid mixture (1×10^{-11} mol per amino acid), which had been converted into the radioactive pyridoxal derivatives *(4)*. For optical detection a further 0.5 μmol of each pyridoxyl amino acid was added prior to analysis. Extinction, fluorescence, and radioactivity of the column eluate were measured. In order to ensure that these measurements were performed at similar pH values (pH 5) for all amino acids an aliquot of eluate was diluted with four parts of sodium citrate buffer (pH 5.28) for the extinction measurements and with 49 parts for the fluorescence determinations.

d) Owing to the chromophoric pyridoxyl group, pyridoxyl amino acids of type *(4)* have spectra resembling that of pyridoxamine (absorption maxima at 255 nm and 328 nm) and also exhibit a characteristic pH-dependent fluorescence (E_{max} 332 nm/F_{max} 400 nm) suitable for detection of these compounds (Table). The molar fluorescence of most pyridoxyl amino acids lies in the same range. On excitation (332 nm) the intensity of fluorescence falls off within minutes.

Detection with the aid of radioactivity measurements is most sensitive. We found about 2000 counts per min for each 1×10^{-12} mol of pyridoxyl amino acid after reaction with $NaBT_4$ of specific activity 3600 mCi/mmol. The specific activity of carrier-free $NaBT_4$ is 116 Ci/mmol.

Pyridoxyl derivatives are suitable not only for the detection of amino acids and amines. On use of pyridoxamines in place of pyridoxal *(2)*, carbonyl compounds can be determined quantitatively with the same degree of sensitivity. The α-keto acids yield the corresponding pyridoxyl amino acids.

We believe that the above method is the most sensitive available for the quantitative determination of amino acids. On use of ninhydrin in automatic amino acid analysis[9], 10^{-9} mol can still just be detected by colorimetry. The sensitivity of the ninhydrin reaction can be enhanced 10 to 100-fold by addition of phenylacetaldehyde and fluorescence measurements[10, 11]. The dansyl method[12] can be used to identify 10^{-12} mol[13] of any amino acid after separation by thin-layer chromatography. However, this test cannot be automated and is limited to amino acids and amines.

Experimental

Solutions of amino acids in 0.5 M phosphate buffer (pH 9.3) are mixed with an equal volume of a freshly prepared 0.4 M pyridoxal solution whose pH has been adjusted to 9.3, and allowed to stand at 8 °C. The molar ratio of pyridoxal and amino acid should be > 5:1. After 30 min the yellow reac-

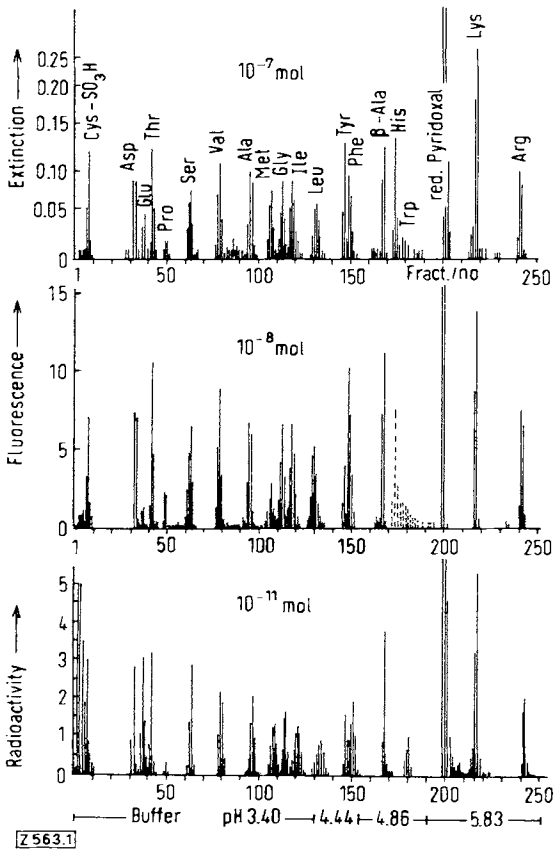


Fig. Column chromatography of a pyridoxyl amino acid mixture and detection of the amino acids. Conditions: Ion-exchange resin Aminex A 5 (BioRad, Richmond, California 94804 (USA)), column 100 × 0.6 cm, packed height 90 cm, temperature 70 °C, flow rate 33 ml/h, pressure 30—35 at, fraction volume 3 ml, elution with 0.2 N (pH 3.40—4.86) and 0.35 N (pH 5.86) sodium citrate buffer.

UV determination (328 nm): 1×10^{-7} mol of each amino acid. Pyridoxyltryptophan partially decomposed.

Fluorometric determination ($E_{332\,nm}/F_{400\,nm}$; relative units): 1×10^{-8} mol of each amino acid. Dashed fractions were adjusted to pH 12 with conc. NaOH and measured at $E_{306\,nm}/F_{370\,nm}$ to achieve better determination of the histidine derivative. Pyridoxyltryptophan partially decomposed.

Radioactive determination (counts/min × 10^{-2}). Activity measurements with liquid scintillation counter (Tri-Carb model 3380, Packard, Downers Grove, Illinois 60515 (USA)), yield 5%. 1×10^{-11} mol of each amino acid; reduction with radioactive $NaBT_4$ of spec. activity 3600 mCi/mmol (= 900 mCi/mg-atom). Pyridoxyltryptophan partially decomposed. No radioactivity at position corresponding to the histidine derivative.

tion mixture is decolorized by addition of $NaBH_4$ solution (100 mg in 1 ml 0.1 N NaOH). The excess of $NaBH_4$ is decomposed by acidification with HCl (pH 1—2) prior to column chromatography.

Received: September 29, 1971 [Z 563 IE]
German version: Angew. Chem. *84*, 255 (1972)
Publication delayed at authors' request

[1] Highly sensitive detection reactions with pyridoxine derivatives, Part 1.

[2] *D. Heyl, S. A. Harris*, and *K. Folkers*, J. Amer. Chem. Soc. *70*, 3429 (1948).

[3] *M. Ikawa*, Arch. Biochem. Biophys. *118*, 497 (1967).

[4] *Th. C. Bruice* and *St. J. Benkovic* in: Bioorganic Mechanisms. Benjamin, New York 1966, Vol. 2, pp. 250ff.

[5] *M. Flavin* and *C. Slaughter*, Biochemistry *5*, 1340 (1966).

[6] *H. Simon* and *D. Palm*, Angew. Chem. *78*, 993 (1966); Angew. Chem. internat. Edit. *5*, 920 (1966).

[7] *A. W. Forrey, R. B. Olsgaard, Ch. Nolan*, and *E. H. Fischer*, Biochimie *53*, 269 (1971).

[8] *J. H. Fellman* and *E. S. Roth*, Biochemistry *10*, 408 (1971).

[9] *S. Moore* and *W. H. Stein*, J. Biol. Chem. *176*, 367 (1948).

[10] *K. Samejima, W. Dairman*, and *S. Udenfriend*, Anal. Biochem. *42*, 222 (1971).

[11] *K. Samejima, W. Dairman, J. Stone*, and *S. Udenfriend*, Anal. Biochem. *42*, 237 (1971).

[12] *W. R. Gray* and *B. S. Hartley*, Biochem. J. *89*, 379 (1963).

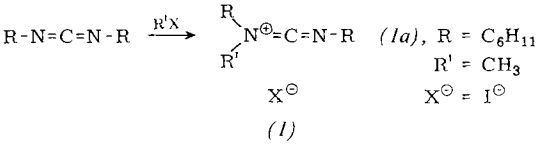
[13] *V. Neuhoff, F. von der Haar, E. Schlimme*, and *M. Weise*, Hoppe-Seylers Z. Physiol. Chem. *350*, 121 (1969).

Carbodiimidium Compounds as Reagents in Organic Chemistry[**]

By *Rolf Scheffold* and *Emil Saladin*[*]

Carbodiimidium compounds of general structure *(1)* (R′ = H) play an important role as intermediates in acid-induced addition reactions of carbodiimides. To the best of our knowledge no reports have so far appeared in the literature describing the isolation of carbodiimidium compounds in substance. According to *Hartke* and *Rossbach*[1], attempts to synthesize them by reaction of aliphatic carbodiimides with anhydrous tetrafluoroboric acid in methylene chloride or by reaction with dimethyl sulfate lead exclusively to dimeric cyclic products.

We have now found that *N,N′*-dicyclohexylcarbodiimide can be alkylated by prolonged heating in pure alkyl bromides or iodides[2]. Treatment with methyl iodide, for example, leads to 75% yields of *N,N′*-dicyclohexylcarbo-



diimidium iodide *(1a)*, which crystallizes as colorless needles having m. p. 111—113 °C. Assignment of structure is based on elemental analysis, the IR spectrum [($CHCl_3$): bands at, *inter alia*, 2119 (ν N=C=N) and 1667 cm^{-1}], and the NMR spectrum [($CDCl_3$): δ = 3.50 ppm (s, 3H of N—CH_3); 3.3—3.6 ppm (broad accumulation of signals, 2H on the α-C of the cyclohexyl groups); 1.0—2.1 ppm (broad accumulation of signals, 20H on the β-C, γ-C, and δ-C of the cyclohexyl groups)].

Carbodiimidium compounds of general structure *(1)*[3] are of interest in many respects as reagents in organic chemistry. To illustrate this we report first on their use in the conversion of alcohols into iodides:

Aliphatic primary and secondary alcohols (including such types as homoallyl and neopentyl alcohols) react with *N*-methyl-*N,N′*-dicyclohexylcarbodiimidium iodide *(1a)* in solvents such as tetrahydrofuran, benzene or hexane at 35°—50 °C to give the corresponding iodides, usually in high yields.

Stereochemistry: The reaction involves inversion of the configuration at the C atom bearing the OH group[4]. For example, in the case of 3β-cholestanol, thermodynamically

[*] Prof. Dr. R. Scheffold and Dipl.-Chem. E. Saladin
Institut de chimie organique, Université de Fribourg, Perolles
CH-1700 Fribourg (Switzerland)

[**] This work was supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, Project No. 4783.

less stable 3α-iodocholestane is formed in more than 84% yield. Particularly noteworthy is the fact that cholest-5-en-3β-ol (cholesterol, as a typical representative of the homoallyl alcohols) is converted in one step into the previously unknown 3α-iodocholest-5-ene[5].

Table: Examples of typical reactions of alcohols with *N*-methyl-*N*,*N'*-dicyclohexylcarbodiimidium iodide *(1a)*.

Educt	Product	Conditions [a]	Yield (%) [b]
1-Octanol	1-Octyl iodide	3 h/35 °C	89
dl-2-Octanol	dl-2-Octyl iodide	2 h/35 °C	81
1,3-Dihydroxypropane	1,3-Diiodopropane	15 h/35 °C	72
3β-Cholestanol	3α-Iodocholestane	15 h/35 °C	84
Cholest-5-en-3β-ol	3α-Iodocholest-5-ene	15 h/35 °C	38
		15 h/35 °C [c]	40
13-Isopropyl-podocarpa-8,11,13-trien-15-ol	13-Isopropyl-15-iodo-podocarpa-8,11,13-triene	48 h/50 °C	18
17β-Hydroxy-androst-4-en-3-one	17α-Iodoandrost-4-en-3-one	62 h/60 °C	38

[a] Each mol of alcohol treated with 2 moles of *(1a)*. Solvent: THF unless otherwise stated.

[b] The yields relate to analytically pure product. The yields of crude iodides are sometimes much higher.

[c] In hexane.

Steric hindrance: Even extremely sterically hindered alcohols such as neopentyl alcohols can be converted under mild conditions, albeit in low yields, into the corresponding iodides. As examples may be mentioned the conversion of 13-isopropylpodocarpa-8,11,13-trien-15-ol (dehydroabietanol) into 13-isopropyl-15-iodopodocarpa-8,11,13-triene[6] and of 17β-hydroxyandrost-4-en-3-one (testosterone) into 17α-iodoandrost-4-en-3-one[7].

Limitations: Substrates containing nucleophilic substituents other than the OH group of the alcohol, *e.g.* amino groups or carboxy groups, cannot be converted directly into the iodides without prior protection.

It seems reasonable to assume that the primary reaction step involves addition[8] of one mol of alcohol RR'CHOH to the highly reactive carbodiimidium system with formation of an isourea as trigonal intermediate, which, under the conditions given, is protonated[9]. The second and usually rate-determining step consists of the nucleophilic substitution of the positively charged urea group by the iodide ion. This substitution proceeds with inversion of configuration at the carbon atom (see Figure).

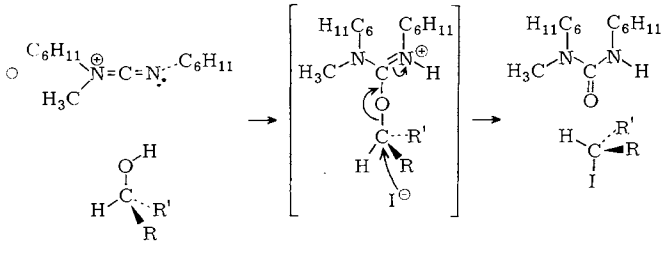


Figure. Schematic representation of the course of the reaction.

N-Methyl-N,N'-dicyclohexylcarbodiimidium iodide (1a)[*]

Freshly distilled *N*,*N'*-dicyclohexylcarbodiimide (42 g, 0.204 mol) was dissolved in methyl iodide (90 ml, 1.45 mol) under nitrogen at room temperature in a 250 ml round-bottom flask fitted with magnetic stirrer, reflux condenser, and a nitrogen bulb. The colorless reaction mixture was stirred for 72 h at a bath temperature of 70 °C. The excess of methyl iodide was then removed from the pale-brown solution by distillation under reduced pressure and the viscous, brown residue thus obtained was dissolved in anhydrous toluene (150 ml) at 40 °C. The crystalline mass which separated out within a few hours was separated from the mother liquor in an inert atmosphere by filtration on a glass Buchner filter fitted with a nitrogen bulb; the reaction flask was then rinsed three times with 25 ml portions of ice-cold anhydrous toluene. The pale-yellowish crystalline mass recovered on the filter was washed with ice-cold anhydrous toluene until colorless crystals were obtained. After 20 hours drying at room temperature/0.1 torr, a total yield of 53 g (75%) of colorless crystals, m. p. 111—113 °C, was obtained. For analysis, the product was recrystallized three times from methyl iodide/hexane and dried at 20 °C/0.005 torr for 48 hours, m. p. 111—113 °C.

Typical example of a alcohol → iodide conversion: 3α-iodocholestane

A mixture of 3β-cholestanol[10] (1.940 g, 5 mmol) and *(1a)* (3.475 g, 10 mmol) was dissolved in tetrahydrofuran (50 ml) in a 100 ml round-bottom flask fitted with a nitrogen bulb. The colorless solution was allowed to stand for 15 hours at 35 °C. The solvent was then removed at reduced pressure in a rotary evaporator. The residue was taken up in 50 ml hexane, transferred to a separatory funnel, and washed three times with 25-ml portions of methanol/water (4:1) to remove *N*-methyl-*N*,*N'*-dicyclohexylurea. The combined washings were extracted three times with 25 ml portions of hexane; the combined hexane phase was dried over sodium sulfate and then filtered through silica gel (*ca.* 10 g). The clear filtrate, after removal of solvent under reduced pressure and subsequent drying at 20 °C/0.1 torr, yielded 2.359 g (95%) of crude iodide. Recrystallization of the crude product from anhydrous acetone (40 ml) afforded 2.086 g (84%) of pure 3α-iodocholestane, colorless needles, m.p. 111—111.5 °C[11].

Received: September 10, 1971 [Z 547a IE]
Revised: December 1, 1971
German version: Angew. Chem. *84*, 158 (1971)

[*] *Note added in proof* (February 8, 1972): A dimer of *(1a)* cannot be ruled out on the basis of the available data.

[1] *K. Hartke* and *F. Rossbach*, Angew. Chem. *80*, 83 (1968); Angew. Chem. internat. Edit. *7*, 72 (1968).

[2] It had been established as long ago as 1925 that *N*,*N'*-di-*n*-propylcarbodiimide does not add methyl iodide: *H. Lecher*, *F. Graf*, *C. Heuck*, *K. Köberle*, *F. Gnädinger*, and *F. Heydweiller*, Liebigs Ann. Chem. *445*, 35 (1925).

[3] *(1a)* is a crystalline, colorless, slightly hygroscopic compound that can be stored in the refrigerator for several months. Variation of R,R', and X⁻ in *(1)* can be realized by suitable choice of carbodiimide and alkylating reagent. The anion I⁻ in *(1a)* can be replaced by X⁻ by treatment with AgX.

[4] Although, strictly speaking, the reaction proceeds with inversion of configuration, it is possible that a certain amount of the iodoalkane shows retention of configuration. This part of the product arises by nucleophilic substitution of the initially formed iodoalkane by iodide ions in solution. Consequently a decrease in stereoselectivity is always observed, if the reaction conditions are too vigorous (too high a temperature, too long a reaction time, too great an excess of reagent).

[5] Recrystallized from acetone three times and dried at 0.01 torr; m. p. 130—130.5 °C. In the NMR spectrum in $CDCl_3$, the signal of the β proton on C-3 appears as a multiplet at δ = 4.90 and that of the olefinic proton on C-6 as a multiplet at δ = 5.30 ppm (TMS = 0).

[6] Colorless, viscous oil. NMR spectrum in $CDCl_3$: δ = 1.09 (s, 3H); 1.20 (s, 3H); 1.22 (d, J = 7 Hz, 6H); 1.45—1.76 (accumulation of signals, 9H); 2.0—3.0 (m, 2H); 2.91 (septet 1H); AB system with 3.20 (d, J = 11 Hz, 1H) and 3.33 (d, J = 11 Hz, 1H); 6.9—7.1 (m, 3H) (TMS = 0).

[7] Recrystallized from anhydrous acetone and dried at 0.01 torr; m. p. 154—155 °C. IR spectrum in chloroform: 1670 cm^{-1} (ν C=O). In the NMR spectrum in $CDCl_3$ the signal of the β-proton on C-17 appears as the X part of an ABX system at δ = 4.40 (q, J_{AX} = 2 Hz, J_{BX} = 6 Hz, 1H) and the signal due to the olefinic proton on C-4 occurs at δ = 5.77 (d, J = 1.5 Hz, 1H).

[8] The isourea hydroiodide formulated as intermediate in the reaction of 2,2-dimethylpropanol (neopentyl alcohol) with *(1a)* in THF can in fact be isolated as colorless crystals after a few hours at 35 °C. This shows that sterically hindered alcohols also undergo smooth addition to the C=N double bond of carbodiimidium system.

[9] The pK^{*}_{MCS} of the isourea hydroiodide formed from *(1a)* and neopentyl alcohol is 9.5. (For the definition of pK^{*}_{MCS} value cf. *W. Simon*. Helv. Chim. Acta *41*, 1835 (1958).

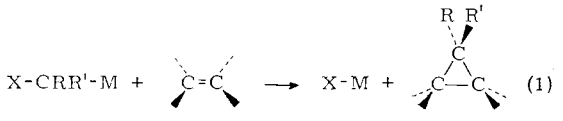
[10] The 3β-Hydroxycholestane used was obtained from Fluka AG, Buchs; its melting point after one recrystallization was 140—142 °C.

[11] The melting point and all spectroscopic data are identical with the values quoted for 3α-iodocholestane by *J. P. Verheiden* and *J. G. Moffat*, J. Org. Chem. *35*, 2319 (1970) and by *A. V. Bayless* and *H. Zimmer*, Tetrahedron Lett. *1968*, 3811.

Organomercury Carbenoids for the Synthesis of Cyclopropane Derivatives[**]

By *Rolf Scheffold* and *Urs Michel*[*]

Organometallic compounds of general structure *(1)* can be used for the synthesis of cyclopropanes[1].



(1) *(2)* *(3)* *(4)* (1)

X = leaving group, *e.g.* halogen

M = metal or metal complex cation

R,R' = H, organic group, halogen, *etc.*

Zinc(II) and copper(I) carbenoids of type *(1)*, with R = R' = H, are of particular importance in preparative organic chemistry; they are unstable and must be prepared *in situ*—from diiodomethane and zinc/copper couple[2] or diethylzinc[3] or from diazomethane and zinc iodide[4]—or they are formed as an intermediate, *e.g.* as in the synthesis of cyclopropane by Cu(I)-catalyzed decomposition of diazomethane[5].

In contrast, the corresponding mercury(II) compounds are considerably more stable and can be isolated in substance. *Seyferth et al.*[6] shown that mercury(II) carbenoids are suitable reagents for the synthesis of 1,1-dihalogenocyclopropanes. Similar methods[7] for the preparation of the cyclopropanes *(4)* (R = R' = H) are, however, comparatively less satisfactory since the mercury(II) carbenoids seem to be insufficiently reactive.

We have investigated the organomercury(II) carbenoids regarding their suitability as reagents for a mild, versatile, and selective synthesis of cyclopropane and alkylcyclopropane derivatives. As first example we report here on the synthesis and reactions of benzylmercurioiodomethane *(1a)*[8].

Addition of an ethereal solution of diazomethane to a solution of benzylmercury iodide *(3a)* in tetrahydrofuran at 0 °C leads to immediate formation of the carbenoid *(1a)*[9] in quantitative yield. This compound, a colorless oil, is so stable towards heat that it remains unchanged for several hours in benzene at 90—100 °C under nitrogen.

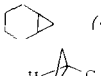
$$\underset{(3a)}{C_6H_5\text{-}CH_2\text{-}Hg\text{-}I} + CH_2N_2 \xrightarrow[\text{quantitative}]{Et_2O,\ THF,\ 0\,^{\circ}C} \underset{(1a)}{C_6H_5\text{-}CH_2\text{-}Hg\text{-}CH_2\text{-}I} + N_2 \qquad (2)$$

IR (CCl_4): Bands at 1500—1600 (broad), 1490 (s), 1450 (s), 690 (s) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.25 ppm, singlet (2 H of the methylene group, satellite signals $J_{^1H-^{199}Hg}$ = 47 Hz[10]); 2.65 ppm, singlet (2 H of the benzyl group, satellite signals $J_{^1H-^{199}Hg}$ = 154 Hz[10]); 7.1—7.2 ppm, multiplet (5 H of the aromatic ring).

Benzylmercurioiodomethane *(1a)* reacts with olefins (molar ratio 1:1) under mild conditions to give benzylmercury iodide *(3a)* and cyclopropane derivatives *(4)* (R = R' = H) in accordance with eq. (1); duration of reaction a few minutes to a few hours at temperatures of 0—90 °C. Depending on the nature of the olefin (solid or liquid) the reaction can be carried out without or with solvent,

Table. Examples of typical cyclopropane syntheses with benzylmercurioiodomethane *(1a)*.

Olefin	Reaction conditions [a]	Product	Yield [b]
 *(2a)*	30 min/50	 *(4a)*	94
 *(2b)*	4 h/70	 *(4b)*	90
 *(2c)*	4 h/80	 *(4c)*	70
 *(2d)*	4 h/90	 *(4d)*	80
 *(2e)*	6 h/90	 *(4e)*	6
	several h/90		no reaction

[a] Molar ratio olefin : carbenoid *(1a)* = 1:1, no solvent. Quoted after the oblique is the bath temperature (°C).

[b] Referred to pure product in reactions using quantities of the order of 10 mmol.

[*] Prof. Dr. R. Scheffold and U. Michel
Institut de chimie organique
Université de Fribourg Pérolles
CH-1700 Fribourg (Switzerland)

[**] This work was supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, Project No. 2185.

e.g. benzene or tetrahydrofuran. The yield of regenerated *(3a)* is usually about 90%; the yield of *(4)* depends on the nucleophilic reactivity of the olefin *(2)* (Table).

The relative reactivity of the olefins increases with increasing nucleophilic character of the C=C bond. Up to now, no such reactions have been observed in the case of α,β-unsaturated carbonyl compounds and benzene.

The stereochemistry of the products is compatible with a *syn*-[1,2] addition on the unhindered side of the olefin.

Side reactions: So far, no insertions have been observed to take place into C—C or C—H bonds.

Experimental:

(All organomercury compounds are to be regarded as being very toxic. It is therefore recommended that relevant safety precautions should be taken).

Benzylmercury iodide

Benzylmercury bromide[11] (62.0 g, 0.167 mol) is dissolved in tetrahydrofuran (200 ml, previously distilled over CaH_2) at 40°C; to this solution is added a solution of pure sodium iodide (27.6 g, 0.184 mol) in anhydrous methanol (100 ml). The color changes to yellow and a white precipitate is formed. The solvent is removed from the mixture by evaporation in a rotary evaporator at a water-bath temperature of 30°C, and the residue thus obtained is taken up in benzene (400 ml, previously distilled over Na). After separation of undissolved sodium bromide (17.0 g), the filtrate is concentrated to 200—300 ml. On cooling, pale-yellow to orange crystals separate from the supersaturated solution. Yield 62.0 g (89%); m.p. 114—115°C; ^{1}H-NMR ($CDCl_3$): δ = 3.32 (s, 2H; no satellite signals), 7.2 (s, 5H).

Benzylmercurioiodomethane

A solution of benzylmercury iodide (4.19 g, 0.01 mol) in tetrahydrofuran (30 ml, previously distilled over KOH and $LiAlH_4$) is cooled to 0—5°C and a cold solution (*ca.* −10°C) of freshly distilled diazomethane in ether[12] is slowly added until liberation of nitrogen ceases. After five minutes the excess of diazomethane and solvent is removed by distillation in a rotary evaporator. After drying (18 h at room temperature/0.3 torr) there remains 4.33 g (100% yield) of a clear colorless oil.

Cyclopropane derivatives

Equimolar amounts of the liquid carbenoid *(1a)* and an olefin *(2a)*—*(2e)* are homogeneously mixed and heated under nitrogen. The progress of the reaction can be estimated from the amount of benzylmercury iodide which crystallizes out on cooling the mixture to room temperature; in the case of complete conversion the cooled reaction mixture is usually solid.

Readily volatile cyclopropanes such as 1-methoxybicyclo-[3.1.0]hexane *(4a)*, tricyclo[3.2.1.0^{2,4}]octane *(4b)*, and bicyclo[4.1.0]heptane *(4d)* can be recovered directly by distillation at 0.1 torr. Towards the end of the distillation the reaction mixture is warmed up (*ca.* 90°C). The benzylmercury iodide melts and further products are liberated. The residue consists of only slightly impure benzylmercury iodide *(3a)*, which can be recrystallized from benzene and re-used.

In the case of less volatile cyclopropanes such as tricyclo-[4.4.1.0^{1,6}]-3,8-undecadiene *(4c)* and *trans*-1,2-diphenylcyclopropane *(4e)* the reaction mixture is eluted with warm hexane. The less soluble benzylmercury iodide is not eluted, and the cyclopropane can be recovered from the eluate in pure form by distillation or chromatography.

Received: October 5, 1971 [Z 547b IE]
German version: Angew. Chem. *84*, 160 (1972)

[1] For a review of literature up to 1968, see *W. Kirmse:* Carbene, Carbenoide und Carbenanaloge. Verlag Chemie, Weinheim 1969.

[2] *H. E. Simmons* and *R. D. Smith*, J. Amer. Chem. Soc. *80*, 5323 (1958); *81*, 4256 (1959).

[3] *J. Furukawa, N. Kawabata*, and *J. Nishimura*, Tetrahedron Lett. *1966*, 3353; *1968*, 3495; Tetrahedron *24*, 53 (1968). In addition to further publications by the authors and co-workers, the reader is referred to the recent publication: *J. Nishimura, J. Furukawa, N. Kawabata*, and *M. Kitayama*, Tetrahedron *27*, 1799 (1971).

[4] *G. Wittig* and *K. Schwarzenbach*, Angew. Chem. *71*, 652 (1959); Liebigs Ann. Chem. *650*, 1 (1961); *G. Wittig* and *F. Wingler*, *ibid. 656*, 18 (1962); Chem. Ber. *97*, 2139, 2146 (1964); *G. Wittig* and *M. Jautelat*, Liebigs Ann. Chem. *702*, 24 (1967).

[5] *E. Müller, H. Kessler*, and *B. Zeeh*, Fortschr. Chem. Forsch. *7*, 128 (1966).

[6] Cf. the work by *D. Seyferth et al.* on Halomethyl-Metal Compounds, Part 45: *D. Seyferth* and *D. C. Mueller*, J. Amer. Chem. Soc. *93*, 3714 (1971).

[7] *D. Seyferth, M. A. Eistert*, and *L. J. Todd*, J. Amer. Chem. Soc. *86*, 121 (1964); *D. Seyferth, R. M. Turkel, M. A. Eistert*, and *L. J. Todd*, *ibid. 91*, 5027 (1969).

[8] The choice of 1-benzylmercurio-1-iodoalkane as organomercury carbenoid *(1)* for the synthesis of cyclopropane derivatives is based on studies of the reaction of organomercury complexes with diazoalkanes, cf. *R. Scheffold, U. Michel*, and *J. Löliger*, Vth Int. Conf. Organometal Chem. Moscow, Abst. *1*, 521 (1971).

[9] The reaction of organomercury chloride RHgCl (R = C_6H_5, $CH_3C_6H_4$, $C_6H_5CH_2$) with diazomethane with formation of RHg—CH_2—Cl was first reported in 1932, cf. *L. Hellermann* and *M. D. Newman*, J. Amer. Chem. Soc. *54*, 2859 (1932).

[10] The intensity ratio of the satellite signals to the main signal is 8:84:8, corresponding to the natural concentration of ^{199}Hg = 16.86%, cf. also *R. Scheffold*, Helv. Chim. Acta *50*, 1419 (1967); *52*, 56 (1969).

[11] Benzylmercury bromide (m.p. 117—118°C) was prepared in the usual way by reaction of the Grignard reagent (from benzyl bromide and magnesium in ether) with mercuric bromide; cf. *L. G. Makarowa* and *A. N. Nesmejanow:* Methods of Elemento-Organic Chemistry, Vol. 4. North Holland Publ. Amsterdam 1967, pp. 16ff.

[12] Diazomethane was prepared in the usual way by reaction of nitrosomethylurea with 50%—KOH in water-ether.

X-Ray Photoelectron Spectroscopy of Iron-Containing Proteins—The Valency of Iron in Ferredoxins

By *Dieter Leibfritz*[*]

Determination of the valency of a metal ion in metal-containing proteins still presents difficulties. Investigation of such complexes by chemical reactions frequently leads to ambiguous results, and ESR and Mössbauer spectroscopy often prove to be of little use where these complexes are diamagnetic or Mössbauer-inactive. X-ray photoelectron spectroscopy (XPE spectroscopy or ESCA)[1], however, has no such limitations and can be used to investigate all metals and elements except hydrogen. For inorganic iron compounds, for example, the chemical shift of the

[*] Dr. D. Leibfritz [**]
Gates and Crelling Laboratory of Chemistry
California Institute of Technology
Pasadena, Calif. 91109 (USA)

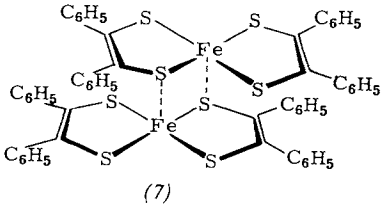
[**] Thanks are due to Prof. *E. Bayer*, Tübingen, Prof. *H. B. Gray*, Pasadena, and Dr. *M. P. Hagenmaier* for the supply of samples, to Dr. *W. Proctor*, Varian, Palo Alto, for the use of an IEE spectrometer, and to the Deutsche Forschungsgemeinschaft for a research stipend.

binding energy of the L_{III} level ($2P_{3/2}$) varies within a range of 6 eV[2]. The line-width also depends very much on the number of unpaired electrons[3]. The following is a report on the use of XPE spectroscopy in the investigation of biochemically important iron complexes.

Solutions of the ferredoxins *(1)*, *(2)*, and *(3)* from *Clostridium pasteurianum (C. pasteurianum)*, *Clostridium acidi-urici (C. acidi-urici)*, and Chromatium (high potential iron protein, HIPIP) were frozen onto the sample holder of the spectrometer, freeze-dried in the apparatus, and immediately measured to ensure that the oxidation state of the iron would not undergo any changes. The ionization energies obtained are listed, together with data for some model compounds, in the following table.

	Compound	IE [eV]	Oxidation State Fe
(1)	*(C. pasteurianum)*	710.0	+3
(2)	*(C. acidi-urici)*	709.9	+3
(3)	(HIPIP)	708.2	+2
(4)	Iron phosvitin	711.0	+3
(5)	Hemin chloride	710.2	+3
(6)	Salen	710.1	+3
(7a)	(oxidized)	710.3	+3
(7b)	(reduced)	707.9	+2
(8)		708.5	+2
(9)		711.8	+3

The iron in the bacterial ferredoxins *(1)* and *(2)*, which occur on isolation in the oxidized form[4], has an ionization energy approximately 2 eV higher than the iron in the reduced form of *(3)*. Even though the absolute values of the ionization energies yielded little information (the various influences of the ligands on lower energy levels cannot generally be determined quantitatively) they should still agree with the ionization energies of model complexes if their structural and physical properties are similar to those of the ferredoxins. The dimeric "dithiolene"-iron complexes, *e.g. (7)*, are often used as suitable model compounds[5].



(7)

The oxidized form of compound *(7)*, *i.e.*, *(7a)*, is in the formal oxidation state +3 (reduced form *(7b)*: +2). The ionization energy of *(7a)* agrees, within experimental error, with the ionization energies of the bacterial ferredoxins, while *(7b)* corresponds closely to the reduced form of HIPIP *(3)*.

Regarding arrangement of the 6—8 Fe atoms in Clostridian-ferredoxins, two models are discussed here: A linear arrangement of the metal ions with iron of different valency at the ends[6], or a cluster-like arrangement of the iron (two clusters having similar properties[7] or only one cluster[8]). According to the XPE spectra (see Figure), compounds *(1)* and *(2)* contain Fe ions of only one type with the identical, or almost identical, ionization energies as required by a cluster model. This is also in agreement with previous X-ray structural investigations[9]. Although the ionization energies of the ferredoxins *(1)* and *(2)* are relatively low for a formal iron(III) complex they are nevertheless in good agreement with a valence tautomeric cluster model, as proposed by *Bayer et al.*[10]. As previously shown by X-ray structural analysis[11], compound *(3)* also contains only one type of iron. (The peaks at 712 eV and higher in the spectrum of bacterial ferredoxin (see Figure) can be ascribed to plasma excitation and impurities.)

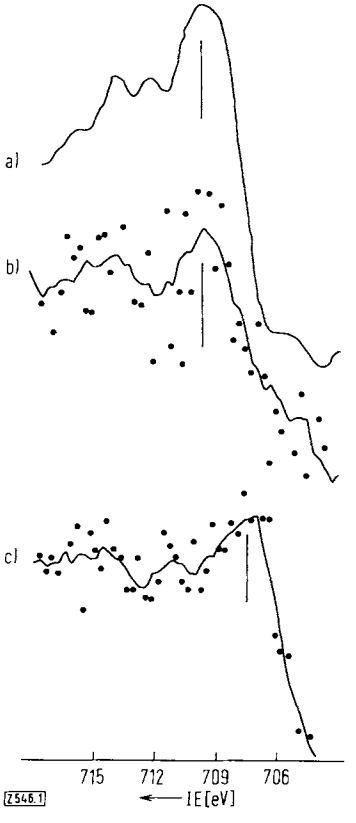
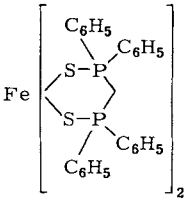


Fig. X-ray electron spectroscopy of the iron $2p_{3/2}$ level in the ferredoxins a) *(1)*, b) *(2)*, and c) *(3)*.

Generally, one can say that Fe^{III} with "soft" ligands[12] (sulfur, porphyrin skeleton) exhibits IE values of about 710.0 ± 0.5 eV (*(1)*, *(2)*, *(5)*, *(6)*, *(7a)*), whereas the values for Fe^{II} are about 708.0 ± 0.5 eV (*(3)*, *(7b)*, *(8)*).

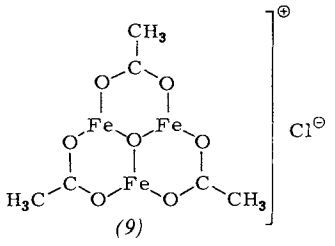


(8)

If Fe^{III} is bound to "hard" ligands (*e.g.* oxygen), the IE values are shown to be 711.0 ± 0.5 eV—cf. "trimeric iron acetate" *(9)* or iron phosvitin *(4)*, where Fe^{III} is tetrahedrally surrounded by oxygen[13].

Considering the low proportion of iron (with reference to the molecular weight), the line-width in the spectra of ferredoxins is somewhat larger than in those of low-molecular iron compounds; nevertheless, it can be deduced that iron

must certainly be present in the low-spin state, for high-spin iron(III) exhibits considerably larger energy half-widths[2] (>1 eV). This is in agreement with magnetic susceptibility determinations[14] and Mössbauer spectroscopic investigations[6].



(9)

The sulfur spectra of *(1)*—*(3)* contain two lines (≈164.0 and ≈162.8 eV), the former being due to cysteine sulfur, the latter to labile sulfur.

Received: September 6. 1971 [Z 546 IE]
German version: Angew. Chem. *84*, 156 (1971)

[1] *K. Siegbahn, C. Nordling, A. Fahlman, R. Nordberg, K. Hamrin, J. Hedman, G. Johansson, T. Bergmark, S. E. Karlsson, I. Lindgren,* and *B. Lindberg:* ESCA; Atomic, Molecular and Solid State Structure Studied by Mean of Electron Spectroscopy. Almquist and Wiksells, Uppsala 1967.

[2] *D. Leibfritz* and *W. Bremser*, Chemiker-Ztg. *94*, 982 (1970).

[3] *C. S. Fadley* and *D. A. Shirley*, Phys. Rev. *A 2*, 1109 (1970).

[4] For a review on iron-sulfur proteins cf. *J. C. M. Tsibris* and *R. W. Woody*, Coordinat. Chem. Rev. *5*, 417 (1970).

[5] *A. Davison, D. V. Howe,* and *E. T. Showl*, Inorg. Chem. *6*, 458 (1967); *A. C. Balch, I. G. Dance,* and *R. H. Holm*, J. Amer. Chem. Soc. *90*, 1139 (1968).

[6] *D. C. Blomstrom, E. Knight, Jr., W. D. Phillips,* and *J. F. Weiher*, Proc. Nat. Acad. Sci. U. S. *51*, 1085 (1964).

[7] *W. H. Orme-Johnson* and *H. Beinert*, Biochem. Biophys. Res. Commun. *36*, 337 (1969).

[8] *M. Poe, W. D. Phillips, C. C. McDonald,* and *W. Lovenberg*, Proc. Nat. Acad. Sci. U. S. *65*, 797 (1970).

[9] *L. C. Sieker* and *L. H. Jansen*, Biochem. Biophys. Res. Commun. *20*, 33 (1965).

[10] *E. Bayer, H. Eckstein, H. Hagenmaier, D. Josef, J. Koch, P. Krauss, A. Röder,* and *P. Schretzmann*, Eur. J. Biochem. *8*, 33 (1969).

[11] *J. Kraut, G. Strahs,* and *S. J. Freer* in *A. Rich* and *N. Davidson:* Structural Chemistry and Molecular Biology. Freeman, San Francisco 1968, p. 55; recent investigations by *H. Kraut et al.* (unpublished) postulate a tetrahedral arrangement of the iron atom.

[12] *R. G. Pearson*, J. Chem. Educ. *45*, 581, 643 (1968).

[13] *J. M. Webb*, Dissertation, California Institute of Technology 1971.

[14] *W. Druskeit, K. Gersonde,* and *H. Netter*, Eur. J. Biochem. *2*, 176 (1967).

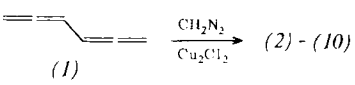
Cyclopropanation Products of Biallenyl

By *Friedrich Heinrich* and *Wolfgang Lüttke*[*]

In the course of our studies on the electronic interactions between conjugated double bonds, between directly linked three-membered rings[1], and between three-membered rings and double bonds[2] our interest was directed towards the compounds *(2)*—*(10)*. All these compounds should be directly accessible from a single starting material, *viz.* biallenyl[3]. All three kinds of interaction listed above are present: thus *(2)* and *(3)* contain the butadiene system, *(4)*—*(7)* a vinylcyclopropane moiety, and *(8)*—*(10)* the bicyclopropyl system.

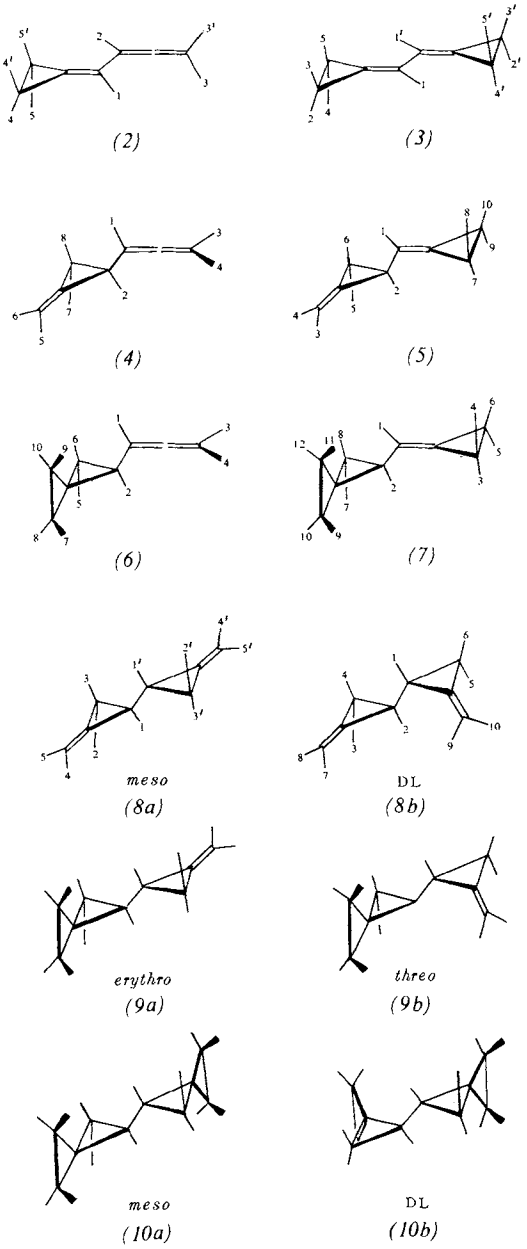
[*] Dipl.-Chem. F. Heinrich and Prof. Dr. W. Lüttke
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

In order to synthesize these novel hydrocarbons we have carried out the reaction of biallenyl *(1)* with diazomethane in the presence of copper(I) chloride. All twelve possible cyclopropanation products could be isolated by preparative gas chromatography.



(1)

Conversion of biallenyl was almost quantitative; about 10% of the resulting hydrocarbon mixture consisted of polymer. The relative yields of compounds *(2)*—*(10)* depend upon the excess of diazomethane used. With diazomethane and biallenyl (solution in *n*-pentane) in the molar ratio 5:1 the nonpolymeric portion of the reaction mixture was shown by gas chromatography to contain (in mol-%): 8% *(2)*, 3% *(3)*, 13% *(4)*, 9% *(5)*, 15% *(6)*, 13.5% *(7)*, 4.5% *(8a)*, 3.5% *(8b)*, 17% *(9a)* and *(9b)*[5], 11.5% *(10a)* and *(10b)*[5].



(2) *(3)*

(4) *(5)*

(6) *(7)*

meso DL

(8a) *(8b)*

erythro *threo*

(9a) *(9b)*

meso DL

(10a) *(10b)*

Table. Spectroscopic data for compounds *(2)*—*(10)*.

	^{1}H-NMR (in CCl_4), τ-values in ppm	IR [a] (cm^{-1})	UV (in cyclohexane) λ_{max} in nm
(2)	τ_1 = 3.70 (d with fine structure, $J_{1,2}$ = 10.4 Hz) τ_2 = 3.82–4.10 (m); $\tau_{3,3'}$ = 4.96–5.12 (m) $\tau_{4-5'}$ = 8.82 (slight splitting)	ν(C=C=C) 1950 ρ(C=C=C—H) 850	228.5 (ε = 20500) 218.5 (ε = 20200)
(3)	$\tau_{1,1'}$ = 3.54 (m, not resolved) $\tau_{2-5'}$ = 8.87 (not resolved)	ν(C—H) 3046, 3027, 2972, 2807 2γ(C=C—H) and ν(C=C) 1783, 1775 (sh), 1738 (sh)	247 (ε = 29100) [b] 238 (ε = 34700) 230 (ε = 25900)
(4)	$\tau_{5,6}$ = 4.39–4.59 [c] τ_1 = 5.00 (m, $J_{1,2} \approx 5$ Hz, $J_{1,3} \approx J_{1,4} \approx 7{,}4$ Hz) $\tau_{3,4}$ = 5.10–5.27; τ_2 = 7.98 (m) τ_7 = 8.46 (m); τ_8 = 8.88 (m)	ν(C=C) 1745 ν(C=C=C) 1953 ρ(C=C=C—H) 852	end absorption (ε_{200} = 11400)
(5)	$\tau_{1,3,4}$ = 4.34–4.55; τ_2 = 7.50–7.79 (m) τ_5 = 8.25–8.58 (m); τ_6 = 8.63–8.92 (m) τ_{7-10} = 8.84 (not resolved)	ν(C=C) 1740 1765	end absorption (ε_{200} = 15600)
(6)	τ_1 = 5.03 (m, $J_{1,2} \approx 5.5$ Hz, $J_{1,3} \approx J_{1,4} \approx 7.5$ Hz) $\tau_{3,4}$ = 5.23; τ_2 = 8.25 (m) τ_5 = 8.72 (4 lines); τ_{6-10} = 8.92–9.27	ν(C=C=C) 1953 ρ(C=C=C—H) 849	end absorption (ε_{200} = 13000)
(7)	τ_1 = 4.48 (d with fine structure, $J_{1,2}$ = 9.0 Hz [c]) τ_2 = 7.97 (m); τ_{3-5} = 8.67 (4 lines) τ_{3-6} = 8.85 (slight splitting) τ_{8-12} = 8.97 (slight splitting)	ν(C=C) 1766	208 (ε = 15000)
(8a) [d]	$\tau_{4-5'}$ = 4.55 (slight splitting) $\tau_{1,1'}$ = 8.09–8.34 (m); $\tau_{2,2'}$ = 8.68–8.97 (m) $\tau_{3,3'}$ = 8.97–9.18 (m)	ν(C=C) 1740 2ν(C=C—H) 1777	end absorption (ε_{200} = 6500)
(8b) [d]	τ_{7-10} = 4.58 (m, not resolved) $\tau_{1,2}$ = 8.15–8.41; $\tau_{3,6}$ = 8.58–8.86 (t with fine structure); $\tau_{4,5}$ = 8.98–9.19	ν(C=C) 1743 2γ(C=C—H) 1779	end absorption (ε_{200} = 6300)
(9a)/ *(9b)* [5]	τ = 4.52 (slight splitting, 2 vinyl-H) τ = 8.24–8.86 and τ = 8.90–9.40 (cyclopropane H in ratio 3:7)	ν(C=C) 1742 2γ(C=C—H) 1777	end absorption (ε_{200} = 2900)
(10a)/ *(10b)* [5]	τ = 8.70–9.39	ν(C—H) 3060, 2985, 2860 ν(Ring) 994, 864	end absorption (ε_{200} = 850)

[a] Characteristic IR frequencies, measured with the neat liquids except for *(3)* (CCl_4 solution).
[b] Cf. UV data for dicyclohexylideneethane: λ_{max} = 259, 250, 241 [11].
[c] Assignment supported by double resonance experiments.
[d] The retention times of the diastereoisomers are utilized in assigning the compounds to the *meso* or DL forms: *(8a)* exhibits a longer retention time than *(8b)* on non-polar columns but a shorter retention time on polar GC columns. This tentative assignment is to be checked in a conformational analysis of *(8a)* and *(8b)*.

A mixture of *(10a)* and *(10b)* was prepared independently by oxidative dimerization of spiropentylmagnesium bromide with copper(II) chloride. NMR and IR data were identical with those given in the Table.

Satisfactory C, H analyses were obtained for all new compounds. The structures were assigned on the basis of their NMR, IR, UV, and mass spectra[6]; reference data were taken from the spectra of biallenyl[3], methylenecyclopropane[7], spiropentane[8], 1-bromomethylenecyclopropane[9, 10], 1-bromo-2-methylenecyclopropane[9, 10], and spiropentyl bromide[10]. The most important spectroscopic data for our compounds are summarized in the Table.

Compounds *(2)*—*(10)*, with the exception of *(3)*, are all liquids at room temperature; *(3)* is a solid. *(2)*, *(3)*, *(4)*, and *(5)* undergo polymerization when stored neat or in solution in a refrigerator; they are stable, however, at −70 °C.

Investigations of the thermal and photochemical properties, as well as a complete analysis of the spectra (with the aim, *inter alia*, of studying conformational equilibria), are currently in progress.

Experimental:

In a cyclopropanation reactor constructed according to *Gaspar* and *Roth*[4] were placed 5 g (0.064 mol) of biallenyl, 5 ml of pentane and 300 mg of cuprous chloride. Diazomethane was generated from nitrosomethylurea [a total of 47 g (0.46 mol) of nitrosomethylurea was used within 7 hours] and blown, by means of a steady stream of nitrogen, into the reaction mixture, which was cooled in an ice/water bath. The reaction mixture was trap-to-trap distilled

under vacuum and separated by preparative scale gas chromatography using a Varian Aerograph Model 90 P4 gas chromatograph [columns: 3 m 10% SE 30 on Chromosorb W DMCS (60/80 mesh) and 3 m 15% 1,2-bis(β-cyanoethoxy)ethane on Chromosorb W DMCS (80/100 mesh)].

Received: November 10, 1971 [Z 566 IE]
German version: Angew. Chem. 84, 263 (1972)

[1] *W. Lüttke, A. de Meijere, H. Wolff, H. Ludwig,* and *H. W. Schrötter,* Angew. Chem. *78*, 141 (1966); Angew. Chem. internat. Edit. *5*, 123 (1966); *A. de Meijere, F. Heinrich,* and *W. Lüttke,* to be published.

[2] *A. de Meijere* and *W. Lüttke,* Tetrahedron *25*, 2047 (1969).

[3] *H. Hopf,* Angew. Chem. *82*, 703 (1970); Angew. Chem. internat. Edit. *9*, 732 (1970).

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

[5] It has not yet been possible to completely separate the *erythro/threo* mixture *(9a)/(9b)* or the *meso*-DL diastereoisomers *(10a)/(10b)*. All data given for *(9)* and *(10)* therefore refer to *ca.* 1:1 mixtures.

[6] The mass spectra were recorded with a combined gas chromatograph/mass spectrometer.

[7] *S. Braun,* Diplomarbeit, Universität Göttingen 1966; *R. W. Mitchell* and *J. A. Merritt,* Spectrochim. Acta *27 A*, 1609 (1971).

[8] *F. F. Cleveland, M. J. Murray,* and *W. S. Gallaway,* J. Chem. Phys. *15*, 742 (1947).

[9] *T. Bässler* and *M. Hanack,* Tetrahedron Lett. *1971*, 2171.

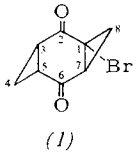
[10] *F. Heinrich* and *W. Lüttke,* unpublished results.

[11] *I. T. Harrison, B. Lythgoe,* and *S. Trippett,* J. Chem. Soc. *1955*, 4016.

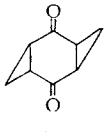
Synthesis and X-Ray Structure Analysis of *anti*-1-Bromotricyclo[5.1.0.0^{3,5}]octane-2,6-dione (*anti*-1-Bromobishomoquinone)

By *Jürg Heller, André S. Dreiding, Rita Grieb,* and *Alfred Niggli*[*]

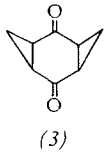
In a preliminary communication[1] we described the synthesis of *anti-* and *syn*-bishomoquinone *(2)* and *(3)*. In connection with certain calculations[2] and with a study of their spectroscopic properties (NMR, IR, UV) as well as those of *anti*-1-bromobishomoquinone *(1)* it was of interest to confirm the previously assigned configurations and to establish the preferred conformations.



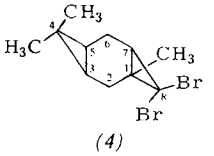
(1)



(2)



(3)



(4)

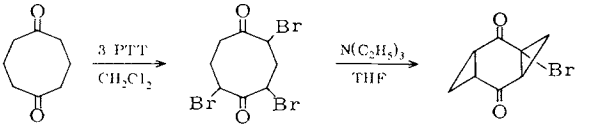
In the bishomoquinone series the conformation of the central ring is of special significance, since the possibility exists that a multi-conjugative interaction can take place between the cyclopropane units and the carbonyl groups[3,4]. It follows from theoretical considerations[4,5] and from experimental observations[6] that the torsional angle about the single bond between a carbonyl and a cyclopropane group influences the magnitude of the conjugative effect between these groups. In the bishomoquinones four such torsional angles are determined by the conformation of the central ring.

If two opposite pairs of adjacent C-atoms in a six-membered ring are each doubly bonded or form part of a three-membered ring, then the six-membered ring assumes a very flat boat conformation[7]. This was shown, with certain reservations (instability of the crystal in the X-ray beam), in a recent X-ray structure analysis by *Reck*[8] of *anti*-8,8-dibromo-1,4,4-trimethyltrichloro[5.1.0.0^{3,5}]octane *(4)*, which crystallizes with three molecules in the unit cell, each molecule having a slightly different conformation: The two mean planes, one defined by C1, C2, C6, and C7, and the other by C2, C3, C5, and C6 in the three conformations enclose a dihedral angle of 180.5, 186.1 or 177.7°, ±4.6°, showing a maximum deviation from coplanarity of about 6.1°.

Since the C—C—C angle at carbonyl groups is larger than the C—C—C angle at methylene groups in equally strained systems an even higher degree of flattening of the six-membered ring is to be expected in the bishomoquinones than in saturated tricyclo[5.1.0.0^{3,5}]octanes such as *(4)*. In the case of *anti*-bishomoquinone *(2)*, however, the measured dipole moment of 1.4 D excludes the possibility of the central ring having a planar conformation[9]. We therefore subjected compound *(1)* to an X-ray structural analysis and found that there is a small, but significant deviation from planarity in the six-membered ring (Fig. 2). In Table 1 the positions of the atoms in *(1)* are described with reference to a mean ring plane in order to permit a direct comparison with the results obtained by *Reck*[8] for *(4)*. The dihedral angle between the two mean planes in *(1)* as defined by *Reck*[8] (see above) is about 5.8° (mean error not determined).

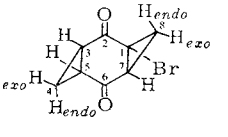
Synthesis of anti-1-bromobishomoquinone (1)

In the bromination of cyclooctane-1,5-dione *(5)*[10] with three equivalents of phenyltrimethylammonium tribromide (PTT)[11] in methylene chloride (25 °C, 1 h) a non-crystal-



(5) *(6)* *(1)*

lizable mixture of products is formed which presumably consists of the stereomeric tribromides *(6)* contaminated with dibromo- and tetrabromo-derivatives of *(5)*. Reaction of this mixture with ten mole equivalents of triethylamine in tetrahydrofuran (THF) (25 °C, 1 h) brings about a double 1,3-dehydrobromination to *anti*-1-bromotricyclo-[5.1.0.0^{3,5}]octane-2,6-dione *(1)*, m. p. 166—167 °C, in 30% yield based on *(5)*.



[*] Prof. Dr. A. S. Dreiding and Dipl.-Chem. J. Heller
Organisch-chemisches Institut der Universität
CH-8001 Zürich, Rämistrasse 76 (Switzerland)
Prof. Dr. A. Niggli and Dr. R. Grieb
Institut für Kristallographie und Petrographie der
Eidgenössischen Technischen Hochschule
CH-8006 Zürich, Sonneggstrasse 5 (Switzerland)

The IR spectrum ($CHCl_3$) shows a weak absorption at 3020 cm^{-1} corresponding to the C—H stretch in the cyclopropane groups and a strong carbonyl band at 1707 cm^{-1}. The 100-MHz NMR spectrum in C_6D_6 solution consists of three groups of signals (integral ratio 1:3:3) and is interpreted as follows: $\delta = 1.94/d \times d$ (10.6, 6.4) (H—C7), 1.45 – 1.05/m (H—C3, H—C5), 1.09/d × d (10.6, −6.8) (*exo*-H—C8), 0.73 – 0.40/m (*exo*-H—C4, *endo*-H—C4), 0.65/d × d (6.4, −6.8) (*endo*-H—C8); ppm (Hz). The 100-MHz NMR spectrum in $CDCl_3$ solution contains four groups of signals (integral ratio 1:3:2:1) and is interpreted as follows: $\delta = 2.50/d \times d$ (10.6, 6.4) (H—C7), 2.40 – 2.05/m (H—C3, H—C5), 200/d × d (10.6, −6.8) (*exo*-H—C8), 1.76/t × d (9.4, −5.6) (*exo*-H—C4), 1.72/d × d (6.4, −6.8) (*endo*-H—C8), 1.44/t × d (5.5, −5.6) (*endo*-H—C4); ppm (Hz). The mass spectrum contains, in addition to the molecular ion peak with $m/e = 214$ (4%), the following important fragments: 146 (3.5) $M^+ - C_4H_4O$, 135 (24) $M^+ - Br$, 68 (21) $M^+ - C_4H_3OBr$, 67 (14) 146 – Br, 27 (100); *m/e* (%).

Compound *(1)* prepared by the above method is identical with the by-product of another reaction to which the *anti* configuration was assigned on chemical grounds[12].

X-ray structure analysis of (1)[13]

The compound crystallizes in the orthorhombic, non-centrosymmetric space group $Pca2_1$ with $a = 11.16$, $b = 8.69$, $c = 8.02_5$ Å; $d_{calc} = 1.834$ g/cm³: $Z = 4$.

Suitable crystals of *(1)* were examined with a Picker four-circle single crystal X-ray diffractometer; a total of 642 reflections were measured, of which 248 had intensities less than three times the standard deviation[14].

respectively (a difference within the range of experimental error). The angles C2—C1—Br, C7—C1—Br, and C8—C1—Br are 113.1, 117.5, and 117.3° (±1.1°) respectively.

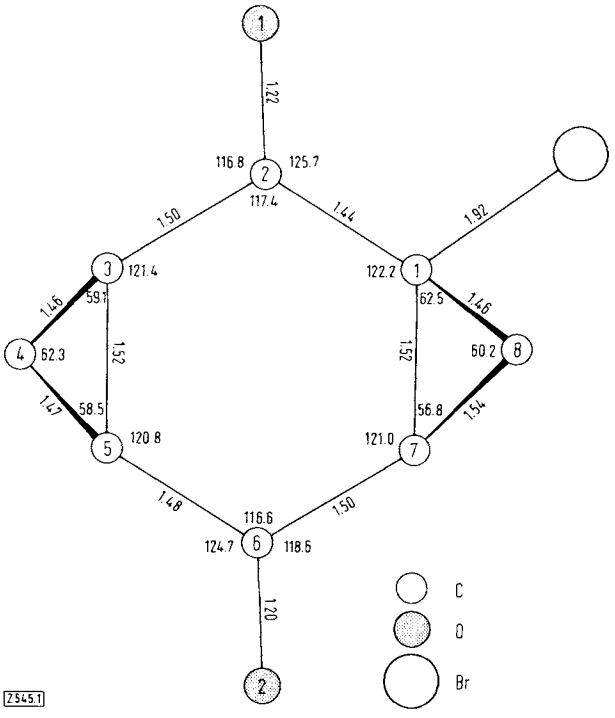


Fig. 1. Bond lengths and angles (average error 0.02 Å and 1.0—1.6° resp.).

Table 1. Deviations of the positions of the atoms of the central ring with respect to a least squares ring plane.

	Δ in Å referred to the least squares plane			
	(1)	*(4)* mol. I [8]	*(4)* mol. II [8]	*(4)* mol. III [8]
C 1	−.014	+.001	+.030	−.035
C 2	+.039	+.003	−.046	+.049
C 3	−.020	−.003	+.012	−.041
C 5	−.029	−.001	+.038	+.019
C 6	+.047	+.005	−.052	−.004
C 7	−.023	−.006	+.018	+.012
χ^2	27.69	0.04	4.41	3.28
ω (%) [a]	<0.05	>99.5	20–25	30–40

[a] ω is the percentage probability that a planar arrangement of the six atoms would give as large an χ^2 as that calculated (three degrees of freedom).

The special position of the bromine atom in the unit cell was unambiguously located by means of a Patterson synthesis. A subsequent three-dimensional Fourier synthesis by the heavy atom technique gave a quadruplication of the C- and O-positions due to the special position of the bromine atom, which, however, could be assigned unambiguously on the basis of the supposed architecture of the molecule.

Fig. 2 shows that the six-membered ring is almost planar. C2 and C6 protrude from the least squares plane of the six C atoms; this deviation from planarity is beyond the range of experimental error.

The angles between the least squares plane of the six-membered ring and those of the three-membered rings C1—C7—C8 and C3—C4—C5 are 75.28° and 77.25°

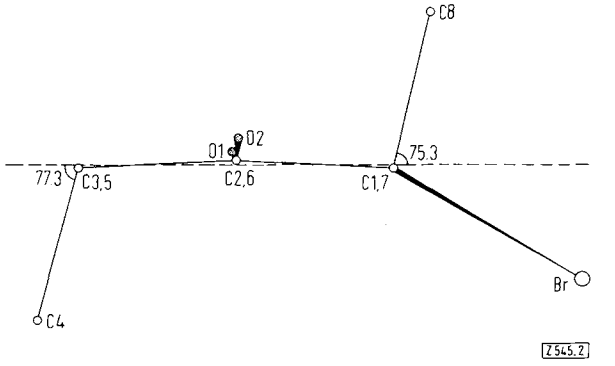


Fig. 2. Deviation of central six-membered ring from planarity (true to scale).

The small, but significant difference between the two O—C—C angles of each carbonyl group can be explained in terms of the intra- and intermolecular steric effects of the large bromine atoms (Fig. 1).

Received: August 13, 1971 [Z 545 IE]
German version: Angew. Chem. *84*, 170 (1972)

[1] *A. Yogev, J. Heller,* and *A. S. Dreiding,* Chimia *23,* 411 (1969).

[2] The investigation of UV spectra and computations were carried out at the Physikalisch-Chemisches Institut der Universität Basel.

[3] *J.-P. Pete,* Bull. Soc. Chim. Fr. *1967,* 357.

[4] *W. A. Bernett,* J. Chem. Educ. *44,* 17 (1967).

[5] *A. D. Walsh,* Trans. Faraday Soc. *45,* 179 (1949); *R. Hoffmann,* Tetrahedron Lett. *1965,* 3819.

[6] *E. M. Kosower* and *M. Ito,* Proc. Chem. Soc. (London) *1962,* 25; *W. G. Dauben* and *G. H. Berezin,* J. Chem. Soc. *89,* 3449 (1967); *M. J. Jorgenson* and *T. Leung, ibid. 90,* 3769 (1968).

[7] *H. Gerding* and *F. A. Haak,* Recl. Trav. Chim. Pays-Bas *68,* 293 (1949); *E. W. Garbisch, jr.* and *M. G. Griffith,* J. Amer. Chem. Soc. *90,* 3590 (1968); *R. J. Jandacek* and *S. H. Simonsen, ibid. 91,* 6663 (1969); *W. D. Kumler, R. Boikess, P. Bruck,* and *S. Winstein, ibid. 86,* 3126 (1964); *M. Mühlstädt, H. van Phiet, J. Graefe,* and *H. Frischleder,* Tetrahedron *24,* 6075 (1968); *H. Frischleder, J. Graefe, H. van Phiet,* and *M. Mühlstädt, ibid. 25,* 2081 (1969).

[8] *G. Reck,* Tetrahedron *26,* 599 (1970).

[9] We thank *P. Bircher* and *T. Winkler* for measuring the dipole moment of *(2).*

[10] *G. I. Glover, R. B. Smith,* and *H. Rapoport,* J. Amer. Chem. Soc. *87,* 2003 (1965).

[11] *A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes,* and *J. Jacques,* Bull. Soc. Chim. Fr. *1961,* 1822.

[12] *J. Heller, A. Yogev,* and *A. S. Dreiding,* Helv. Chim. Acta, in press.

[13] Complete publication: *R. Grieb* and *A. Niggli,* in preparation.

[14] After anisotropic refinement $R = 0.072$.

Transition Metal Carbene Complexes as π-Ligands—[Ethoxy-(2,6-dimethoxyphenyl)carbenetetracarbonyliron(0)]tricarbonyliron(0)[1]

By *Ernst Otto Fischer, Eberhard Winkler, Gottfried Huttner,* and *Dieter Regler*[*]

During our studies on the preparation of carbenecarbonyliron complexes we allowed pentacarbonyliron to react with 2,6-dimethoxyphenyllithium (molar ratio 1:1) at low temperature in tetrahydrofuran. After ethylation of the resulting acyl metalate, chromatography of the reaction

$$Fe(CO)_5 \xrightarrow[2.\ [(C_2H_5)_3O]BF_4/CH_2Cl_2]{1.\ C_6H_3(OCH_3)_2Li/THF} Fe_2C_{18}H_{14}O_{10}$$

product gave a small yield of deep red crystals whose total analysis showed them to have the composition $Fe_2C_{18}H_{14}O_{10}$ (m. p. 98 °C).

In accord with the above composition, the molecular ion appears at *m/e* 502 (based on ^{56}Fe) in the mass spectrum (50 eV, Atlas CH4). The fragmentation behavior of the compound indicates the presence of seven CO ligands. Correspondingly, the IR spectrum (KBr) contains seven ν_{CO} absorptions at 2083 s, 2025 vs, 2004 vs, 1981 vs, 1965 vs, 1935 s, 1895 m cm^{-1} which point to a low symmetry of the $Fe_2(CO)_7$ group. The band at 1895 cm^{-1} evidences a CO ligand having partial bridging character. ^{1}H-NMR studies unexpectedly show that a solution of the crystals contains two components, presumably in equilibrium. The spectrum ([D_6]acetone) shows a strongly split group of signals for the phenyl protons at 3.5—4.0 τ, three singlets at 5.59, 6.02, and 6.00 τ in the ratio 1:2:1, which can be assigned to the methoxy groups, and two triplets at 8.67 and 9.00 τ in the ratio 1:1 for the methyl protons of the ethoxy group. The signals of the methylene protons are masked by the very intense singlets of the methoxy groups.

These data were not sufficient to deduce the structure of the new compound. An X-ray structure analysis[2] indicated the geometry shown in the Figure.

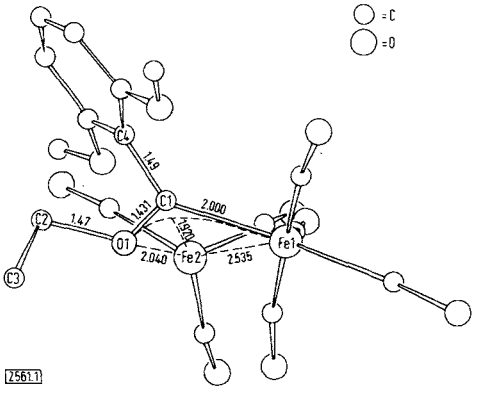


Fig. Structure of $Fe_2C_{18}H_{14}O_{10}$.

The molecule contains a tetracarbonylethoxy-(2,6-dimethoxyphenyl)carbeneiron moiety (central metal: Fe 1) that is linked to an $Fe(CO)_3$ group by the carbene system Fe1—C1—O1. In contrast to mononuclear carbene complexes, the carbene group is not strictly planar: The carbene carbon atom C1 protrudes by 0.197 Å from the best plane through the atoms Fe1, C1, C4, and O1. Nevertheless, the arrangement of the substituents on C1 is much closer to a trigonal-planar configuration than to a tetrahedral one. As a result of the π bonding to Fe2, the C1—O1 bond length, which is of the order of 1.33 Å in mononuclear carbene complexes[3], is increased to that of a C—O single bond. The compound can therefore be regarded as the first example of a complex in which the four-electron three-center π system located on the carbene system Fe1—C1—O1 acts as a π ligand towards the acceptor $Fe(CO)_3$. Further investigations on $Fe_2C_{13}H_{12}O_9$, a yellowish brown compound having m. p. 39 °C, are currently in progress to elucidate the ligand properties of carbene complexes.

Experimental:

1,3-Dimethoxybenzene (4.14 g, 30 mmol) in ether (50 ml) and *n*-butyllithium (30 mmol) in *n*-hexane (15 ml) are mixed at room temperature and stirred for 3 h. The resulting turbid yellow solution is added dropwise at −50 °C to $Fe(CO)_5$ (5.83 g, 30 mmol) in tetrahydrofuran (100 ml).

[*] Prof. Dr. E. O. Fischer, Dr. E. Winkler, Dr. G. Huttner, and Dipl.-Chem. D. Regler
Anorganisch-chemisches Laboratorium der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

After removal of the solvent at −20 °C the deep red reaction mixture is dissolved in methylene chloride (20 ml) and treated at −20 °C with $[(C_2H_5)_3O]BF_4$ (5.70 g, 30 mmol) in methylene chloride (20 ml). The solvent is removed in a vacuum, the residue extracted with *n*-hexane, and the extract filtered and concentrated to a volume of 20 ml. Elution with *n*-hexane on a chromatographic column (2 × 55 cm; Merck silica gel) prepared with hexane and maintained at −10 °C gives unreacted $Fe(CO)_5$ and $Fe_3(CO)_{12}$, as well as a yellow unstable oil that has not yet been investigated. The next, deep red zone containing the novel complex is eluted with hexane/benzene (3:1). Recrystallization from pentane gives 250 mg of $Fe_2C_{18}H_{14}O_{10}$ (yield 1.6%).

Received: November 18, 1971 [Z 561 IE]
German version: Angew. Chem. *84*, 214 (1972)

[1] Transition metal carbene complexes, Part 41. — Part 40: *E. O. Fischer* and *M. Leupold*, Chem. Ber. *105*, 599 (1972).

[2] 1956 independent non-zero diffractometer data; *R* factor 0.06.

[3] *O. S. Mills* and *A. D. Redhouse*, J. Chem. Soc. *A 1968*, 642.

CONFERENCE REPORTS

German—Danish Symposium on Organic Chemistry

The Universities of Aarhus, Hamburg, Kiel, Copenhagen, and Odense organised a German—Danish Symposium on Organic Chemistry at Odense (Denmark) on September 4 and 5, 1971.

From the lectures:

Structural Studies on Constituents of Umbelliferae[**]

By *Bent Eichstedt Nielsen*[*]

Coumarins, polyacetylenes, monoterpenoids, and sesquiterpenoids are examples of secondary plant constituents that frequently occur in Umbelliferae.

The coumarins found in Umbelliferae include numerous optically active compounds. The centers of chirality are usually situated in the isoprenoid side chains, which are linked either directly or *via* ether bonds to the aromatic skeleton. Isoprenoid C_5 side chains may also be incorporated into a condensed heterocyclic ring system, as *e. g.* in the dihydrofurocoumarins and dihydropyranocoumarins. Side chains and ring systems of this type are also found in other naturally occurring compounds, *e. g.* chromones, isoflavones, and quinoline alkaloids. Accordingly, investigations of the stereochemistry of these systems are of general interest. Furthermore, knowledge of the stereochemistry of the optically active coumarins is of interest for the study of their biosynthesis.

Chemical correlations have been used for the stereochemical investigations on coumarins. Either optically active degradation products were isolated and their configuration determined by synthesis and comparison with compounds of known configuration, or stereospecific syntheses were carried out.

A number of dihydrofurocoumarins and dihydropyranocoumarins contain two centers of chirality in the basic skeleton. One of these centers is at a benzylic carbon atom carrying either a hydroxyl or an acyloxy group which can be removed upon hydrogenolysis. The product of hydrogenolysis can be compared with corresponding compounds containing only one center of asymmetry whose configuration has been determined by degradation reactions. For the compounds with two centers of chirality, it is then only necessary to determine the relative configurations. This is achieved *e. g.* by spectroscopic studies on synthetic epimers or by observation of the thermal stability and of the reactivity toward mineral acids.

From our work on acetylenes and terpenoids, mention may be made of the determination of the configuration of the naturally occurring alkyne falcarinol and the isolation and structural elucidation of some monoterpene esters having a cyclohexadiene skeleton.

[*] Lektor Dr. B. Eichstedt Nielsen
Kemisk Laboratorium B
Danmarks farmaceutiske Højskole
Universitetsparken 2
DK-2100 København Ø (Denmark)

[**] The experimental work was carried out by *E. Lemmich*, *J. Lemmich*, *P. K. Larsen*, *B. E. Nielsen*, and *P. A. Pedersen*.

Catalysis by Phthalocyanine Complexes

By *Heinz Kropf*[*]

The phthalocyanine (Pc) complexes of Cu, Zn, Pd, Pt, Ag, Hg, Ni, Fe, Co, and Mn catalyze the initial step in the autoxidation of benzene hydrocarbons, *i. e.* chain initiation in the absence of hydroperoxide, by reaction of a metal-Pc—O_2 complex with the hydrocarbon. As soon as hydroperoxide is formed, other catalysis mechanisms are observed:

1. In the autoxidation of phenylalkanes and phenylcycloalkanes in the presence of the Pc complexes of Cu, Zn, Pd, Pt, Ag, and Hg, the metal-Pc—O_2 complex reacts with dimeric hydroperoxide to form alkylperoxy radicals; at higher temperatures, the Pc complex itself reacts with dimeric hydroperoxide. In the autoxidation of diphenylcycloalkanes, the bimolecular collision of the dimeric hydroperoxide on the catalyst surface can be detected. The relative reactivities of the phenylcycloalkanes and diphenylcycloalkanes can be explained by an extended I-strain theory.

2. The Pc complexes of Fe, Co, and Mn are deactivated by monomeric hydroperoxide as a result of the formation of a

[*] Prof. Dr. H. Kropf
Institut für Organische Chemie und Biochemie der Universität
D-2 Hamburg 13, Papendamm 6 (Germany)

Pc-hydroperoxide addition product. The known secondary catalysis occurs at the same time.

3. Ni-Pc is poisoned by chemisorption of products formed by a special chain termination reaction.

VO-Pc, on the other hand, catalyzes autoxidation entirely by decomposition of the dimeric hydroperoxide on the catalyst surface. In the presence of alkali metal-Pc, a base-catalyzed autoxidation occurs after a metal-hydrogen exchange with hydroperoxide.

In the decomposition of cumyl hydroperoxide in the presence of Pc complexes, three groups of Pc complexes can be distinguished:

1. Fe, Co, and Mn complexes: the Pc complexes are attacked during the fast reaction.

2. Ni, Cu, Zn, Mg, and Al(OH) complexes: reaction proceeds much more slowly, and the Pc complexes remain unchanged.

3. VO-Pc: decomposition proceeds autocatalytically.

Finally, Pc complexes (Ni > Fe > Co > Cu) have been found to be hydrogenation, dehydrogenation, and hydrogenolysis catalysts in the system allyl alcohol/*n*-propanol/propionaldehyde/acrolein; the products formed on hydrogenolysis are propane, propene, and allene or propyne, depending on the Pc complex used. In the case of Cu-Pc, sudden changes in activity occur at 280—290 °C; these may be explained by phase transformations.

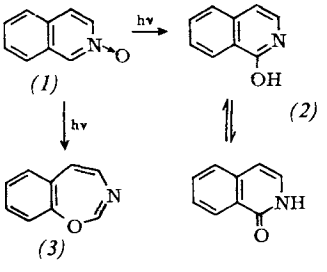
Photochemistry of Aromatic Amine Oxides

By *Christian Lohse*[*]

The photoisomerization of isoquinoline *N*-oxides such as *(1)*[1] to isocarbostyrils *(2)* in polar solvents and benz[*f*]-[1,3]oxazepines *(3)* in non-polar solvents could be shown to proceed *via* singlet excited states.

Earlier reports have explained the solvent effect on the product distribution in these rearrangements in terms of a possible oxaziridine intermediate. This compound could not be observed, in fact laser experiments showed the formation of isocarbostyril from isoquinoline *N*-oxide within the time of a laser pulse (20 ns)[2].

A triplet excited state of isoquinoline *N*-oxides was observed, and it could be shown that this state is responsible for the deoxygenation of the *N*-oxides to the parent amines. This process can be used for oxidation of organic compounds in their excited state to yield products different from those obtained by ground state oxidations.



[*] Dr. C. Lohse
Odense Universitet,
DK-5000 Odense (Denmark)

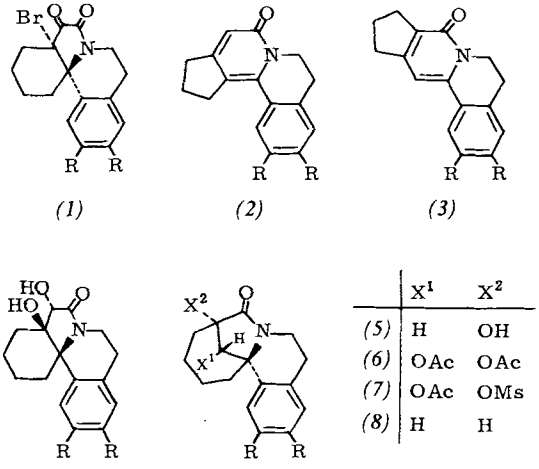
[1] *G. G. Spence, E. C. Taylor,* and *O. Buchardt,* Chem. Rev. *70,* 231 (1970).

[2] *C. Lohse,* J. Chem. Soc., in press.

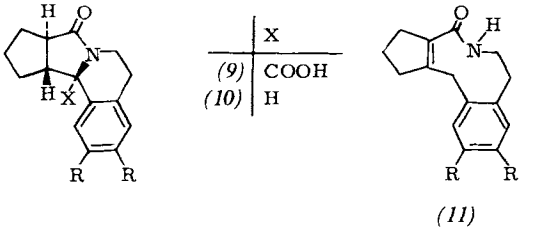
Rearrangements of Spirolactams with Synthetic *cis*- and *trans*-Erythrinanes as Example

By *Albert Mondon*[*]

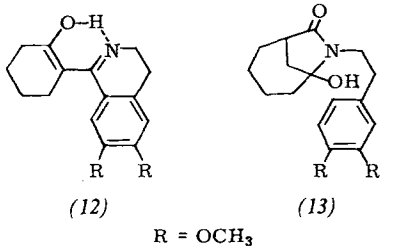
Wolff-Kishner reduction of the bromo keto lactam *(1)* gives not only compounds having the erythrinane skeleton[1] but also products with rearranged ring systems, such as *(2)* and *(5)*. The structure of *(2)* is shown by the UV spectrum with $\lambda_{max} = 348$ nm ($\log \varepsilon = 4.28$), which is similar to that of 6-phenyl-α-pyridone and agrees with that of the synthetic structural isomer *(3)*[2]; an independent synthesis of *(2)* has recently been achieved[3], so that the structure of the rearrangement product has now been fully verified.



	X^1	X^2
(5)	H	OH
(6)	OAc	OAc
(7)	OAc	OMs
(8)	H	H



	X
(9)	COOH
(10)	H



R = OCH_3

Closely related to the structural elucidation of *(5)* are comprehensive studies on a phenomenon that was first observed for the dihydroxy lactam *(4)* and its diacetate *(6)*[4]. Though the acetylation and hydrolysis are trivial reaction steps, they each involve a rearrangement of the skeleton, which can be detected only through the NMR spectra. Whereas *(4)*, as a typical *trans*-erythrinane, gives two widely separated singlets for the two aromatic protons[5], *(6)* gives only one singlet for two protons at a relatively high field strength.

[*] Prof. Dr. A. Mondon
Institut für Organische Chemie der Universität
D-23 Kiel, Olshausenstrasse 40/60 (Germany)

Since the NMR spectra of *(5)* and its acetate agree with that of *(6)* in the region of the aromatic protons, *(5)* and *(6)* should have the same basic skeleton. The interconversion of these compounds has not yet been achieved, but the new ring system has been confirmed for *(6)* by degradation reactions and for *(5)* by independent synthesis of the compound containing no hydroxyl groups.

Degradation of the mesylate acetate *(7)* corresponding to the diacetate *(6)* to give the carboxylic acid *(9)* was recently reported[4]. Thermal decarboxylation leads to the saturated lactam *(10)* and to the unsaturated lactam *(11)*, which is formed by cleavage of the C—N bond and a hydrogen shift. An interesting reaction is the extensive rearrangement of *(9)* by dilute sulfuric acid, which leads on gentle heating to the excellently crystallizing yellow chelate *(12)*. The amide obtained from homoveratrylamine and 2,2-ethylenedioxy-1-cyclohexanecarboxylic acid also gives *(12)* on Bischler-Napieralski ring closure, and so confirms its structure.

The ring system of *(5)* can also be synthesized directly from 3-oxo-1-cycloheptanecarboxylic acid and homoveratrylamine *via* the hydroxy lactam *(13)* by ring closure with hydrofluoric acid[6]; the excellently crystallizing cyclization product *(8)* is found to be identical with the compound containing no hydroxyl group that is obtained from *(5)* on reduction of the tosylate[3].

[1] *A. Mondon*, Chem. Ber. *104*, 270 (1971).

[2] *R. Schickfluss*, Diplomarbeit, Universität Kiel 1965.

[3] *A. Mondon* and *E. Oelrich*, unpublished.

[4] *S. Mohr*, *A. Mondon*, *G. Vilhuber*, and *Chr. Fischer*, Angew. Chem. *81*, 933 (1969); Angew. Chem. internat. Edit. *8*, 914 (1969).

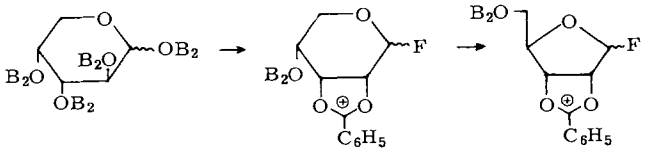
[5] *A. Mondon* and *P.-R. Seidel*, Chem. Ber. *104*, 2937 (1971).

[6] *G. Aumann*, Diplomarbeit, Universität Kiel 1970.

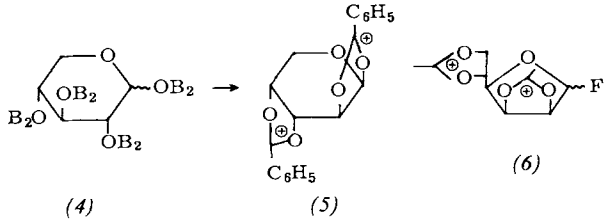
Rearrangement of Carbohydrate Esters with Anhydrous Hydrofluoric Acid

By *Christian Pedersen*[*]

Carbohydrate esters form glycosyl fluorides after reaction for a short time (approximately 15 min) with anhydrous hydrofluoric acid; longer exposure leads to further reactions. These reactions have been followed with the aid of the NMR spectra in hydrofluoric acid as the solvent.



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

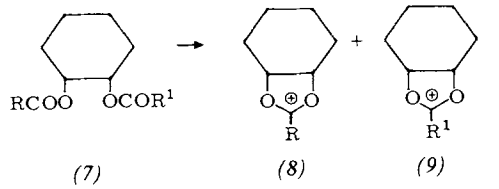


(4) *(5)* *(6)*

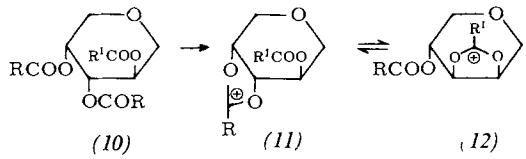
[*] Prof. Dr. C. Pedersen
Organisk-kemisk Laboratorium
Danmarks tekniske Højskole
DK-2800 Lyngby (Denmark)

After reaction with HF for 24 hours, tetrabenzoylarabinopyranose *(1)* gives the benzoxonium ion *(2)*, which is converted into *(3)* on reaction for a further 3 to 4 days. The inversion on C-2 is thus followed by a ring contraction. When tetrabenzoylxylopyranose *(4)* is dissolved in HF, the very stable dibenzoxonium ion *(5)* is formed in the course of 24 hours, with inversion on C-2 and C-3.

Many other carbohydrate esters also react with inversion and/or ring contraction on treatment with anhydrous hydrofluoric acid. Thus some glucofuranose, mannofuranose, and glucopyranose derivatives give the same stable dioxolanylium ion *(6)* on treatment with HF for 24 to 48 hours.



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



(10) *(11)* *(12)*

To gain a better understanding of these reactions, the behavior of some model compounds toward HF was investigated. Esters of *cis*-1,2-cyclohexanediol react with HF to form dioxolanylium ions. If the mixed esters *(7)* are used as the starting materials, the isomeric ions *(8)* and *(9)* may be formed. Our investigations have shown that this reaction is kinetically controlled, and that the less stable ion is often formed. Thus the acetate nitrobenzoate *(7)*, $R=CH_3$, $R^1=p\text{-}NO_2C_6H_4$, yields only the nitrobenzoxonium ion *(9)*, $R^1=p\text{-}NO_2C_6H_4$, whereas the acetate methoxybenzoate *(7)*, $R=CH_3$, $R^1=p\text{-}CH_3OC_6H_4$, yields only the acetoxonium ion *(8)*, $R=CH_3$. *cis*-1,2-Cyclopentanediols behave similarly.

To determine the thermodynamic stability of the dioxolanylium ions, the reaction between esters of 1,5-anhydroarabinitol *(10)* and HF was investigated. *(10)* reacts with HF to give mainly the ion *(11)*, which exists in equilibrium with the isomeric ion *(12)*. The position of this equilibrium is an expression of the relative stabilities of these two ions. When *(10)*, $R=CH_3$, $R^1=C_6H_5$, is dissolved in HF, only the benzoxonium ion *(12)* is obtained (NMR spectrum). Only the acetoxonium ion *(11)*, on the other hand, is formed from *(10)*, $R=CH_3$, $R^1=p\text{-}NO_2C_6H_4$. From these and other experiments it can be concluded that the stabilities of the dioxolanylium ions vary as follows with the substituent on C-2: $p\text{-}NO_2C_6H_4 < CH_3 < C_6H_5 < p\text{-}CH_3OC_6H_4 = p\text{-}CH_3C_6H_4$.

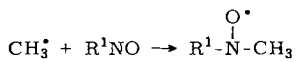
Free-Radical Alkylation with Sulfoxides and Fenton's Reagent

By *Kurt Torssell*[*]

Methyl radicals *(1)* are formed in the Fe^{3+}-induced decomposition of hydrogen peroxide in DMSO[1]. They have

[*] Prof. Dr. K. Torssell
Chemical Institute, University of Aarhus
DK-8000 Aarhus C (Denmark)

also been detected[3] by the nitroxide method[2], in a quantity so large that we found it interesting to check the reaction on a preparative scale.

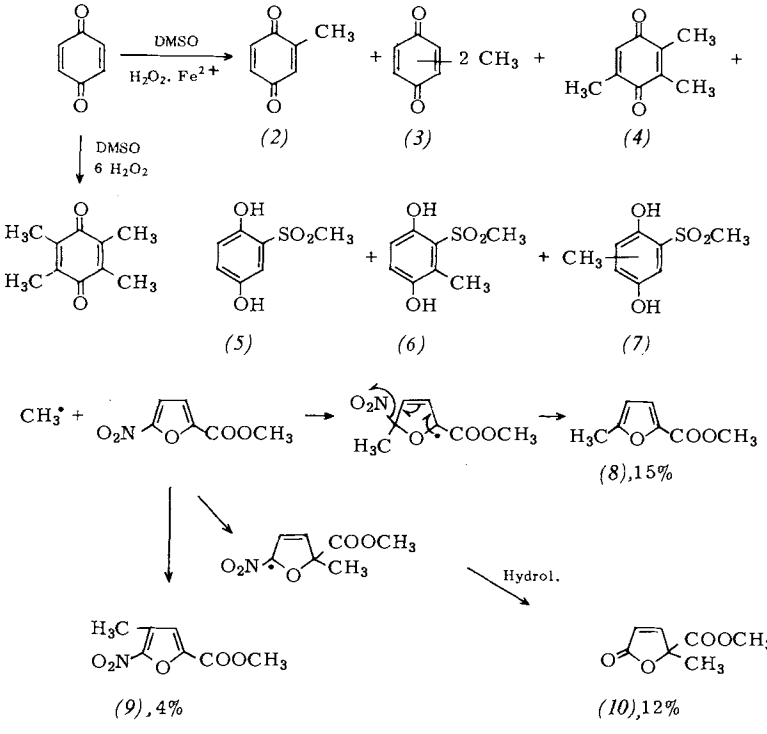


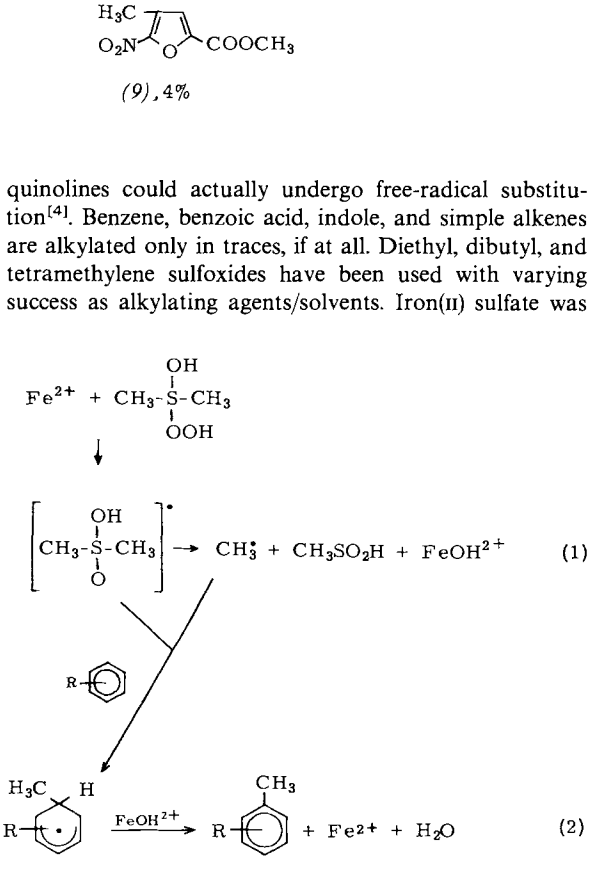
(1)

The nitroxide method has been largely used in our laboratory for the detection and structural elucidation of radicals, and it is also suitable for use as a kind of "synthetic spectroscopy" for the interpretation of free-radical reactions. It was found that reactive substrates such as quinones, nitroaromatic compounds, thiophenes, furans, pyridines, and quinolines could actually undergo free-radical substitution[4]. Benzene, benzoic acid, indole, and simple alkenes are alkylated only in traces, if at all. Diethyl, dibutyl, and tetramethylene sulfoxides have been used with varying success as alkylating agents/solvents. Iron(II) sulfate was found to be most suitable as the catalyst. On photolysis of hydrogen peroxide in DMSO, the alkylated product was formed in a lower yield.

Trinitrobenzene gave *e.g.* trinitrotoluene (25 °C, 1.5 equivalents of H_2O_2, 0.2 equivalents of $FeSO_4$, 1 hour) in 67% yield. The products *(2)*—*(7)* were formed from benzoquinone. Methyl 5-nitrofuran-2-carboxylate gave the products *(8)*—*(10)*, the formation of which can be explained by free-radical attack on C-5, C-4, and C-2 respectively. The replacement of the nitro group by methyl is remarkable.

The reaction course can be represented by the reaction sequences (1) and (2).





(2)

[1] *W. T. Dixon, R. O. C. Norman,* and *A. L. Buley,* J. Chem. Soc. *1964,* 3625.

[2] *S. Forshult, C. Lagercrantz,* and *K. Torssell,* Acta Chem. Scand. *23,* 522 (1969); *K. Torssell,* Tetrahedron *26,* 2759 (1970).

[3] *C. Lagercrantz* and *S. Forshult,* Acta Chem. Scand. *23,* 811 (1969).

[4] *B.-M. Bertilsson, B. Gustafsson, J. Kühn,* and *K. Torssell,* Acta Chem. Scand. *24,* 3590 (1970); *U. Rudqvist* and *K. Torssell, ibid. 25,* 2183 (1971).

EPR Spectroscopy as a Method of Conformational Analysis

By *Jürgen Voss*[*]

On the basis of the Heisenberg uncertainty principle

$$\Delta t \times \Delta H \geq 5.7 \times 10^{-8} \text{ gauss s}$$

it is shown that the EPR time scale allows the observation of states with lifetimes of the order of microseconds. Thus species that are converted into one another by rotation

[*] Dr. J. Voss
Institut für Organische Chemie und Biochemie der Universität
D-2 Hamburg 13, Papendamm 6 (Germany)

about formal single bonds appear as distinct isomers, and it is difficult to differentiate conceptually between conformers and configurational isomers.

This phenomenon is illustrated by the radical-anion of terephthalaldehyde. Its EPR spectrum shows the presence of a *cis* form and a *trans* form together, the lifetimes of these forms being 5×10^{-7} s[1]. Similarly, the preparation of biacetylsemidione yields a mixture of isomers in which the *trans* form predominates in a ratio of 95:5. The configuration can be assigned on the basis of steric considerations and particularly of the complex-forming properties (only the *cis* form gives a Li chelate)[2].

Conformation analysis in the true sense is possible by EPR spectroscopy with the aid of the relation

$$a_{CH}^{H} \approx B\,\rho_c \times \cos^2\theta$$

a_{CH}^{H} = HFS coupling constant

B = constant of proportionality $\quad\quad$ ρ_c = spin density

For example, from the coupling constants of the alkyl protons in the radical-anions of oxalic esters ("dialkoxysemidiones"), it is possible to determine the time-averaged dihedral angle θ between the C—H bond and the z axis of the π-electron system[3]. For primary alkyl groups, $\theta = 47°$, while for secondary alkyl groups, $\theta = 60°$; these values can be shown to be plausible by estimation of the space requirements from Newman projections. This also provides an explanation for the surprisingly small value $\theta = 42°$ for the neopentyl ester, while the deviation from the normal in the case of the cyclobutyl derivative ($\theta = 49°$) is attributed to ring strain.

An example of the determination of a dynamic quantity is the calculation of the activation energy $E_a = 8.6 \pm 0.5$ kcal/mole for the rotation of the angled NO group of the nitrosobenzene radical-anion from the temperature dependence of its EPR spectrum[4].

[VB 328 IE]
German version: Angew. Chem. *84*, 219 (1972)

[1] *A. H. Maki*, J. Chem. Phys. *35*, 761 (1961).

[2] *G. A. Russell* and *R. D. Stephens*, J. Phys. Chem. *70*, 1320 (1966).

[3] *J. Voss*, Tetrahedron *27*, 3753 (1971).

[4] *W. Kaminski* and *K. Möbius*, Z. Naturforsch. *25a*, 635 (1970).

Reactions and Compounds with Molecular Nitrogen

By *Wilhelm Preetz*[*]

It has recently been shown that molecular nitrogen, which was previously considered to be very inert, can undergo a number of chemical reactions under mild conditions. Because of the importance of nitrogen assimilation in Nature, a great deal of interest has been shown in the search for models displaying the ability to bind nitrogen. Since transition metal ions appear to play a key role in the enzymatic fixation of nitrogen attention has mainly been directed to the following two possibilities:

1. Complexes with elements of the higher sub-groups, *i.e.* of the type $[Ru(NH_3)_5(N_2)]Cl_2$, which were discovered by *Allen* and *Senoff*[1];

2. The binding of nitrogen by Ziegler catalysts, *e.g.* Cp_2TiCl_2 (Cp = π-cyclopentadienyl), and reduction to ammonia in the presence of organomagnesium compounds, as was first reported by *Volpin* and *Shur*[2].

Comparison of the electronic structure of the N_2 molecule with those of the isoelectronic ligands CO, CN^-, C_2H_2, and NO^+ reveals only slight differences. Because of its stable triple bond, low polarizability, and weak donor properties, the N_2 molecule is the least conducive to bonding. The best partners prove to be metal ions having a fully occupied t_{2g} level (d^6 system) in which the electrons are not too firmly bound. The most favorable of such partners are, therefore, low-valency transition metals of the higher groups which are able to effect back-bonding on donation of electrons to the unoccupied π^*-state of the N_2 molecule. A maximum stability seems to occur with Os^{II}.

In the complexes previously isolated and characterized by structural analysis, the nitrogen is bound to the metal ion in the direction of its molecular axis ($M \leftarrow :N \equiv N:$; "end on"). In the case of enzymatic nitrogen fixation, however, bonding *via* the π-system perpendicular to the molecular axis ($M \leftarrow \overset{\ddot{N}}{\underset{\ddot{N}}{|||}}$; "edge on") must be taken into consideration since, *e.g.*, C_2H_2 inhibits uptake of N_2. All mononuclear nitrogen complexes (the known symmetrical binuclear complexes[3] of the type M—N≡N—M are excluded here) show an intense, sharp IR band in the range 2050—2150 cm^{-1}, which is indicative of an "end on" bonded N_2 molecule. Compared with the known stretching vibration at 2331 cm^{-1} in the Raman spectrum of free N_2, a long-wave shift of about 200—250 cm^{-1} is observed in the case of nitrogen complexes, corresponding to the loosening of the bond between the N atoms; simultaneously the N—N bond length, which is 1.098 Å in the free molecule, increases by about 0.02 Å. The degree of loosening of the bond—as shown by IR spectroscopic investigations—is very much dependent on the nature of the nearest and near neighbors.

All nitrogen complexes are reactive and therefore suitable for planned substitution reactions. Much preparative work remains to be done to establish the most favorable metal ions for bonding to N_2 and the most suitable ligand environment, thus opening a wide new field of study in coordination chemistry.

Lecture at Kiel on October 28, 1971 [VB 332 IE]
German version: Angew. Chem. *84*, 267 (1972)

[*] Prof. Dr. W. Preetz
Institut für anorganische Chemie der Universität
23 Kiel, Olshausenstrasse 40—60 (Germany)

[1] *A. D. Allen* and *C. V. Senoff*, Chem. Commun. *1965*, 621.

[2] *M. E. Volpin* and *V. B. Shur*, Nature *209*, 1236 (1966).

[3] *C. M. Elson, J. Gulens*, and *J. A. Page*, Can. J. Chem. *49*, 207 (1971).

Structure of coordinated nitrate groups in complexes with specific metal-nitrate interactions is considered by *C. C. Addison, N. Logan,* and *S. C. Wallwork.* The ligand NO_3 can engage in several different kinds of bonding: it can act as a monodentate to terdentate, in each case symmetrical or unsymmetrical, ligand or assume a bridging function. Thus $Co(NO_3)_3$ contains symmetric and $[Co(NO_3)_4]^{2-}$ unsymmetric bidentate NO_3 groups. Monodentate NO_3 ligands are present in $[Au(NO_3)_4]^-$ while α-$Cu(NO_3)_2$ contains NO_3 bridges. Apart from the factors that could be responsible for the kind of coordination in a given compound, the authors discuss the stereochemistry of the compounds and their vibrational spectra. [Structural Aspects of Co-ordinated Nitrate Groups. Quart. Rev. Chem. Soc. *25*, 289—322 (1971); 85 references, 14 figures, 13 tables with numerous examples]

[Rd 421 IE -E]

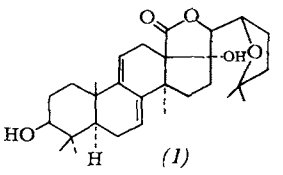
The chemistry of disulfur monoxide is reviewed by *A. R. Vasudeva Murthy, T. R. Narayanan Kutty,* and *D. K. Sharma* (up to 1970). Sulfur combines with oxygen to give a variety of oxides, the formation of those having high sulfur contents of the formula S_xO, $x = 2$—7, having been studied relatively little. Such lower oxides probably tend to undergo polymerization. Studies of the sulfur-oxygen system under varying conditions of temperature and pressure could possibly also provide an insight into atmospheric pollution by sulfur oxides.—S_2O can be prepared by combustion of S in O_2 at reduced pressure, by reaction of sulfur vapor and SO_2 in an electric discharge, by reaction of a metal oxide with S, and from sulfur-halogen compounds. Its properties are discussed in detail. [Chemistry of Disulfur Monoxide. Internat. J. Sulfur Chem. *6*, 161—175 (1971); 76 references]

[Rd 456 IE -M]

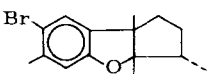
The UV spectroscopic properties of simple compounds having N—N and N—O bonds are surveyed by *J. Kuhn, W. Hug, R. Geiger,* and *G. Wagnière.* The electronic structure of NO, aminoxyl, nitrosomethane, azomethane, trimethylamine oxide, azomethane *N,N'*-dioxide, NO_2, nitromethane, nitroethylene, and methyl nitrite was determined by a SCF CI calculation including all valence electrons that was performed by the CNDO method; essential agreement was obtained between the calculated and measured spectrum. Furthermore, predictions could be made regarding the symmetry and relative energy levels of nonbonding orbitals. [Die elektronische Struktur einfacher stickstoff- und sauerstoffhaltiger Verbindungen. Helv. Chim. Acta *54*, 2260 to 2277 (1971); 28 references]

[Rd 457 IE -M]

Toxins from marine invertebrates, *i.e.* from echinoderms and mollusks, are the subject of a review by *P. J. Scheuer.* Heightened interest in this field became apparent about ten years ago; nevertheless, our knowledge of the chemical constituents of marine organisms is incomparably more sketchy than the information available about those of terrestrial fauna and flora. The physiologically active substances of the echinoderms are mainly triterpenoid glycosides: holothurins [aglycones: holothurinogenins, *e.g. (1)*] and asterosaponins. The active constituents of



(1)



(2)

the mollusks are primarily sesquiterpenes; aplysins, *e.g. (2)*, constituents of the digestive gland. [Toxins from Marine Invertebrates. Naturwissenschaften *58*, 549—554 (1971); 48 references]

[Rd 458 IE -M]

Aromatic amino acids in the metabolism of higher plants are discussed in an article by *H. Kindl.* The metabolism of higher plants is characterized by a great variety of reactions and by a remarkable specificity with regard to species. Aromatic amino acids and their derivatives undergo, *e.g.*, chain lengthening by one C atom or are degraded to benzoic acid derivatives, phenols, and aliphatic compounds. The hydroxylation reactions differ considerably from those in mammalian tissues. The genus- and species-specificities of numerous reaction sequences are so pronounced that chemical-taxonomic demarcations can often supplement morphological findings. [Aromatische Aminosäuren im Stoffwechsel höherer Pflanzen. Naturwissenschaften *58*, 554—563 (1971); 157 references]

[Rd 459 IE -M]

The use of polyphosphoric acid for the synthesis of polymeric aromatic heterocycles by cyclopolycondensation reactions is reviewed by *N. Yoda* and *M. Kurihara.* The new types of polyheterocycles which can be prepared by these methods are discussed in detail, as is also the mechanism of macromolecular syntheses in phosphoric acid solutions. Examples of such polymeric aromatic heterocycles which can be prepared by these methods are: polybenzoxazinones, polyquinazolinediones, poly-4-phenyl-1,2,4-triazoles, polybenzimidazoles, and polybenzothiazoles. Polyimidazopyrrolones, polybenzimidazobenzophenanthrolines, polyisoindoloquinazolinediones, and spiropolyimides can be prepared by double cyclization. [New Polymers of Aromatic Heterocycles by Polyphosphoric Acid Solution Methods. Macromol. Rev. *5*, 109—193 (1971); 111 references]

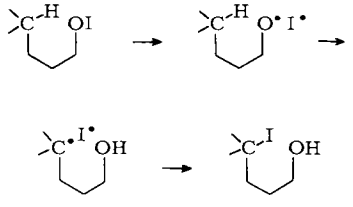
[Rd 468 IE -M]

Oxidation, reduction, and addition reactions of sulfenyl halides are reviewed by *E. Kühle.* The recent increase in the number of publications concerned with this topic is due partly to the industrial availability of trichloromethanesulfenyl chloride and its derivatives and to the synthesis of new types of sulfenyl halides. Addition takes place with multiple bonds (C=C, C≡C, C=N, C≡N, C=O, C=S) and small rings (oxiranes, thiiranes), *etc.* Addition-elimination reactions are also considered, *e.g.* to diazo compounds with elimination of N_2 and to C=S and P=S bonds with elimination of alkyl halide. Preparative examples are given for the reaction discussed. [One Hundred Years of Sulfenic Acid Chemistry. Oxidation, Reduction, and Addition

Reactions of Sulfenyl Halides. Synthesis *1971*, 563—586; 176 references]

[Rd 463 IE –M]

The hypoiodite reaction, a versatile method for intramolecular substitution of non-activated centers, is discussed in a review by *J. Kalvoda* and *K. Heusler*. The reaction permits, *e.g.* the synthesis of tetrahydrofuran, lactone, and γ-cyano ketone groupings, even on complicated skeletons such as steroids. Essential features of the reaction are the *in situ* formation and homolysis of a RO—I bond and subsequent reactions of the resulting alkoxy radicals. Several reaction schemes are discussed and a series of experimental examples is given. The course of the reaction can be represented by a reaction scheme formulated by *D. H. R. Barton:*



Compounds containing, *e.g.*, ONO, OCl, OBr, or NHI in place of OI react analogously. [Die Hypojodit-Reaktion (Verfahren zur intramolekularen Substitution an nicht-aktivierten C-Atomen). Synthesis *1971*, 501—526; 152 references]

[Rd 461 IE –M]

The occurrence of polychlorobiphenyls and their environmental significance are reviewed by *R. Edwards*. The chlorinated hydrocarbons used as pesticides and the polychlorobiphenyls have many common properties; however, the latter are considerably more stable, both chemically and thermally. They have been widely used industrially since about 1930 and are carried into rivers and the sea in waste water. An increasing number of studies are concerned with their occurrence in the environment and with their toxicology, particularly regarding possible long-term effects. The pronounced resemblance to a number of pesticides causes interference in analyses. [The Polychlorobiphenyls, their Occurrence and Significance: A Review. Chem. Ind. (London) *1971*, 1340—1348; 70 references]

[Rd 460 IE –M]

Oxidation of alkenes with mercury(II) salts is the topic discussed in a review by *H. Arzoumanian* and *J. Metzger*. Alkenes react with Hg(II) salts in an addition reaction (solvomercuration) or in a redox reaction with oxidation of the alkene and reduction of the mercury. The oxidation products vary widely with the substrate: α-alkenes give α,β-unsaturated carbonyl compounds; alkenes having no terminal methylene group (linear disubstituted alkenes, cyclic alkenes, phenyl-substituted alkenes) afford various oxidation products depending upon the substituents; and conjugated dienes yield α,β-unsaturated carbonyl compounds and unsaturated cyclic ethers. [Oxidation of Olefins with Mercuric Salts. Synthesis *1971*, 527—536; 69 references]

[Rd 462 IE –M]

The polymerization of vinyl- and related compounds in the presence of sulfur compounds is dealt with in a review by *P. Ghosh*. For example, peroxy compounds, diazothioethers, sulfonyl azides, organic sulfoxy compounds, sulfuric acid, sulfuryl chloride, salts of reducing sulfoxy compounds, and thioureas are suitable as polymerization initiators. Compounds that can be used as initiators and/or modifiers for the polymerization are, *inter alia*, sulfur, organic sulfides, and H_2S. Dimethyl sulfoxide can be used as both initiator and solvent for the polymerization. The author also discusses the copolymerization of sulfur chlorides with diolefins and the synthesis of polymers containing sulfoxy groups. [Participation of Sulfur Compounds in Vinyl and Related Polymerization. Macromol. Rev. *5*, 195—227 (1971); 131 references]

[Rd 469 IE –M]

The coordination chemistry of scandium is treated comprehensively in a review by *G. A. Melson* and *R. W. Stotz*. The known coordination compounds are arranged in groups according to the donor atoms oxygen, nitrogen, and halogen. Generally scandium prefers the coordination number six, *i.e.*, the stereochemistry of an (often distorted) octahedron. However, the occurrence of coordination numbers other than six is not ruled out. Very few details of structures and bonding properties are known. [The Coordination Chemistry of Scandium. Coord. Chem. Rev. *7*, 133—160 (1971); 225 references, 6 tables]

[Rd 476 IE –H]

The application of magnetic resonance methods in the elucidation of bonding properties of transition metal compounds is reviewed by *D. R. Eaton* and *K. Zaw*. Electron spin resonance (ESR) and nuclear spin resonance (NMR) provide the investigator with complementary information, since ESR measures modifications of central ion energy states caused by the ligands, whereas NMR sees shifts of ligand transitions caused by the central ion. The theory of ESR and NMR and results on selected transition metal compounds are given. [Magnetic Resonance Methods in the Study of the Electronic Structures of Transition Metal Complexes. Coord. Chem. Rev. *7*, 197—227 (1971); 189 references, 3 figures, 5 tables]

[Rd 478 IE –H]

Leitfaden der Farbstoffchemie (A Guide to Dyestuffs Chemistry). By *P. Rys* and *H. Zollinger*. Chemische Taschenbücher Vol. 13. Edited by *W. Foerst* and *H. Grünewald*. Verlag Chemie GmbH, Weinheim/Bergstr. 1970. 1st Edit., xi, 220 pp., 16 illustrations, 16 tables, paperback DM 22.—.

The present book classifies dyes according to their chromophore systems into azo, nitro and nitroso, polymethine, aza-[18]annulene, di- and triarylcarbonium, sulfur, and carbonyl dyes. Each group has its own chapter and comprehensive introductions are given.

The more general and theoretical chapters give details of reaction mechanisms, the relationship between chemical composition and color, color measurements, and the thermodynamic and kinetic principles of application.

The text is concise but clear and ample references are given. The book is a valuable and useful piece of work, based on the principles of modern organic and physical chemistry.

Udo Mayer [NB 25 IE]

Kleines Chemisches Praktikum (Small Chemical Laboratory Manual). By *E. Dane* and *F. Wille*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 7th Edit., xii, 189 pp., 23 illustrations, paperback, DM 19.80.

Significantly, the student will often refer to much used textbooks or laboratory manuals simply by the names of their authors. This also applies to "Dane/Wille", which is now in its 7th revised edition. In 190 pages, this attractive, handy, and well-produced book deals with about 400 experiments and explanations, inculcating a basic knowledge of inorganic chemistry. The subject matter is arranged according to classical principles: in the inorganic section according to the periodic system, supplemented by chapters on atomic structure, chemical bonding, equilibrium, electrolytes, oxidation and reduction, acids and bases, and qualitative and quantitative analysis; and in the organic section according to the sequence of compounds by functional groups (still usual in the majority of basic textbooks), supplemented by chapters on plastics, chromatography, qualitative organic analysis, resonance and substitution in aromatic substances.

When it first appeared (1960) "Dane/Wille" heralded a new approach for books of this type: its concise presentation of the subject matter and its description of experiments pointed a new way to the reform of chemistry teaching for medical students (the methods used then varied much more from university to university than they do now).

However, "Dane/Wille" can nowadays really be appreciated only from the historical point of view; as shown by the new regulations for the certification of doctors, since the book was first published the modern concept of "concentrating" the subject matter has taken precedence over the classical principle of "spreading out" the material, because this is the only way of bringing the teaching of fundamental physical and chemical principles in the preclinical part of a medical course into line with the further biochemical, physiological-chemical, and general practical needs of the student. Thus, for a practical course it would seem essential to open up well-defined and specific fields of interest by means of appropriate experimental work and to teach critical assessment of the results—if possible by further experiments. This, however, tends to shift the emphasis of the practical and theoretical teaching of a very wide subject to an in-depth examination of specific problems.

In this connection it should be mentioned that the above approach has already found expression in another book, "Chemie für Mediziner" (Chemistry for Medical Students) by *K. Beyermann*. A similar approach was adopted even earlier in the brochures on laboratory work for medical students written by *K. Dimroth* and *C. Mahr* or by *G. Hartmann* and *S. Hünig* on the Marburg and Würzburg models respectively. If we go by the criteria that form the basis of the above concepts of medical training—and these have for several years proved very successful—then "Dane/Wille" can no longer meet the requirements for a modern laboratory manual, in spite of the services it has rendered in the past.

Theophil Eicher [NB 26 IE]

Gmelin-Durrer: Metallurgie des Eisens (Metallurgy of Iron). Fourth fully revised edition, continued by *G. Trömel*. Supplement to Gmelins Handbuch der anorganischen Chemie, 8th Edit., System No. 59, "Iron", Part A, Volumes 3 to 5, Verlag Chemie GmbH, Weinheim/Bergstr. 1968. Volume 2. General Requirements for the Industrial Reduction of Iron Ores. Raw Materials. The Industrial Processes Apart from the Blast Furnace, Volume 2a: Text Part, vi, 350 pp., Volume 2b: Figure Part, iv, 188 pp., 452 figures cloth, together DM 492.—.

The present volume concludes the discussion of the raw materials for the reduction of iron ores and their preparation prior to smelting. The industrial reduction methods are then discussed, apart from those that are carried out in the blast furnace. As in the other volumes of the 4th edition, the text part and the figure part are separate in volume 2, which was produced with the aid of data from the European Coal and Steel Community.

The first part contains the following sections: Physico-Chemical Principles of the Reduction; Survey of Raw Material Requirements; Survey of the Principal Deposits of Iron and Manganese Ores; Properties of Iron Ores and Iron Ore Agglomerates that are Important for the Industrial Reduction; Survey of the Production of Coal and Lignite Cokes. The second part contains the sections Reduction in the Low Shaft Furnace; Reduction in the Electric Furnace; The Direct Reduction Processes; The Uses of Pre-Reduced Materials.

A very comprehensive subject index in German and English makes it easy to find the various processes.

The literature is evaluated up to, and in some cases beyond, Spring 1967.

Ekkehard Fluck [NB 29a IE]

Gmelin-Durrer: Metallurgie des Eisens (Metallurgy of Iron). Fourth fully revised edition, continued by *G. Trömel* and *W. Zischkale*. Supplement to Gmelins Handbuch der anorganischen Chemie. 8th Edit., System No. 59, "Iron",

Part A, Volumes 3 to 5, Verlag Chemie GmbH, Weinheim/Bergstr. 1971. Volume 3, Part 1. Blast-Furnace Installations. Blast-Furnace Operation. Pig Iron and By-Products. World Pig-Iron Production Situation. Volume 3a: Text Part, vi, vii, 320 pp., Volume 3b: Figure Part, vi, i, 137 pp., 304 figures, cloth, together DM 487.—.

The present volume of "Gmelin-Durrer" has been written by engineers from West German ironworks and from the Verein Deutscher Eisenhüttenleute in collaboration with the Institut für Eisenhüttenwesen der Technischen Universität Clausthal and the Gmelin-Institut in Frankfurt. Together with Volume 4, which is still in preparation, it deals with blast furnace installations. As can be seen from the sections described below, Volume 3 is also concerned with iron production practice, blast furnace products, and world iron production data.

The first section deals with the blast furnace installation and the topics discussed include furnace types, blast furnace profiles, the refractory lining of blast furnaces and hot metal ladles, the cooling of blast furnaces, blast production and air heating, monitoring of the blast furnace operation, the casting bay, and finally the purification of blast furnace gases. Blast furnace operation, *i.e.* the practice of pig-iron production, the production of special steels, and the treatment of the pig iron outside the blast furnace, forms the subject of the second section. Considerable space is given in this section to the processes for the removal of phosphorus and sulfur from the liquid pig iron. The products from the blast furnace, *i.e.* pig iron, blast furnace slag, blast furnace gas, and blast furnace flue dust, are described in the third section. The final section begins with a comparison of blast furnace operating results, and continues with a discussion of world pig iron production, locations of ironworks, raw material supply, raw material treatment, characteristic running parameters *etc.*

As in the earlier volumes of the 4th edition, the text part and the figure part of the present volume are separate.

The literature is evaluated up to, and in some cases, beyond 1968/1969.

Ekkehard Fluck [NB 29b IE]

Knauers Buch der modernen Chemie (Knauer's Textbook of Modern Chemistry). By *J. Rudolph*. Droemersche Verlagsanstalt Th. Knauer Nachf., München 1971. 1st Edit., 360 pp., 285 illustrations (mostly in color), bound, DM 22.—[*].

This book serves two purposes. On the one hand it provides a comprehensive introduction to the fundamentals of chemistry and hence is a useful tool for the layman who, perhaps as a student, is trying to learn some chemistry or to refresh his memory on what he once knew but has now forgotten. On the other hand, it guides the reader quickly and very skilfully *via* the basic principles of the subject to many modern problems which are being actively pursued in research laboratories or which, because of their importance in our everyday life, are felt to be in urgent need of solution.

Among the subjects treated are atomic structure, new elements, orbitals, Hückel theory, cyclopropenylium ion and cyclobutadiene, metal complexes, nitrogen fixation, Ziegler catalysts, fuel cells, lead and sulfur dioxide in the air, inert gas compounds, cyclohexasulfur, the Merrifield method, vitamin B_{12}, fast reactions, and of course the genetic code and survival of the fittest.

[*] An English translation will be published by Ruppert Hart-Davis, London.

The book has no bias toward any one particular field, nor is any attempt made to give the impression that everything is attractive and childishly simple. The reader himself has to make the effort to understand the meaning of orbital diagrams, how spectra arise (also in the field of nuclear resonance), and how the properties of alloys are described by phase diagrams.

On the whole, the author places more value on an understanding of physical principles than on burdening the memory with facts. For example, he attempts to explain the procedure of X-ray structure analysis and to clarify the phase problem. While he mentions the highly developed art of stereospecific synthesis of complex organic molecules, he does not adduce concrete examples or describe individual steps in detail. His treatment of chemical reactions and mechanisms is comparatively simple.

The book not only imparts a knowledge of facts, methods, and applications, it also takes a stand on many modern problems. It criticizes and gives food for thought on matters concerning universities, research, industry, and advertising. The author expresses sound opinions on many subjects. He is objective and clearly has at his command an astonishing wealth of information. Only occasionally is a scientific or technical problem misrepresented: for example, the reasons for the decline of coalmining (p. 143) or the use of enzymes in detergents (p. 331). In some places one might perhaps have expected more precise descriptions, in comparison with other parts of the book (*e.g.* hydrophobic bonding, p. 306). There are many small points, for example in the field of chemical pedagogy (p. 161) and the training of students with physical equipment (p. 236), but these should not be taken too seriously because they are generalizations based on isolated instances. It would have been better, too, if the author had refrained from expressing opinions on nonchemical subjects. Notable examples of this are his statements about the type of men which had in earlier times erected great cathedrals (p. 151), about the church itself (pp. 157, 221), and about soldiers marching in step (p. 244). On the other hand, the reviewer was glad to find common sense being brought to bear on reports concerning the reputed evil intentions on the part of some chemists and companies (*e.g.* plant protection and war gases, p. 177).

The book is manageable in size, readable, and very clearly written. It has many excellent diagrams and illustrations, although these unfortunately do not always appear at the proper places. Even the specialist who finds that his particular field has not been dealt with in sufficient detail will have to admit that the treatment of complex topics and the introduction of the reader to the problems of today are exemplary from the didactic point of view. A conscious attempt has been made to avoid the style of *Schenzinger*'s "Anilin", which in its time was very successful. In the way it is written the book is more reminiscent of *Watson*'s "Double Helix", with its open, critical, and relaxed approach.

Although the work is in the nature of a textbook, the anti-authoritarian *Zeitgeist* can be detected in places. This is by no means designed simply to attract and please the younger reader. On the other hand, the author loses no opportunity to point out the achievements of individual scientists, and the text is liberally provided with short historical and biographical interludes.

This book has been written for a very wide readership. Every enlightened person from the age of 14 upward should read it. Many people who in their professional lives seem to be far removed from the sphere of chemistry (teachers of

Greek, for example, or judges or politicians) will realize how much their existence depends on chemistry and how much joy and wonder can be derived from a knowledge of nature. Specialists too may benefit from an overall view of a large part of the field of modern chemistry, from seeing their own particular subject within the context of chemistry as a whole.

Hans Musso [NB 32 IE]

Catenanes, Rotaxanes and Knots. By *G. Schill.* Academic Press, New York–London, 1971. 1st Edit., vii, 192 pp., numerous figures, bound $ 11.00.

This book is no. 22 in the series "Organic Chemistry; A Series of Monographs", edited by *A. T. Blomquist*, which has quickly acquired a high reputation through many excellent monographs on interesting and topical fields from the pens of experts.

The book opens with a brief account of the history, structure, nomenclature, and stereochemistry of the types of compounds named in the title. The general part (19 pages) ends with a few words on their natural occurrence. The second part begins with the fundamental methods for the synthesis of [2]-catenanes. This is followed by a detailed description of experimental efforts to solve this problem, which is fascinating for any preparative chemist (about 100 pages). Special emphasis is placed on the characterization and proof of structure of the compounds and the demonstration of their structure by mass spectroscopy. The subsequent sections on [3]-catenanes and [2]-rotaxanes are similarly arranged (about 10 pages each). The last section presents concepts and investigations on knots and on doubly twisted and higher catenanes and rotaxanes (11 pages). A table containing all compounds of this type so far isolated concludes the text (10 pages).

The book is clearly, sensibly, and critically written. It is not a distilled extract of the existing material, with a straightforward description of the successes, but rather a systematically arranged account of all syntheses and approaches, including those that were unsuccessful, abandoned, or unpublished. Once the reader has worked his way into the book (which will not be without effort to some), he will be caught up in the dramatic development of every single step, with all its disappointments and difficulties. Impressed by the experimental work and the tenacity with which the aim has been pursued, he will be unable to lay the book aside. The drive of the initiator and the author's independent contribution can be discerned in many places. It is not intended as a textbook for younger students; however, the advanced chemist will learn much from it, even if he is not, and does not intend to become, involved in this particular field. This type of presentation demonstrates how a clear and simple, but experimentally very difficult concept can be empirically realized in the end by classical methods.

The printing and the numerous, sometimes large formulas are generally free from errors and very good. In places, the reader could progress more easily if the text dealing with a certain compound and its formula were closer together. It is often necessary to interrupt one's train of thought to search for a formula on the preceding or following page. The steric structures of many compounds are shown very clearly by the figures in a number of places (*e. g.* pages 1, 3, and 60). It would also have been useful in many other formulas of the twisted structures to indicate the parts of the molecule that lie in front and those that lie behind by means of thicker and thinner lines in order to enhance the perspective impression. It would certainly be useful, once the summit is reached on p. 120, to recapitulate briefly the straightforward path from the simple starting material to [2]-catenane, *e. g.* for readers who wish to prepare a lecture on the basis of this book. In view of the many pages carrying little or no print (about 15), it should have been possible to reproduce some mass spectra in connection with the proof of the structure on p. 122.

This book should find a place in every chemical library; every chemist is recommended to read it, including those who are not concerned with organic compounds.

Hans Musso [NB 33 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 4036/4037, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (06201) 4031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE
International Edition
VOLUME 11 · NUMBER 4
APRIL 1972
PAGES 249–346

Carrier-Bound Biologically Active Substances and Their Applications

By Hans Dieter Orth and Wolfgang Brümmer[*]

Stable catalysts can be obtained by fixation of enzymes on suitable supports. The principal methods for their preparation and their properties are described. The use of supported enzymes in routine biochemical analysis as "insoluble reagents" for automatic analyzers and for enzyme electrodes appears particularly interesting. For preparative transformations and syntheses, the supported enzymes offer the advantage that many processes that were formerly operated batchwise can be run continuously to give protein-free products. The use of supported proteinases as specific adsorbents provides a simple method for the isolation of various naturally occurring inhibitors. This principle, which is the basis of affinity chromatography, has now also been adapted to the purification of enzymes and other biologically active substances on suitable supported effectors.

1. Introduction

Recent years have seen the development of a field of biochemistry known as "enzyme engineering", the aim of which is to extend the use of the specific catalytic properties of enzymes. Efforts were made at first to stabilize enzymes by inclusion in or by fixation on water-insoluble supports so that they could be used repeatedly. Polymer-bound enzymes of this type can be used not only as specific catalysts but also as selective adsorbents, *e.g.* for naturally occurring inhibitors. Conversely, this new technique, which is known as affinity chromatography, also allows the isolation of many enzymes in a very pure state by selective adsorption on suitable insolubilized inhibitors or other specific effectors (substrate or coenzyme analogs, antibodies).

The object of the present progress report is to illustrate the possible applications of supported enzymes for transformations and of supported effectors for isolations with the aid of selected examples.

2. Binding of Proteins to Supports

2.1. Methods

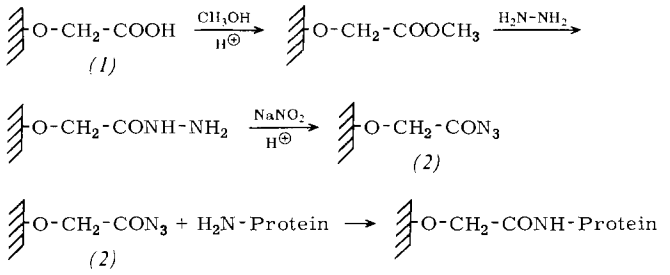
Numerous publications dealing with the binding of biologically active proteins to insoluble supports have appeared during the past few years. Important contributions to the development of this new field of enzymology have been made by the research groups of *Katchalski*, *Goldstein*, *Manecke*, *Porath*, *Axen*, *Kay*, *Hornby*, *Lilly*, *Crook*, *Cuatrecasas*, and *Anfinsen*. (For reviews see [1—15].)

There is no standard method for the preparation of supported proteins. Special reaction conditions, and in many cases special "tailor-made" supports are required to ensure substantial retention of the biological activity of the individual protein to be bound. There are three principles in common use at present for the fixation of proteins, and particularly of enzymes:

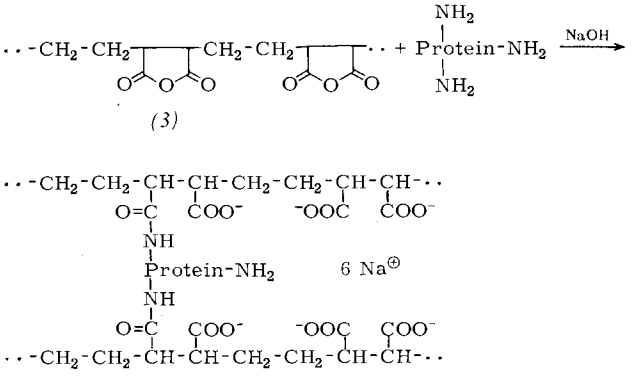
1. Ionic binding on hydrophilic ion exchangers[16–20]. As long as certain physical conditions are maintained, such as ionic strength and pH value, enzymes having a relatively high content of acidic amino acids, *e.g.* the aminoacylase from *Aspergillus oryzae* (see later), remain firmly bound to DEAE-cellulose or DEAE-Sephadex even at relatively high substrate concentrations[16, 17].

2. Entrapment in hydrophilic gels by photocatalytic copolymerization of acrylamide and *N,N'*-methylenebis(acrylamide) in the presence of the enzyme[21–23]. However, this method is suitable only for enzymes transforming low molecular weight substrates, since those of high molecular weight cannot pass through the pores of the gel to reach the enzyme molecules enclosed in the gel matrix. A critical discussion of the method, based on investigations on immobilized cholinesterase, has been published by *Degan* and *Miron*[23].

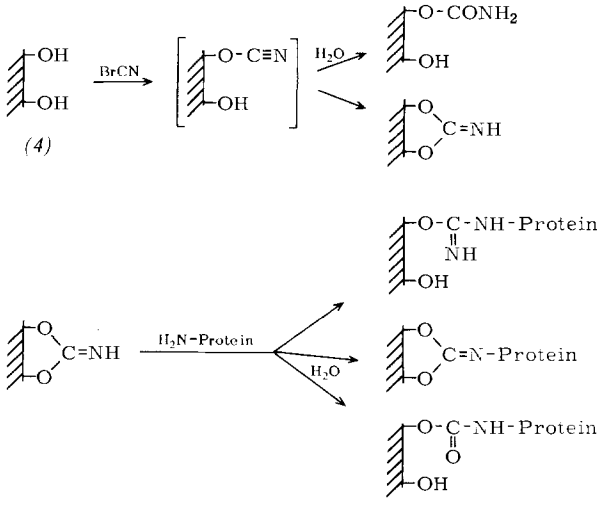
[*] Dr. H. D. Orth and Dr. W. Brümmer
E. Merck, Biochemische Abteilung
61 Darmstadt 2, Postfach 4119 (Germany)



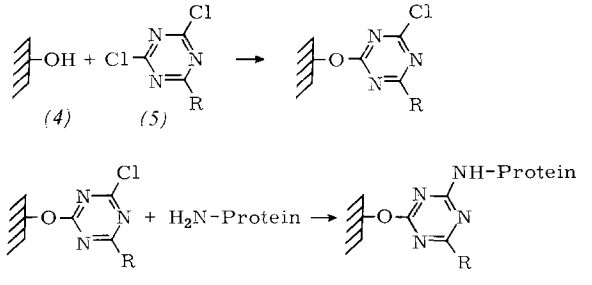
Scheme 1. Conversion of carboxymethyl cellulose *(1)* into the reactive azide form *(2)* and reaction with proteins [29, 39, 40].



Scheme 2. Binding of proteins to a copolymer of ethylene and maleic anhydride *(3)* (EMA) [31, 32].



Scheme 3. Activation of polysaccharides *(4)* such as agarose and cellulose with BrCN and reaction with proteins [25].



Scheme 4. Activation of polysaccharides *(4)* such as agarose and cellulose with cyanuric acid derivatives *(5)*, R = *e.g.* NH_2 (2-amino-4,5-dichloro-*s*-triazine), and reaction with proteins [28, 29].

3. Binding to hydrophilic natural[24–29] or synthetic[30–34] polymers or to inorganic substances such as glass[35–38] by covalent linkage *via* functional groups of the enzyme protein that are not essential to enzyme activity. This applies not only to the terminal α-amino group(s) of the enzyme molecule, but frequently also to the basic ε-amino groups of the lysines, the hydroxyphenyl side chains of the tyrosines, the guanidyl side chains of the arginines, and the imidazolyl groups of some histidines, and these may therefore be favored as points of attachment[9].

The support usually has to be converted into an active form before the reaction with the proteins. Some typical support substances are listed in Schemes 1—4.

Mention should also be made here of an interesting method that has recently been developed by *Novais* for the coordinate binding of enzymes to surfaces of cellulose or glass that have been activated by treatment with chelate-forming transition metal salts, particularly titanium salts[41].

2.2. Steric Conditions

Mild conditions must be used for the fixation of biological macromolecules in order to preserve their steric structure which is essential to their activity. The support matrix must therefore be hydrophilic and highly porous[25, 40, 42]. The reaction conditions that may be considered are moderate ionic strengths, pH values between about 4 and 10, and temperatures between 0 and about 35 °C. To guarantee the conservation of the steric structure and the free accessibility of the active center, it is also favorable in many cases to attach the macromolecule to the support *via* a side chain ("spacer") instead of attaching it directly. This can be achieved *e.g.* by the use of an α,ω-diaminoalkane or an ω-amino carboxylic acid[14, 15, 42].

For sterically unhindered contact with substrates and effectors, it is also necessary to avoid covalent linkage of too many groups of the macromolecule to the support. Since the binding occurs mostly *via* NH_2 groups and the p*K* values of the terminal NH_2 groups of peptides are lower compared with those of the NH_2 groups in the lysine side chains, it is possible to ensure, by variation of the pH, that binding occurs mainly *via* the terminal α-NH_2 group, provided that this group is not masked by the steric arrangement of the polypeptide chain. Thus immune globulin that had been coupled to activated agarose at pH 9 took up only 7% of the calculated quantity of insulin, whereas immune globulin fixed at pH 6.5 took up 77%[14].

3. Properties of Insoluble Enzymes

3.1. Stability

Most of the supported enzymes described so far are considerably more stable than the corresponding soluble enzymes[9], so that provided a suitable support and mild coupling conditions are used, this property may be regarded as characteristic of supported enzymes. Binding to an insoluble support evidently provides better protection for

the native conformation of the enzyme against denaturing effects. With continuous use, the stability is further increased by the influence of the substrate.

As an example of the stabilization of supported proteinases due to reduced autolysis, Figure 1 shows the variation with time of the residual activity of bovine trypsin in the soluble and bound forms after preincubation at 55 °C[39].

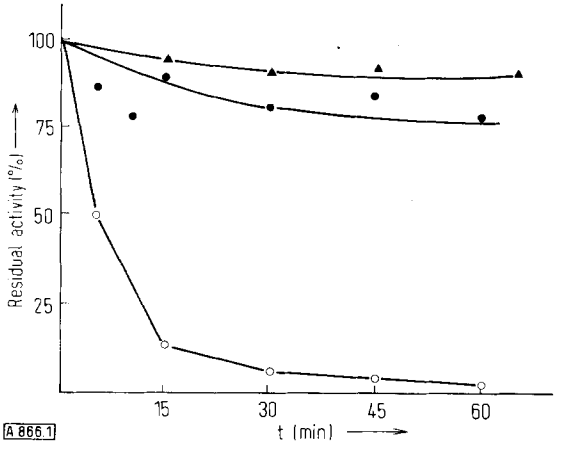


Fig. 1. Residual activity of trypsin (bovine) (○), CMC-bound trypsin (●), and MA-bound trypsin (▲) after preincubation at 55 °C, measured with casein as the substrate [39]. CMC = carboxymethyl cellulose, MA = crosslinked copolymer of 1,4-bis(vinyloxy)butane and maleic anhydride.

3.2. Activity

Supported enzymes are generally less active than the corresponding native enzymes. Enzymes that act on low molecular weight substrates exhibit an average residual activity of 40—80% after fixation[9], while hydrolases bound to polymers retain only 5—40% of their activity for their high molecular weight substrates[25,27]. Higher values have occasionally been reported[24,26]. However, this partial loss of activity is offset by the fact that insoluble enzymes can be used repeatedly. Some reasons for the modified activity of the bound enzymes are discussed below.

4. Parameters Influencing the Properties of Insolubilized Enzymes

4.1. Steric Hindrance

An enzyme molecule is generally fixed to the support, not at one point of attachment, but at several. This results in a certain amount of crosslinking, which, together with possible intramolecular crosslinking of the activated matrix itself, hinders the access of a substrate to a bound or enclosed enzyme molecule. This is particularly true of enzymes such as proteinases, amylases, and nucleases, which degrade high molecular weight substrates[1,4,5,9]. *Cresswell* and *Sanderson*[44] investigated this effect for an insolubilized microbial proteinase (pronase from *Streptomyces griseus*) bound to a diazotized copolymer of leucine and *p*-aminophenylalanine[43]. A linear relation was found between the residual proteolytic activity and the logarithm of the molecular weight of the substrate. The proteolytic activity decreases with increasing molecular weight of the substrate, and a stage is ultimately reached where only the enzyme molecules attached directly to the surface of the porous particles are still active. The same is true of proteinase inhibitors, *i.e.* the fraction of the bound enzyme that they can inhibit decreases as their molecular weight increases[27,32,45]. The situation is similar to that in exclusion chromatography of proteins on crosslinked dextran gels, in which the fraction of the pore volume accessible to a protein depends on the molecular weight of the protein.

4.2. Electrostatic Interactions

Mere steric hindrance is observed only with uncharged supports or uncharged substrates. With ionic supports, it is accompanied by the electrostatic interaction between the support and similarly or oppositely charged enzyme substrates. This effect becomes particularly obvious under conditions where substrate saturation of the bound enzyme cannot be achieved. This has been demonstrated *e.g.* in the activation of chymotrypsinogen A and chymotrypsinogen B by trypsin bound to a support having anionic groups (carboxymethyl cellulose, see Scheme 1)[39]. The two proenzymes have the same molecular weight (25000) but different electric charges (isoelectric points at pH 9.5 and 5.2 respectively). Under the reaction conditions used seven times as much bound trypsin was required for the activation of negatively charged chymotrypsinogen B as for the positively charged chymotrypsinogen A[39]. If the support matrix and the substrate are oppositely charged, a higher substrate concentration occurs on the surface of the support than in the surrounding solution. Conversely, if the support and the substrate carry like charges, electrostatic repulsion leads to a decreased substrate concentration in the microenvironment of the bound enzyme. Inequality of the substrate distribution between the external and internal phase causes the bound enzyme to exhibit apparently a higher or a lower affinity, respectively, for its substrate[4,46].

The $H^{\oplus}$ ions behave similarly. As was shown by *McLaren*, these ions concentrate on negatively charged solid surfaces and cause a "surface pH" that can be up to two units lower than in the external phase[47,48]. These effects and their influence on the pH-activity profiles of bound enzymes were later investigated by *Goldstein et al.*[3,4]. The electrostatic interaction may be advantageous where the support and the enzyme substrate are oppositely charged. Thus if the substrate concentration decreases during an enzymatic reaction, the reaction rate of the supported enzyme decreases to a much smaller degree than that of the free enzyme[49].

4.3. Diffusion

Another factor that influences the substrate concentration in the microenvironment of a bound enzyme, and hence

also the activity of the enzyme, is diffusion. This is shown by the fact that insoluble enzymes exhibit their maximum activity only at sufficiently high stirring speeds in the reaction mixture[50–52]. The influence of diffusion on the activity of a bound enzyme depends on the maximum reaction rate V_{max} of the individual enzyme, the diffusion coefficient of the substrate, and the thickness of the diffusion zone[46].

If, however, instead of merely one-step enzymatic reactions, one considers reaction sequences catalyzed in a cascade by several enzymes, as in physiological processes in the cell, the local accumulation of a metabolite in the microenvironment of a structure-bound enzyme sequence due to limited diffusion can make the system as a whole particularly effective.

Mosbach and *Mattiasson*[53] have investigated this effect for a supported three-component system, in which β-galactosidase, hexokinase, and glucose-6-phosphate dehydrogenase were fixed together on BrCN-activated Sephadex (see Fig. 2). In this system, in which the reaction rate depends on the concentration of the intermediate products, it was found that the supported "multienzyme system" is more effective than the three individual enzymes in solution, since the initially formed glucose does not diffuse away immediately into the external phase, but remains available in high concentrations for the subsequent enzymatic reaction steps.

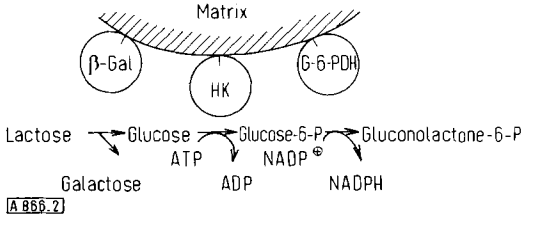


Fig. 2. Schematic representation of a three-step sequence with supported enzymes [β-galactosidase (β-Gal)—hexokinase (HK)—glucose-6-phosphate dehydrogenase (G-6-PDH)] (after [53]).

It can be seen here that the study of the properties of supported enzymes can also contribute to a deeper insight into the physiological mode of action of many cellular enzymes that are bound to membranes and structures.

5. Binding of Enzyme Effectors on Supports

5.1. Formation of the Covalent Bond

The effectors are always linked to the supporting resins by covalent bonds. Binding by adsorption, ionic interaction, or inclusion in porous polymers is not stable under the conditions (high ionic strength, extreme pH values, *etc.*) that are often necessary for the elution of substances purified by affinity chromatography. Under these conditions, physically coated supports bleed, *i.e.* their capacity is reduced, and they ultimately become unsuitable for affinity chromatography.

Amino groups of the effector molecules are used in many cases for covalent binding; the methods described earlier for the binding of proteins (Section 2.1) can be used for this purpose too. Carboxamide linkages are formed not only by the azide method but also in many cases by carbodiimide activation; in addition, the carbonyl group may be situated either on the support (see Section 2.1) or on the effector. Supports having amino groups can be obtained by the introduction of suitable side chains (see Section 2.2). The free end of the side chain may also carry an aromatic amino group, so that an aromatic effector can be attached by diazo coupling. Unlike proteins, low molecular weight effectors need not be bound to the support in aqueous solution, but can also be fixed in organic solvents[5,14,15,54,55].

5.2. Adsorption, Elution, and Influence of the Side Chain

The substance to be purified, *e.g.* an enzyme, may be adsorbed from crude extracts or from prepurified solutions. The affinity resins are used in batch and in column chromatography methods. The batch method can be used only if the dissociation constant of the complex formed by the two reactants is low, *i.e.* if the complex is stable. The column method, on the other hand, can be used even if the dissociation constant of the complex is high. In this case, the dissolved reactant is not fixed during chromatography, but is merely retarded, and elution presents no problems.

The decomposition of complexes having low dissociation constants, on the other hand, usually requires drastic changes in the conditions, such as heating, extreme pH values, high ionic strengths, or high concentrations of denaturing agents. This often leads to irreversible inactivation of the macromolecules to be desorbed[14,15]. Milder elution conditions are sufficient if the stability of the complex can be reduced. This is possible by shortening the side chain by which the reactant is attached to the support. However, the capacity of the treated support simultaneously decreases.

Microbial β-galactosidase is inhibited by *S*-(*p*-aminophenyl)-β-D-1-thiogalactopyranoside. The degree to which the enzyme is retained by the agarose-bound inhibitor varies with the length of the side chains. The retention of the enzyme by support A is practically zero, and that by support B is only slightly better. There is no need for severe elution conditions in either case. If, on the other hand, the columns are packed with support C (Fig. 3), the β-galactosidase is very strongly bound and 0.1 M borate buffer (pH 10) is required for elution[42,56].

The dependence of the support capacity on the length of the side chain has been determined for the agarose-bound Staphylococcus nuclease inhibitor 3'-(4-aminophenylphosphoryl)deoxythymidine-5'-phosphate[42]. With direct binding (corresponding to Figure 3, A), the capacity is 2 mg of nuclease/ml of gel. If *N'*-acetylethylenediamine is introduced as a side chain (corresponding to Fig. 3, B), the binding capacity increases to 8, and with *N'*-succinylbis(aminopropyl)amine as the side chain (corresponding to Fig. 3, C) to 10 mg of nuclease/ml of gel. In all three cases, the columns contained 2 μmole of inhibitor/ml of packed gel.

Elution with effector solution, *e.g.* the elution of L-asparaginase with D-asparagine[57], has also been reported (see also Section 8.1).

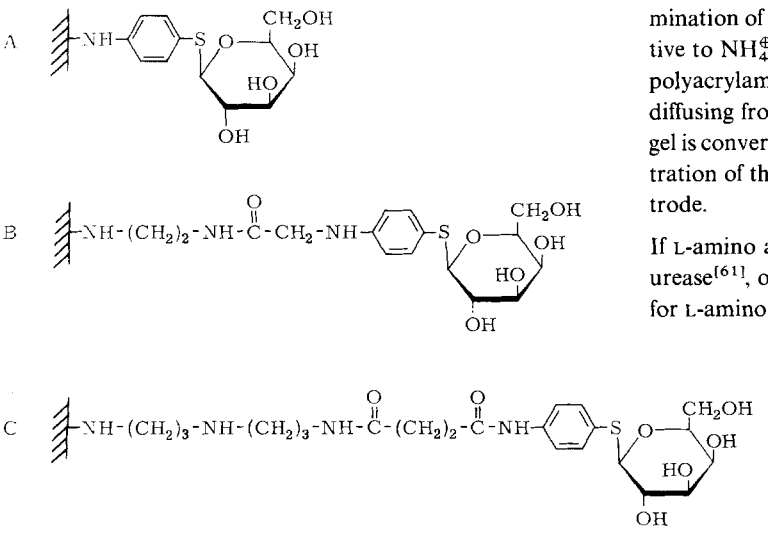


Fig. 3. Agarose-bound *S*-(*p*-aminophenyl)-β-D-thiogalactopyranoside [42]. A directly bound, B bound *via N'*-acetylethylenediamine, C bound *via N'*-succinylbis(aminopropyl)amine.

6. Use of Insolubilized Enzymes in Analysis

6.1. Automatic Analyzers and Enzyme Electrodes

Hicks and *Updike* used insolubilized enzymes entrapped in crosslinked polyacrylamide gel for the determination of oxidizable substrates in an automated analysis system[22]. They used microcolumns packed with granulated enzyme gel, through which the solutions for analysis were passed. The determination of glucose was carried out *e.g.* with insoluble glucose oxidase, corresponding to Scheme 5.

$$\text{Glucose} + O_2 \xrightarrow{\text{GOD}} \text{Gluconic acid} + H_2O_2 \qquad \text{(a)}$$

$$H_2O_2 + \underset{\text{reduced, colorless}}{\text{color indicator}} \xrightarrow{\text{POD}} H_2O + \underset{\text{oxidized, blue}}{\text{color indicator}} \qquad \text{(b)}$$

Scheme 5. Determination of glucose with glucose oxidase (GOD) and peroxidase (POD).

The H_2O_2 formed oxidizes, in the presence of peroxidase, a color indicator such as *o*-tolidine that is colorless in the reduced state. The intensity of the resulting color corresponds to the glucose concentration in the solution under analysis. If a sensitive oxygen electrode is used instead of the indicator reaction (b), a "reagentless" determination of glucose is achieved[58].

To make the process independent of the flow rate, *Hicks* and *Updike* developed an enzyme electrode[59]. This consists of a highly sensitive O_2 electrode encased in a layer of gel 25—50 μm thick containing entrapped glucose oxidase. If this probe is immersed in body or tissue fluid, O_2 and glucose diffuse into the enzyme layer, where the O_2 concentration is reduced by the enzymatic oxidation of glucose, and can be recorded as a change in the electrode potential. The principle is similar to that of the measurement of $H^{\oplus}$ concentrations with the pH electrode.

Guilbault and *Montalvo* have described an enzyme electrode operating on the same principle for the continuous determination of urea[60]. A cationic glass electrode that is sensitive to $NH_4^{\oplus}$ ions is enclosed in a thin layer of crosslinked polyacrylamide gel in which urease is trapped. The urea diffusing from the solution under analysis into the enzyme gel is converted into $HCO_3^{\ominus}$ and $NH_4^{\oplus}$ ions, and the concentration of the $NH_4^{\oplus}$ ions is immediately sensed by the electrode.

If L-amino acid oxidase is entrapped in the gel instead of urease[61], one obtains an enzyme electrode that is specific for L-amino acids.

6.2. Sequence Analysis of Nucleotides and Peptides

Even more complicated analytical investigations, such as the sequence determination of oligoribonucleotides, have been automated with the aid of supported enzymes.

Neu and *Heppel* proposed a method for the sequence analysis of tRNA that, unlike the usual method (enzymatic fragmentation of the RNA with specific endonucleases and exonucleases), allows a stepwise degradation from the free 3'-OH end of the terminal nucleoside[62]. This degradation occurs in two steps. The first step consists in the periodate oxidation of the exposed vicinal OH groups of the ribose of the terminal nucleoside, followed by elimination of the terminal base. In the second step, the newly formed phosphate monoester is split off with alkaline phosphatase; this exposes the vicinal OH groups of the next ribose. The reaction sequence is then repeated, as illustrated in Scheme 6.

Cycle I:

1st step ..ApGpC $\xrightarrow[\text{iodate}]{\text{per-}}$ "oxidized" ..ApGpC

$\xrightarrow[\text{pH 10.5}]{\text{glycine}}$ ..ApGp + cytosine

2nd step ..ApGp $\xrightarrow[\text{phosphatase}]{\text{alkaline}}$ ..ApG

Cycle II:

1st step ..ApG $\xrightarrow[\text{iodate}]{\text{per-}}$ "oxidized" ..ApG

$\xrightarrow[\text{pH 10.5}]{\text{glycine}}$ ..Ap + guanine

etc.

Scheme 6. Stepwise sequencing of an oligonucleotide. A = adenine, G = guanine, C = cytosine (after [62], modified).

However, if the phosphatase is not quantitatively eliminated after the second reaction step, the protective phosphate group of the following nucleoside, which then also reacts, is

partly removed during the first reaction step of the next cycle. Thus after a few reaction cycles the results become ambiguous[63]. *Zingaro* and *Uziel* largely overcame this difficulty by the use of insolubilized phosphatase, which was covalently bound to ethylene-maleic anhydride copolymer (EMA)[64]. The supported enzyme is still sufficiently active toward native RNA. The authors are now trying to construct an automatic RNA sequenator working on this principle[64].

Lee has reported the successful binding of ribonuclease T_1 to BrCN-activated Sepharose[65]. The advantage of using the bound enzyme is that the specific fragmentation of the RNA can be interrupted by simple centrifugation at any time that is favorable for the separation of the fragments or their subsequent sequencing.

This also applies in principle to the hydrolysis of proteins with supported specific endopeptidases and exopeptidases. Promising results were obtained by *Schwabe*[66] in preliminary experiments on the sequencing of peptides with an insolubilized leucine aminopeptidase. This enzyme was not covalently bound to a support, but was used in the form of an adsorbate on calcium phosphate gel.

7. Use of Insolubilized Enzymes to Obtain Reaction Products

7.1. Transformations

Of the 2000 or so enzymes known at present, only a few (mainly hydrolases) have found industrial application. In addition to bacterial proteinases for the detergent industry, proteinases, amylases, and amyloglucosidases are nowadays produced on the ton scale for the food industry[67]. As "industrial chemicals", these technical enzymes must naturally be stable and cheap products. The possibility of the replacement of these enzymes by supported types will depend on economic factors. Only cheap supports and simple methods for the fixation of the enzymes can be considered for these purposes.

7.1.1. Production of L-Methionine

Tosa et al. have developed a process for the continuous resolution of acetylated D,L-methionine by aminoacylase from *Aspergillus oryzae* adsorbed on DEAE-cellulose or DEAE-Sephadex[16, 17]. They use an enzyme column heated to 50 °C, through which the racemate solution flows in the upward direction. The enzyme deacetylates only the L-form, which can then be separated and isolated in the crystalline state. The column loses 40% of its activity only after an operating time of 4 weeks. This loss can be compensated without changing the column by introduction of a suitable quantity of soluble enzyme, which is then fixed. The pilot plant, which is shown schematically in Figure 4, is claimed to allow an output of up to 20 tons per month[68].

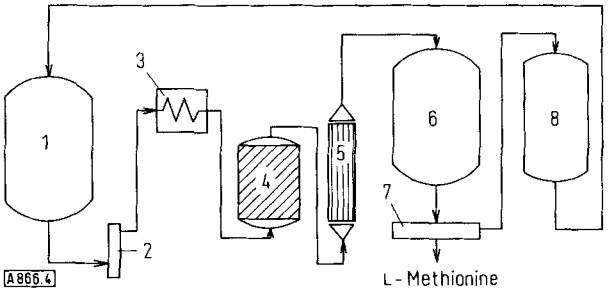


Fig. 4. Scheme of the continuous production of L-methionine from racemic acetyl-D,L-methionine by aminoacylase from *Aspergillus oryzae* adsorbed on DEAE-Sephadex [68].
1, Acetyl-D,L-methionine; 2, filter; 3, heat exchanger; 4, enzyme column; 5, evaporator; 6, crystallization vessel; 7, separator; 8, racemization vessel.

The superiority of the continuous process with the supported enzyme over the batch process with soluble enzyme is shown by the fact that with equal quantities of enzyme and under optimum conditions in each case, ten times as much L-methionine was obtained by the continuous enzyme reaction as by the batch process[17].

7.1.2. Saccharification of Starch and Production of Invert Sugar

Smiley et al. investigated the suitability of insolubilized amyloglucosidase from various species of *Aspergillus* for the continuous saccharification of partly hydrolyzed starch solutions. Since the viscous substrate solutions tend to block the column after a short operating time[19], a continuous feed stirred tank reactor was used. A 30% substrate solution was fed, with stirring at 55 °C, into a reaction vessel containing supported amyloglucosidase, and the glucose solution formed almost quantitatively was removed continuously[20]. The enzyme, which was adsorbed on DEAE-cellulose, showed no loss of activity during an operating time of 3—4 weeks. *Wilson* and *Lilly* used the same enzyme for the saccharification of starch, but in this case the enzyme was covalently bound to DEAE-cellulose activated with 2-amino-4,6-dichloro-*s*-triazine[49] (see also Scheme 4). The process was carried out in a column at 55 °C. A bed volume of insolubilized enzyme of only 5 × 13 cm yielded 3.8 kg of glucose/100 hours operating time, with no decrease in the activity of the bound enzyme. However, this process has not yet been used on an industrial scale. *Smiley* has recently been working on a process for the production of invert sugar by isomerization of glucose with supported microbial glucose isomerase[69]. Since glucose is a cheaper raw material than sucrose, this route could be more economical than *e.g.* the inversion of cane sugar by invertase from yeast.

7.1.3. Production of 6-Aminopenicillanic Acid

6-Aminopenicillanic acid, the starting material for numerous synthetic penicillins, is mainly produced microbiologically in industry by cleavage of benzylpenicillin with the enzyme penicillin amidase, which occurs in *E. coli*[70]. *Self, Kay,* and *Lilly* investigated the possibility of replacing this batch process by a continuous procedure based on the isolated, supported enzyme[71]. This would avoid the need for the complex fermentation process, the reaction would be easier to optimize, and the reaction product would be free from by-products and impurities.

The enzyme, which is easily isolated from *E. coli*, was covalently bound to DEAE-cellulose that had been activated

with a cyanuric acid derivative, 2,4-dichloro-6-carboxymethylamino-*s*-triazine. Unlike the relatively labile native enzyme, the insolubilized enzyme showed no loss of activity even after 11 weeks in the continuous column process at 37 °C. A special advantage of this process is that the 6-aminopenicillanic acid obtained is free from soluble, contaminating enzyme; subsequent purification is therefore unnecessary. The material obtained by microbiological reaction, on the other hand, must be carefully freed from protein impurities, which could lead to allergic reactions on the subsequent therapeutic use of penicillins. An interesting suggestion by *Shaltiel et al.* is that supported nonspecific proteinases may be used to split these proteins into immunologically inactive fragments[72].

7.1.4. Steroid Transformations

Another therapeutically important class of substances in which microbiological transformations play a decisive role is the steroids. However, the use of supported enzymes appears to present much greater difficulties here because of the instability of the steroid-transforming enzymes. *Mosbach* and *Larsson* attempted to use enzymes entrapped in polyacrylamide gel for the 11β-hydroxylation of Reichstein's "compound S" (17α,21-dihydroxy-4-pregnene-3,20-dione, 11-deoxycortisone) to obtain hydrocortisone and for the dehydrogenation of hydrocortisone to form prednisolone (11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione)[73].

Since the isolation of the 11β-hydroxylase required for the first reaction from the fungus *Curvularia lunata* was unsuccessful because of the instability of the enzyme, intact cells were polymerized into the gel and used in this form in the reaction. The Δ^1-dehydrogenase required for the second reaction step was concentrated from *Corynebacterium simplex*, but after entrapment in the gel it had only 7% of its original activity.

7.2. Syntheses

7.2.1. Synthesis of Poly-I:C

A particularly successful application of a supported synthesizing enzyme, the polynucleotide phosphorylase from *Micrococcus luteus*, was achieved by *Hoffmann et al.*[74] in the synthesis of the interferon inducer poly-I:C, a substance that is very effective against virus infections. This synthetic ribonucleic acid, consisting of paired homopolymer strands of polyriboinosinic acid (poly I) and polyribocytidylic acid (poly C), was required in large quantities for pharmacological and clinical testing. The two homopolymeric nucleotides are synthesized by enzymatic polymerization of the respective nucleoside-5'-diphosphate with polynucleotide phosphorylase. However, it proved very expensive to obtain large quantities of the enzyme. Moreover, great difficulty was encountered in the isolation of the polynucleotides from large incubation mixtures by exhaustive extraction with phenol, the enzyme being destroyed in every case.

The difficulties were overcome by covalent binding of the enzyme to a support, BrCN-activated cellulose. In the course of six months, during which the insolubilized enzyme was intermittently used for 40 polymerization cycles, there was no decrease in the synthesis output. The enzyme could now be separated from the reaction product by simple centrifugation. The homopolymers synthesized by the cellulose-bound enzyme corresponded in all their properties to those prepared with soluble enzyme.

7.2.2. Synthesis of Trinucleotides

Gassen made use of the synthetic properties of ribonuclease covalently bound to a highly substituted carboxymethyl cellulose to obtain the trinucleotides UAA, UAG, and UGA, which had previously been obtainable only by difficult chemical synthesis[75]. These trinucleotides, which are the termination codons of protein biosynthesis, are required for special investigations on the course of cell-free protein synthesis. Though ribonuclease normally catalyzes only degradation reactions, it can also be used for syntheses in the presence of a cyclic nucleoside phosphate as a donor and a nucleoside as an acceptor[76, 77]. However, it is practically impossible to make preparative use of this effect for the production of oligonucleotides, since the enzyme cannot be quantitatively removed from the reaction mixture[77]. The complete elimination of the enzyme is essential, since the oligonucleotides synthesized would otherwise be hydrolyzed during workup. Ribonuclease firmly bound to the support, on the other hand, is easily removed by centrifugation and can be used repeatedly.

8. Use of Supported Biologically Active Substances as Specific Adsorbents

The adsorbents mentioned are excellently suited for the isolation of proteins by affinity chromatography, which is superior to the usual methods because of its high specificity.

8.1. Purification and Isolation of Enzymes

The first purification of an enzyme by affinity chromatography was described by *Lerman*[78], who is also one coauthor of the first publication on the isolation of antibodies by this method[79]. As early as 1910, *Starkenstein*[80] observed the strong binding of amylase to insoluble starch, and *Holmbergh*[81] in 1933 reported the separation of α- and β-amylase by adsorption onto starch. Relatively few purifications of enzymes by affinity chromatography were described until the introduction of agarose as a support material (1967/68)[82]; examples of these earlier reports are the purification of flavokinase from liver on flavin-cellulose[83], the purification of flavin mononucleotide (FMN)-dependent enzymes on flavin phosphate-celluloses[84], and the purification of DNA polymerase on DNA-cellulose, the DNA having been fixed to the cellulose by UV irradiation[85].

Carboxypeptidase A, α-chymotrypsin, and Staphylococcus nuclease were the first enzymes to be purified by affinity chromatography on agarose derivatives[82]. The bound inhibitors were L-tyrosine-D-tryptophan for carboxypeptidase A, D-tryptophan methyl ester or *N*-ε-aminocaproyl-

D-tryptophan methyl ester for α-chymotrypsin, and 3'-(4-aminophenylphosphoryl)deoxythymidine-5'-phosphate for the nuclease. Diluted acetic acid (pH 3) was used for elution in all three cases.

The high specificity of the method can be seen by the fact that phosphodiesterase from spleen, which, like staphylococcus nuclease, hydrolyzes nucleic acids to 3'-phosphorylated fragments, was not retained by the support carrying Staphylococcus nuclease inhibitor[82]. Since this nuclease inactivated with diazotized 3'-(4-aminophenylphosphoryl)deoxythymidine-5'-phosphate was not adsorbed, it was possible to show with the same column the cause of the residual activity of the inactivated nuclease, *i.e.* a residual content of native enzyme[86].

The adverse effect of strong steric hindrance on the complex formation was demonstrated by the fact that α-chymotrypsin was adsorbed much more strongly by the support to which the inhibitor was bound *via* the ε-aminocaproic acid residue than in the case of direct binding. Here again, the enzyme inactivated with diisopropyl fluorophosphate was no longer adsorbed. If the enzyme was chromatographed at lower ionic strength, it was more strongly bound, but this offered no advantage, since the possibility of non-specific adsorption of other proteins simultaneously increased[82].

Enzymes for therapeutic use cannot generally be administered orally. For successful intravenous application, the purity of these enzymes must be extremely high to minimize immunological defense reactions.

Asparaginase from *E. coli*, which is therapeutically active against several types of leukemia, was isolated by expensive multi-stage purification processes (heat treatment, solvent precipitation, gel filtration, column chromatography). The products obtained had specific activities of 270—400 units/mg[87, 127]. By affinity chromatography on ε-aminocaproyl-D-asparagine-agarose, the asparaginase from *E. coli* extracts can be obtained in a much higher purity in a single step (specific activity 10000 units/mg) (Fig. 5). Elution is carried out with effector solution (1 mmol/l D-asparagine).

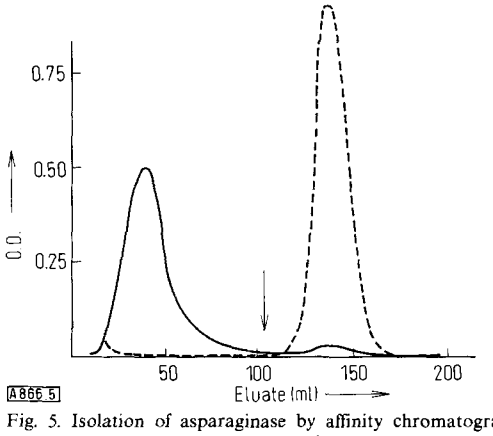


Fig. 5. Isolation of asparaginase by affinity chromatography of an *E. coli* extract on agarose-bound ε-aminocaproyl-D-asparagine. 0.001 M D-asparagine solution in buffer was used for the desorption of the asparaginase (arrow) [57]. ——: protein (measured at 280 nm); – – –: asparaginase (measured at 570 nm).

Though asparaginase hydrolyzes the enantiomorph D-asparagine of the natural substrate L-asparagine at pH 8.6 (pH value in the chromatography) at 5.5% of the rate of hydrolysis of L-asparagine, the D-asparagine-agarose could be used more than ten times without appreciable loss of capacity[57].

Papain was purified by affinity chromatography on an agarose-bound inhibitor peptide[88] and on agarose-bound 4-aminophenylmercury(II) acetate[89]. In this last case, $HgCl_2$ solution was used for elution. Since mercury reacts with SH proteins in general, a mercury resin can be used as a group-specific chromatography resin.

Affinity chromatography on supported coenzymes permits the adsorption of all enzymes whose catalytic activity depends on these coenzymes. Since these enzymes form complexes of different strengths with the bound coenzyme, they are eluted successively by increasing salt concentration in the eluant more or less completely separated from one

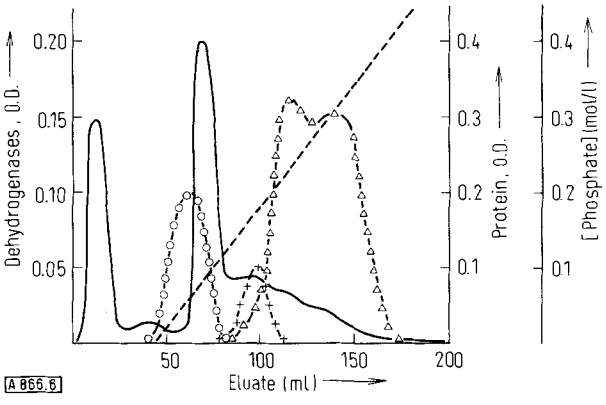


Fig. 6. Isolation of glucose-6-phosphate dehydrogenase (○), lactate dehydrogenase (+), and threonine dehydrogenase (△) by affinity chromatography of a dialyzed *Ps. oxalaticus* extract on NAD-cellulose [90]. Dehydrogenases (see above), (measured at 366 nm); ——: protein (measured at 280 nm); – – –: phosphate gradient (mol/l).

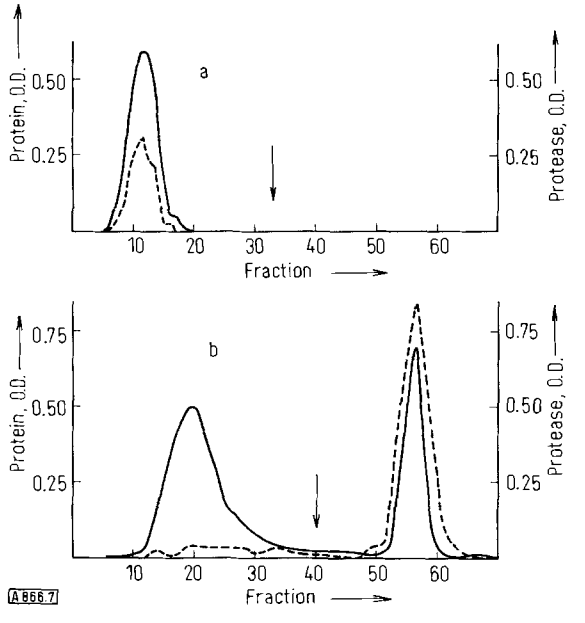


Fig. 7. a) Chromatography of a prepurified wheat malt extract on unsubstituted agarose. b) Isolation of the proteinases from the same wheat malt extract by affinity chromatography on a hemoglobin-agarose column. 0.1 N Acetic acid is used for the elution of the proteinases (arrow) [91].
——: protein (measured at 280 nm); – – –: proteinase (measured at 670 nm).

another. Thus glucose-6-phosphate dehydrogenase, lactate dehydrogenase, and threonine dehydrogenase were adsorbed from a *Ps. oxalaticus* extract on NAD-cellulose and separated from one another by elution with increasingly concentrated phosphate buffer[90]. The NADP-dependent glucose-6-phosphate dehydrogenase was retarded least (Fig. 6).

Difficulty was encountered in the isolation of the proteinases from wheat malt, since the proteinases aggregate with other contaminating proteins. Affinity chromatography on covalently bound substrate (hemoglobin) led to a preparation that showed only proteolytically active bands on disk electrophoresis (Fig. 7)[91].

A survey of communications on this topic is presented in Table 1.

Affinity chromatography can also be used for enzymological problems besides the isolation of enzymes. Pig carboxypeptidase B, in addition to its known specificity against basic amino acids, has a slight specificity similar to that of carboxypeptidase A, which suggests that it is contaminated

Table 1. Isolation of enzymes by affinity chromatography.

Enzyme	Support	Effector	Ref.
On bound inhibitors:			
Acetylcholinesterase	Agarose	4-Ammoniophenyltrimethylammonium dibromide	[92]
	Agarose	4-Ammoniophenyltrimethylammonium dichloride	[93]
	Agarose	Trimethyl-[*N*-methyl-*N*-(4-aminophenyl)-3-carbamoyloxyphenyl]ammonium chloride	[93]
L-Asparaginase	Agarose	D-Asparagine	[57]
Carboxypeptidase A	Agarose	L-Tyrosyl-D-tryptophan	[82]
	Agarose	D-Tryptophan	[94]
	Cellulose	Glycyl-D-phenylalanine	[95]
Carboxypeptidase B	Agarose	D-Alanyl-L-arginine	[96]
	Agarose	D-Tryptophan	[94]
	Carboxymethyl-Sephadex	D-Arginine	[97]
	Carboxymethyl-Sephadex	D-Phenylalanine	[97]
	Cellulose	Glycyl-D-arginine	[95]
Chymotrypsin	Agarose	D-Tryptophan methyl ester	[82]
	Cellulose	Glycyl-D-phenylalanine	[95]
	Ethylene-maleic anhydride copolymer	Trypsin-kallikrein inhibitor	[128]
Dihydrofolate reductase	Agarose	4-Amino-10-methylpteroylglutaminic acid	[98]
	Aminoethyl-Biogel P-150	4-Amino-10-methylpteroylglutaminic acid	[99]
β-Galactosidase	Agarose Polyacrylamide	4-Aminophenyl-β-D-thiogalactopyranoside	[56]
Kallikrein	Ethylene-maleic anhydride copolymer (modified)	Trypsin-kallikrein inhibitor	[129]
Neuraminidase	Agarose	*N*-(4-Aminophenyl)oxamidic acid	[100]
Papain	Agarose	Glycylglycyl-(*O*-benzyl)-L-tyrosine-L-arginine	[88]
Pepsin	Agarose	Poly-L-lysine	[101]
Plasmin	Ethylene-maleic anhydride copolymer (modified)	Trypsin-kallikrein inhibitor	[129]
Plasminogen	Agarose	L-Lysine	[102]
RNase (pancreatic)	Agarose	5'-(4-Aminophenylphosphoryl)uridine 2',3'-cyclophosphate	[103]
Staphylococcus nuclease	Agarose	3'-(4-Aminophenylphosphoryl)deoxythymidine 5'-phosphate	[82]
Thrombin	Agarose	4-Chlorobenzylamine	[104]
Trypsin	Agarose	Ovomucoid	[105, 106]
	Cellulose	4-(4'-Aminophenoxypropoxy)benzamidine	[107]
	Ethylene-maleic anhydride copolymer	Trypsin-kallikrein inhibitor	[128]
Tyrosine hydroxylase	Agarose	3-Iodotyrosine	[108]
On bound substrates:			
DNA polymerase	Cellulose	DNA	[85]
	Agarose	DNA	[109]
Flavokinase	Cellulose	Flavin	[83]
Phosphomonoesterases	Cellulose	Phosphate	[110]
Phosphodiesterases	Cellulose	Glycerophosphate	[110]
Proteases (from wheat)	Agarose	Hemoglobin	[91]
Tyrosinase	Cellulose	Phenol	[78]
On bound coenzymes:			
Glucose-6-phosphate dehydrogenase	Cellulose	NAD	[90]
Glycolate apooxidase	Cellulose	FMN	[84]
Lactate dehydrogenase	Cellulose	NAD	[90]
NADPH-cytochrome c apooxidase	Cellulose	FMN	[84]
Pyridoxine phosphate apooxidase	DEAE cellulose	FMN	[84]
Threonine dehydrogenase	Cellulose	NAD	[90]
On bound allosteric effectors:			
Chorismate mutase	Agarose	L-Tryptophan	[111]
3-Deoxy-D-arabinoheptulonate 7-phosphate synthetase	Agarose	L-Tyrosine	[112]
On bound group-specific reagents:			
Papain	Agarose	4-Aminophenylmercury(II) acetate	[89]

with this enzyme. Purification by affinity chromatography on agarose-bound inhibitor increased the specific activity without removing the carboxypeptidase A-like activity. A control experiment showed that carboxypeptidase A was not retained by the column. We are therefore dealing here with a secondary activity[96].

Ribosomes for protein biosynthesis in cell-free systems can be selected by affinity chromatography to such a degree that a certain protein is synthesized preferentially. The incorporation of radioactive amino acids into tyrosine aminotransferase was increased by a factor of more than ten by the use of ribosomes from hepatoma cells that had been concentrated on pyridoxamine phosphate-agarose, the supported coenzyme of transamination[113].

8.2. Isolation of Naturally Occurring Inhibitors

The isolation of naturally occurring enzyme inhibitors by affinity chromatography from crude extracts or partially purified solutions on covalently bound enzymes has been described by several authors.

Most of the articles on this topic were published by *Fritz*, *Werle*, and others, who purified proteinase inhibitors on insolubilized proteinases[114–118]. Examples of the isolation of proteinase inhibitors with insolubilized trypsin are given in Table 2. A DNase I inhibitor has been isolated from calf thymus extracts on agarose-bound DNase I[119]. RNase bound to CM-cellulose has been used for the purification of an RNase inhibitor from rat liver[120].

Table 2. Preparative isolation of some naturally occurring proteinase inhibitors by affinity chromatography on insolubilized trypsins. EMA = ethylene-maleic anhydride copolymer; CM = carboxymethyl.

Inhibitor from	Support	Ref.
Pancreas (pig)	EMA, modified	[114]
Pancreas (sheep)	EMA, modified	[114]
Lung, liver (ox)	EMA	[114]
Leech	EMA, modified	[114]
Leech	CM-cellulose	[114]
Seminal vesicles (guinea pig)	EMA, modified	[114]
Seminal plasma (boar)	Polyacrylamide	[114]
Seminal plasma (man)	CM-cellulose	[116]
Wheat germs	CM-cellulose	[117]
Peanuts	CM-cellulose	[117]
Sea anemone	CM-cellulose	[118]

8.3. Use in Immunology

Water-insoluble antigens are used for the isolation of the corresponding antibodies, which can be obtained free from other serum components and free from antigens in this way[5]. Unprecipitable, incomplete antibodies and antibodies that cannot be precipitated because of their low concentration in the serum can also be isolated by affinity chromatography and quantitatively determined[5].

Most natural antigens have several centers for complex formation with antibodies. Each center is associated with one specific antibody. The covalent binding of the antigen to the support may render one center or another inaccessible to its antibodies, so that complex formation cannot occur. In this case, affinity chromatography yields an antibody population whose spectrum differs from that of the antibody population in whole blood. Since the various antibodies form complexes of different strengths with the various centers of the antigen, non-uniform elution of antibodies from the insoluble antigen can modify the spectrum of the antibody population too. The easily eluted components are then enriched[5].

Campbell et al.[79] were the first to bind crystalline bovine albumin covalently to an insoluble polymeric support, *i.e.* *p*-aminobenzyl cellulose, by diazo coupling for purification of bovine albumin antiserum from rabbits. After adsorption, the complex was washed with 1% NaCl solution until free from protein, and was then dissociated at pH 3.2. The yield was influenced by the contact time between the antibody and the insolubilized antigen. 86% of the precipitable antibody that had been adsorbed by the insolubilized antigen could be recovered by immediate elution, whereas only 56% could be recovered 12 hours later.

Another example is the purification of insulin antibodies on agarose-bound insulin[121]. It was found that different insulin-agarose derivatives differed in their immunoreactivity:

insulin-Phe(B1)-agarose	38%
insulin-Lys(B29)-agarose	59%
acetylinsulin-Lys(B29)-agarose	72%

Supported haptens have also been used as an immunoadsorbent for antibodies[122]. There have been fewer descriptions of the opposite application, *i.e.* the isolation of an antigen on a covalently bound antibody. One example is the isolation of insulin from serum on agarose-bound insulin antibodies[123].

8.4. Use in Nucleic Acid Chemistry

The interaction known as hybridization between DNA and complementary RNA, between complementary oligonucleotides, and between nucleotides and nucleosides can also be used in affinity chromatography. Thus T_4-specific RNA has been chromatographed on cellulose-bound T_4-DNA[124]. Phe-tRNA and Lys-tRNA have been concentrated on pT- and pU-cellulose and on pA-cellulose respectively[125]. Thymidylate-cellulose retained mainly adenosine and polyadenylate[126][*].

Received: December 17, 1971 [A 866 IE]
German version: Angew. Chem. *84*, 319 (1972)
Translated by Express Translation Service, London

[*] While this article was in press, another review on affinity chromatography came to our notice: *R. H. Reiner* and *A. Walch*, Chromatographia *4*, 578 (1971).

[1] *R. Goldman, L. Goldstein,* and *E. Katchalski* in *G. R. Stark:* Biochemical Aspects of Reactions on Solid Supports. Academic Press, New York 1971.

[2] *E. Katchalski* in *P. Desnuelle, H. Neurath,* and *M. Ottesen:* Structure-Function Relationships of Proteolytic Enzymes. Munksgaard, Copenhagen 1970, pp. 198ff; *E. Katchalski, I. Silman,* and *R. Goldman,* Advan. Enzymol. *34*, 445 (1971).

[3] *L. Goldstein* in *D. Perlman:* Fermentation Advances. Academic Press, New York 1969, pp. 391ff.

[4] *L. Goldstein* and *E. Katchalski,* Z. Anal. Chem. *243*, 375 (1968).

[5] *I. H. Silman* and *E. Katchalski,* Annu. Rev. Biochem. *35*, 873 (1966).

[6] *A. D. McLaren* and *L. Packer*, Advan. Enzymol. *33*, 269 (1970).

[7] *F. Friedberg*, Chromatogr. Rev. *14*, 121 (1971).

[8] *K. Mosbach*, Sci. Amer. *224* (3), 26 (1971).

[9] *G. J. H. Melrose*, Rev. Pure Appl. Chem. *21*, 83 (1971).

[10] *J. Gryszkiewicz*, Folia Biol. *19*, 119 (1971).

[11] *G. Kay*, Proc. Biochem. *3* (8), 36 (1968).

[12] *G. Manecke*, Pure Appl. Chem. *4*, 507 (1962).

[13] *G. Manecke*, Naturwissenschaften *51*, 25 (1964).

[14] *P. Cuatrecasas* and *C. B. Anfinsen* in *S. P. Colowick* and *N. O. Kaplan:* Methods in Enzymology. Academic Press, New York 1971, Vol. 22, pp. 345ff.

[15] *P. Cuatrecasas* and *C. B. Anfinsen*, Annu. Rev. Biochem. *40*, 259 (1971).

[16] *T. Tosa, T. Mori, N. Fuse*, and *I. Chibata*, Agr. Biol. Chem. *33*, 1047 (1969).

[17] *T. Tosa, T. Mori*, and *I. Chibata*, Agr. Biol. Chem. *33*, 1053 (1969).

[18] *H. Suzuki, Y. Ozawa*, and *H. Maeda*, Agr. Biol. Chem. *30*, 807 (1966).

[19] *M. J. Bachler, G. W. Strandberg*, and *K. L. Smiley*, Biotechnol. Bioeng. *12*, 85 (1970).

[20] *K. L. Smiley*, Biotechnol. Bioeng. *13*, 309 (1971).

[21] *P. Bernfeld* and *J. Wan*, Science *142*, 678 (1964).

[22] *G. P. Hicks* and *S. J. Updike*, Anal. Chem. *38*, 726 (1966).

[23] *Y. Degan* and *T. Miron*, Biochim. Biophys. Acta *212*, 362 (1970).

[24] *L. Goldstein, M. Pecht, S. Blumberg, D. Atlas*, and *Y. Levin*, Biochemistry *9*, 2322 (1970).

[25] *R. Axen* and *S. Ernback*, Europ. J. Biochem. *18*, 351 (1971).

[26] *D. Gabel* and *B. v. Hofsten*, Europ. J. Biochem. *15*, 410 (1970).

[27] *C. K. Glassmeyer* and *J. D. Ogle*, Biochemistry *10*, 786 (1971).

[28] *G. Kay* and *M. D. Lilly*, Biochim. Biophys. Acta *198*, 276 (1970).

[29] *E. M. Crook, K. Brocklehurst*, and *C. H. Wharton* in *S. P. Colowick* and *N. O. Kaplan:* Methods in Enzymology. Academic Press, New York 1971, Vol. 19, pp. 963ff.

[30] *G. Manecke*, Biochem. J. *107*, 2P (1968).

[31] *L. Goldstein* in *S. P. Colowick* and *N. O. Kaplan:* Methods in Enzymology. Academic Press, New York 1971, Vol. 19, pp. 935ff.

[32] *L. Goldstein, Y. Levin*, and *E. Katchalski*, Biochemistry *3*, 1913 (1964).

[33] *S. A. Barker* and *R. Epton*, Proc. Biochem. *5* (8), 14 (1970).

[34] *A. Conte* and *K. Lehmann*, Hoppe-Seylers Z. Physiol. Chem. *352*, 533 (1971).

[35] *H. H. Weetall*, Science *166*, 615 (1969).

[36] *H. H. Weetall*, Biochim. Biophys. Acta *212*, 1 (1970).

[37] *W. F. Line, A. Kwong*, and *H. H. Weetall*, Biochim. Biophys. Acta *242*, 194 (1971).

[38] *P. J. Robinson, P. Dunnill*, and *M. D. Lilly*, Biochim. Biophys. Acta *242*, 659 (1971).

[39] *W. Brümmer, N. Hennrich, M. Klockow, H. Lang*, and *H. D. Orth*, Europ. J. Biochem. *25*, 129 (1972).

[40] *M. A. Mitz* and *L. J. Summaria*, Nature *189*, 576 (1961).

[41] *S. A. Barker, A. N. Emery*, and *I. M. Novais*, Proc. Biochem. *6* (10), 11 (1971).

[42] *P. Cuatrecasas*, J. Biol. Chem. *245*, 3059 (1970).

[43] *J. J. Cebra, D. Givol, I. H. Silman*, and *E. Katchalski*, J. Biol. Chem. *236*, 1720 (1961).

[44] *P. Cresswell* and *A. R. Sanderson*, Biochem. J. *119*, 447 (1970).

[45] *R. Haynes* and *K. A. Walsh*, Biochem. Biophys. Res. Commun. *36*, 235 (1969).

[46] *W. E. Hornby, M. D. Lilly*, and *E. M. Crook*, Biochem. J. *107*, 669 (1968).

[47] *A. D. McLaren*, Enzymologia *21*, 356 (1960).

[48] *A. D. McLaren*, Advan. Enzymol. *29*, 28 (1966).

[49] *J. H. Wilson* and *M. D. Lilly*, Biotechnol. Bioeng. *11*, 349 (1969).

[50] *M. D. Lilly* and *A. K. Sharp*, The Chem. Eng. *215*, CE 12 (1968).

[51] *W. E. Hornby, M. D. Lilly*, and *E. M. Crook*, Biochem. J. *98*, 420 (1966).

[52] *I. H. Silman, M. Albu-Weissenberg*, and *E. Katchalski*, Biopolymers *4*, 441 (1966).

[53] *B. Mattiason* and *K. Mosbach*, Biochim. Biophys. Acta *235*, 253 (1971).

[54] *G. Feinstein*, Naturwissenschaften *58*, 389 (1971).

[55] *J. K. Inman* and *H. M. Dintzis*, Biochemistry *8*, 4074 (1969).

[56] *E. Steers jr., P. Cuatrecasas*, and *H. B. Pollard*, J. Biol. Chem. *246*, 196 (1971).

[57] *T. Kristiansen, M. Einarsson, L. Sundberg*, and *J. Porath*, FEBS-Lett. *7*, 294 (1970).

[58] *S. J. Updike* and *G. P. Hicks*, Science *158*, 270 (1967).

[59] *S. J. Updike* and *G. P. Hicks*, Nature *214*, 986 (1967).

[60] *G. G. Guilbault* and *J. G. Montalvo*, J. Amer. Chem. Soc. *92*, 2533 (1970).

[61] *G. G. Guilbault* and *E. Hrabankova*, Anal. Lett. *3*, 53 (1970).

[62] *H. Neu* and *L. Heppel*, J. Biol. Chem. *239*, 2927 (1964).

[63] *M. Uziel* and *J. X. Khym*, Biochemistry *8*, 3254 (1969).

[64] *R. A. Zingaro* and *M. Uziel*, Biochim. Biophys. Acta *213*, 371 (1970).

[65] *J. C. Lee*, Biochim. Biophys. Acta *235*, 435 (1971).

[66] *C. Schwabe*, Biochemistry *8*, 795 (1969).

[67] *H. Uhlig*, Naturwissenschaften *57*, 261 (1970).

[68] *M. D. Lilly* and *P. Dunnill*, Proc. Biochem. *6* (8), 29 (1971).

[69] *K. L. Smiley* , Chem. Engng. News *49* (7), 86 (1971).

[70] *M. Cole*, Proc. Biochem. *2* (4), 35 (1967).

[71] *D. A. Self, G. Kay, M. D. Lilly*, and *P. Dunnill*, Biotechnol. Bioeng. *11*, 337 (1969).

[72] *S. Shaltiel, R. Mizrahi, Y. Stupp*, and *M. Sela*, Europ. J. Biochem. *14*, 509 (1970).

[73] *K. Mosbach* and *P. Larsson*, Biotechnol. Bioeng. *12*, 19 (1970).

[74] *C. H. Hoffman, E. Harris*, and *S. Chodroff, S. Michelson, J. W. Rothrock, E. Peterson*, and *W. Reuter*, Biochem. Biophys. Res. Commun. *41*, 710 (1970).

[75] *H. G. Gassen*, Biochem. Biophys. Res. Commun. *44*, 1410 (1971).

[76] *M. R. Bernfield*, J. Biol. Chem. *241*, 2014 (1966).

[77] *H. G. Gassen*, FEBS-Lett. *14*, 225 (1971).

[78] *L. S. Lerman*, Proc. Nat. Acad. Sci. USA *39*, 232 (1953).

[79] *D. H. Campbell, E. Lüscher*, and *L. S. Lerman*, Proc. Nat. Acad. Sci. USA *37*, 575 (1951).

[80] *E. Starkenstein*, Biochem. Z. *24*, 210 (1910).

[81] *O. Holmbergh*, Biochem. Z. *258*, 134 (1933).

[82] *P. Cuatrecasas, M. Wilchek*, and *C. B. Anfinsen*, Proc. Nat. Acad. Sci. USA *61*, 636 (1968).

[83] *C. Arsenis* and *D. B. McCormick*, J. Biol. Chem. *239*, 3093 (1964).

[84] *C. Arsenis* and *D. B. McCormick*, J. Biol. Chem. *241*, 330 (1966).

[85] *R. M. Litman*, J. Biol. Chem. *243*, 6222 (1968).

[86] *P. Cuatrecasas*, J. Biol. Chem. *245*, 574 (1970).

[87] *H. A. Whelan* and *J. C. Writon jr.*, Biochemistry *8*, 2386 (1969).

[88] *S. Blumberg, I. Schechter*, and *A. Berger*, Europ. J. Biochem. *15*, 97 (1970).

[89] *L. A. A. E. Sluyterman* and *J. Wijdenes*, Biochim. Biophys. Acta *200*, 595 (1970).

[90] *C. R. Lowe* and *P. D. G. Dean*, FEBS-Lett. *14*, 313 (1971).

[91] *G. K. Chua* and *W. Bushuk*, Biochem. Biophys. Res. Commun. *37*, 545 (1969).

[92] *N. Kalderon, I. H. Silman, S. Blumberg*, and *Y. Dudai*, Biochim. Biophys. Acta *207*, 560 (1970).

[93] *J. D. Berman* and *M. Young*, Proc. Nat. Acad. Sci. USA *68*, 395 (1971).

[94] *G. R. Reeck, K. A. Walsh, M. A. Hermodson*, and *H. Neurath*, Proc. Nat. Acad. Sci. USA *68*, 1226 (1971).

[95] *J. R. Uren*, Biochim. Biophys. Acta *236*, 67 (1971).

[96] *M. Sokolovsky* and *N. Zisapel*, Biochim. Biophys. Acta *250*, 203 (1971).

[97] *H. Akanuma, A. Kasuga, T. Akanuma*, and *M. Yamasaki*, Biochem. Biophys. Res. Commun. *45*, 27 (1971).

[98] *B. T. Kaufman* and *J. V. Pierce*, Biochem. Biophys. Res. Commun. *44*, 608 (1971).

[99] *J. S. Erickson* and *C. K. Mathews*, Biochem. Biophys. Res. Commun. *43*, 1164 (1971).

[100] *P. Cuatrecasas* and *G. Illiano*, Biochem. Biophys. Res. Commun. *44*, 178 (1971).

[101] *B. Nevaldine* and *B. Kassell*, Biochim. Biophys. Acta *250*, 207 (1971).

[102] *D. J. Deutsch* and *E. T. Mertz*, Science *170*, 1095 (1970).

[103] *M. Wilchek* and *M. Gorecki*, Europ. J. Biochem. *11*, 491 (1969).

[104] *A. R. Thompson* and *E. W. Davie*, Biochim. Biophys. Acta *250*, 210 (1971).

[105] *G. Feinstein*, FEBS-Lett. *7*, 353 (1970).

[106] *N. C. Robinson, R. W. Tye, H. Neurath*, and *K. A. Walsh*, Biochemistry *10*, 2743 (1971).

[107] *G. W. Jameson* and *D. T. Elmore*, Biochem. J. *124*, 66 P (1971).

[108] *W. N. Poillon*, Biochem. Biophys. Res. Commun. *44*, 64 (1971).

[109] *M. S. Poonian, A. J. Schlabach*, and *A. Weissbach*, Biochemistry *10*, 424 (1971).

[110] *P. D. G. Dean, S. R. Willetts*, and *J. E. Blanch*, Anal. Biochem. *41*, 344 (1971).

[111] *B. Sprossler* and *F. Lingens*, FEBS-Lett. *6*, 232 (1970).

[112] *W. W. C. Chan* and *M. Takahashi*, Biochem. Biophys. Res. Commun. *37*, 272 (1969).

[113] *J. V. Miller jr., P. Cuatrecasas*, and *E. B. Thompson*, Proc. Nat. Acad. Sci. USA *68*, 1014 (1971).

[114] *H. Fritz, B. Brey, M. Müller*, and *M. Gebhardt* in *H. Fritz* and *H. Tschesche*: Proceedings of the First International Research Conference on Protein Inhibitors. de Gruyter, Berlin 1971, pp. 28 ff.

[115] *M. Laskowski jr.* and *R. W. Sealock* in *P. D. Boyer*: The Enzymes. Academic Press, New York 1971, Vol. 3, pp. 375 ff.

[116] *E. Fink, E. Jaumann, H. Fritz, H. Ingrisch*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *352*, 1591 (1971).

[117] *H. Fritz, M. Gebhardt, R. Meister, K. Illchmann*, and *K. Hochstrasser*, Hoppe-Seylers Z. Physiol. Chem. *351*, 571 (1970).

[118] *H. Fritz, B. Brey*, and *L. Béress*, Hoppe-Seylers Z. Physiol. Chem. *353*, 19 (1972).

[119] *U. Lindberg* and *S. Eriksson*, Europ. J. Biochem. *18*, 474 (1971).

[120] *A. A. M. Gribenau, J. G. G. Schoenmakers, M. van Kraalhamp*, and *H. Bloemendal*, Biochem. Biophys. Res. Commun. *38*, 1064 (1970).

[121] *P. Cuatrecasas*, Biochem. Biophys. Res. Commun. *35*, 531 (1969).

[122] *L. Wofsy* and *B. Burr*, J. Immunol. *103*, 380 (1969).

[123] *Y. Ahanuma, T. Kuzuya, M. Hayashi, T. Ide*, and *N. Kuzuya*, Biochem. Biophys. Res. Commun. *38*, 947 (1970).

[124] *E. K. F. Bautz* and *B. D. Hall*, Proc. Nat. Acad. Sci. USA *48*, 400 (1962).

[125] *S. Erhan, L. Northrup*, and *F. A. Leach*, Proc. Nat. Acad. Sci. USA *53*, 646 (1969).

[126] *E. G. Sander, D. B. McCormick*, and *L. D. Wright*, J. Chromatogr. *21*, 419 (1966); see also *H. Schott* and *G. Greber*, Angew. Chem. *82*, 448 (1970); Angew. Chem. internat. Edit. *9*, 465 (1970).

[127] *A. Arens, E. Rauenbusch, E. Irion, O. Wagner, K. Bauer*, and *W. Kaufmann*, Hoppe-Seylers Z. Physiol. Chem. *351*, 197 (1970).

[128] *H. Fritz, H. Schult, M. Neudecker*, and *E. Werle*, Angew. Chem. *78*, 775 (1966); Angew. Chem. internat. Edit. *5*, 735 (1966).

[129] *H. Fritz, B. Brey, A. Schmal*, and *E. Werle*, Hoppe-Seylers Z. Physiol. Chem. *350*, 617 (1969).

Chemical Plant Protection — Past, Present, and Future[**]

By Klaus Sasse[*]

Dedicated to Professor Richard Wegler on his 65th birthday

Chemical plant protection greatly contributes to ensuring good harvests and is therefore of considerable agricultural and economic importance. After thirty years of systematic research we are now in possession of powerful chemical agents active against most of the significant enemies of cultivated plants, but the constant change in nature always calls for more and better plant protection agents. These agents play a mostly well-known part in environmental pollution and in the overall toxic situation, and one of the aims of future development is to reduce further the dangers to man and the environment.

1. The Causes of Damage to Cultivated Plants

Darwin described the equilibrium in nature in terms of the struggle for survival. When man began to exploit and change nature, he disturbed this equilibrium and took up the fight against the forces that constantly try to re-establish it.

Plants have of course always had their share of natural enemies, because animals (and many lower plants) cannot synthesize organic substances from carbon dioxide and water and must feed on plants or other animals.

Man has long known, therefore, that he cannot reap all that he sows, but he was ignorant of many of the reasons for this failure. The most obvious was the damage done by insects, which constitute the largest zoological class, with over half a million known species, at least 5000 of which cause damage to plants. Besides these, mites, slugs, birds, and rodents have for centuries been uninvited guests to our cultivated crops.

By contrast, the causes of plant diseases remained mysterious for a very long time, although—as many historical documents[1] testify—the diseases themselves were recognized long ago. Thus, blight and mildew of corn belong to the punishments for disobedience under Mosaic law (Deuteronomy, XXVIII, 22). The Romans celebrated a yearly festival, the Robigalia, which was supposed to protect their cereal crops from rust. In his Naturalis Historia (Vol. 17/18), *Pliny the Elder* described in 77 AD several remedies against cereal diseases. While it was known even in ancient times that some human diseases such as leprosy are transmitted by contact or air, only in the last century was it established that parasites cause plant diseases; this emerged from the detailed investigations of *De Bary* on the

[*] Dr. K. Sasse
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG,
509 Leverkusen-Bayerwerk (Germany)

[**] Based on a lecture to the General Meeting of the Gesellschaft Deutscher Chemiker at Karlsruhe on September 17, 1971.

biology and physiology of fungi (1853), and those of *Kühn* on the role of fungi in infections and diseases (1858). Not much later, it became possible to attribute numerous plant diseases to bacteria and viruses following the publication of *Pasteuer*'s (1822—1895) and *Koch*'s results (1876).

Besides animal parasites, phytopathogenic fungi, bacteria, and viruses, damage is also caused by weeds, since these take the light, moisture, and nutrients from the cultivated plants. It depends on numerous local factors which of these causes of plant damage are involved, and to what extent, and since nature is dynamic their combination changes all the time both qualitatively and quantitatively whenever a change in the environment, *e.g.* as a result of cultivation and plant protection, favors or disfavors certain species in the ecological community.

Particularly important in this connection are the infection and infestation of previously unaffected areas through trade in seeds, plants, and other produce. Thus, catastrophic damage was caused to French vineyards successively by powdery mildew, phylloxera, and downy mildew in the second half of the last century as new varieties were introduced; the Colorado beetle, which reached Europe from the USA during World War I, spread from France to Germany, and then deep into Eastern Europe; the blue mold of tobacco introduced into Britain from the USA in 1958, swept across Europe to the Middle East and North Africa.

2. Effects of Damage to Agricultural Produce

2.1. The Economic Aspect

A low yield in agricultural countries means a marked drop in the gross national product, threatening the foundations of the economy; this in turn can lead to inflation, disruption of economics, social unrest, and possibly political changes. For example, late blight almost fully destroyed the potato crop in Ireland in 1845/46, which was responsible for the death of 250000 people through starvation and for the emigration of 2.5 million people. The same disease caused a famine in Germany in 1916/17 (rutabaga winter). Around 1870, coffee rust devastated coffee plantations in Ceylon to such an extent that the cultivation of this plant was abandoned altogether and the plantations changed over to tea. The migration of the Mexican boll weevil from Mexico to the southern states of the USA around the turn of the century roughly halved the harvests, so that many farms were abandoned and many people—especially negroes—lost their livelihood. The Panama disease forced farmers in various places in the Caribbean to abandon the cultivation of bananas over large areas in the first half of this century; thus, in 1940, the area producing bananas dropped to about one-half in Jamaica, the greatest banana exporter, this product providing 52% of its export earnings.

2.2. Effect on World Food Supplies

A sufficient amount of wholesome food is essential for health and work. The question arises whether, and if so how, future generations can be assured of a minimum existence level of food intake in view of the population explosion. In the absence of widespread contraception or a rise in the standard of living, which has a similar effect, the population of the world will increase from 3.5 to 6 billions in the next 30 years. According to data released by the Food and Agriculture Organization (FAO) of the UN, 500 million people are at present undernourished and 1.5 billion are incorrectly or insufficiently nourished.

The hunger of the world is protein hunger. Adequate food consists of 25% of food from animal sources and 75% of food from vegetable sources. It seems paradoxical that agricultural productivity is lowest in the agricultural countries (Table 1)[2]. Raising this productivity in such

Table 1. Yields per unit area (in 100-kg units per hectare).

Area	Rice			Wheat	
	1945	1955	1965	1964/65	% of world production
Japan	20	30	50		
India and Pakistan	13	13	16		
USSR				10.9	27.9
Europe (without USSR)				20.9	22.9
North America and Central America				16.4	20.2
Asia (without China and USSR)				8.6	11.9
China				6.9 [a]	6.0

[a] Value for 1953.

Table 2. Means of raising agricultural production.

a) Increasing the cultivated land area
b) Improving the choice of location for certain cultivated plants
c) Treating and improving the soil (loosening, irrigation, drainage, and fertilization)
d) Selection and breeding
e) Rationalizing the agricultural operations
f) Improving the structure of the agricultural sector
g) Combating pests and weeds
h) Correct handling of seeds and harvested produce (transport, storage, and preservation)

countries by the means listed in Table 2 is vital for adequate nutrition of the world. It is estimated that plant protection alone can double the rice yield in Asia.

2.3. The Agricultural (Economic) Aspect

In highly industrialized countries the most important aspect of agricultural production is not whether it can feed the population, but whether it would be profitable to do so. The main factors that ensure profitability are a high yield per unit area, good-quality marketable produce and—since labor is getting scarcer and dearer—rationalization of production methods. The data in Tables 3 and 4 show how much agricultural measures can raise the yield per unit area: in the USA figures doubled for wheat and cotton and trebled for corn *(Zea mays)* in 30 years.

Table 3. Data for potato cultivation in Germany.

Period	Area involved (ha)	Yield (100-kg units/ha)
1901—1905	1262000	61.7
1921—1925	1360000	71.6
1941—1945	1141000	94.7
1947	851000	124.5
1950	684000	170.3

Table 4. Yields of various crops in the USA.

Crop	Yield (100-kg units/ha)			
	1938	1948	1958	1968
Wheat	8.4	11.4	17.4	18.0
Corn	16.3	25.0	30.3	46.1
Cotton	2.6	3.4	5.1	5.6

2.4. The Health Aspect

Contamination of the food by insects, insect excrement, fungi, bacteria, viruses, and other plants or their parts reduces the quality, and—what is more important—can be harmful to human and animal health[3].

The toxic alkaloids of the cereal parasite *Claviceps purpurea* (ergot alkaloids) used to cause a great deal of poisoning (ergotism). In most civilized countries, therefore, the maximum permissible ergot content of cereals or flour is fixed by law. The increased incidence of cirrhosis and cancer of the liver, mainly in Asia, has been ascribed to a disease known as "yellow rice", caused by *Penicillium islandicum* and *P. citrinum*. Aflatoxins, produced by *Aspergillus* species and especially *A. flavus*, are particularly toxic, often causing serious liver damage when consumed by pigs, cattle, and turkeys as impurities in groundnuts, groundnut meal, and corn.

Insects and their fragments in food are not only nauseating, but often a health hazard. The level to which such contamination in flour must be suppressed is therefore also fixed by law in many countries.

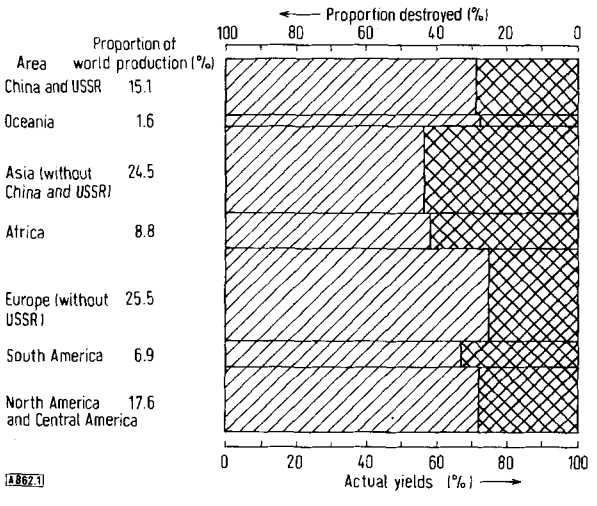


Fig. 1. Regional distribution of the total yields and the proportion of damage to agricultural produce.

Many weeds contain alkaloids and saponins that are poisonous to warm-blooded animals and can therefore cause severe accidents on ingestion.

From all these aspects, making more and better food is one of our greatest tasks. The total damage done by various harmful species amounts to some 35% of the world agricultural production that we would otherwise reach (Fig. 1), *i.e.* it amounts to 70—80 billion dollars.

3. Development of Chemical Plant Protection

Prior to the 19th century there was no etiologically well-founded way of dealing with plant diseases and plant-damaging parasites. The earliest folk methods[4, 5] had a mystical character, and the introduction of mechanical measures first brought some degree of success. As regards chemicals, only inorganic compounds and substances of plant origin could initially be used. Only fragmentary historical records exist of how it was discovered which of these agents were really effective.

3.1. Insecticides

By the middle of the 19th century several insecticides were already known, such as nicotine from tobacco, pyrethrins from the sap of pyrethrum flowers, and rotenoids from the roots of leguminous plants. Petroleum and its fractions were also used against insects at that time. The only other insecticides were arsenic preparations (which are now forbidden in many countries because of their poor biological degradability and high human toxicity) and hydrocyanic acid (which can be used only in enclosed spaces).

The first purely organic and metal-free insecticide, 4,6-dinitro-2-methylphenol (Antinonnin), was put to use in Germany in 1892 against the tussock moth (*Lymantria monacha*), but the low plant tolerance and relatively high toxicity prevented it from gaining wider use. A measure of success was later achieved with aliphatic thiocyanates (1932), phenothiazine (1934), and nitrocarbazoles (1938).

The big breakthrough, leading to a universal contact insecticide, came with *P. Müller*'s discovery of *p,p'*-dichlorodiphenyl-1,1,1-trichloroethane (DDT). Owing to its broad insecticidal spectrum, DDT has had unprecedented success since 1940 in plant protection and in the improvement of hygiene throughout the world. Only this compound has enabled us to combat and in many places fully eradicate the *Anopheles* mosquito, clothing louse, and the tsetse fly, which transmit malaria, typhus, and sleeping sickness, respectively (see Section 7 for the ban on DDT).

The insecticidal properties of other chlorinated hydrocarbons, such as γ-hexachlorocyclohexane, toxaphene, and polycyclic polychloro compounds, were discovered in 1941—45. Since chlorinated hydrocarbons, which are ingestional and contact poisons, generally have a high chemical stability, they exert a prolonged action, but they are dangerous because for the same reason they accumulate in warm-blooded animals and in the environment.

G. Schrader's important work on organic phosphorus compounds, started in the mid-thirties, reached its first peak in 1944 with the discovery of parathion (E 605). Many active organic phosphorus compounds were later found, but none more advantageous and more widely applicable than parathion. In spite of intensive work for the past 30 years, the field of organophosphorus insecticides is still not closed. After 1950 came the development of some systemic preparations (systox group) belonging to this class, which provide plants with internal prophylaxis mainly against harmful sucking insects.

With the development of chlorocarbons and organophosphorus compounds in the past 25 years, man now has the tools needed to keep the main insect pests of almost all cultivated plants under control. These pesticides are supplemented by the cholinesterase inhibitors *N*-methyl- and *N,N*-dimethylcarbamates of phenols, heterocyclic enols, and oximes.

3.2. Fungicides

It was believed for centuries that plants become diseased mainly because the soil is unhealthy for the seeds, and so seed treatment to counteract this started very early. After the use of wine and urine, the salt treatment of cereals began, *e. g.* in Britain, in the 17th century. After about 1760, the salt was replaced by copper sulfate, but this compound proved unsatisfactory, because of its germ-damaging properties. The true importance of copper as a fungicide lies in mixtures of copper sulfate and lime (Bordeaux liquid, *Millardet*, 1885) and copper oxide chloride, which are still used in some fields, mainly in viniculture.

Sulfur as a fungicide has a history at least as long. It served as a cleaning agent over 2000 years ago (it is mentioned in the Iliad and the Odyssey). The first authenticated use of sulfur as a fungicide is associated with *Forsyth* (1803), who recommended a spray mixture of tobacco, sulfur, lime, and elder buds for mildew on fruit trees. Wettable sulfur is still used as a fungicide. Another early fungicide was formaldehyde: it was first used as a disinfectant in 1888 and as a seed-treatment agent in 1895.

In 1910 *Hiltner*, a German phytopathologist, discovered the action of mercuric chloride against the Fusarium wilt of cereals, mercuric chloride having already been known as a bactericide. Attempts to replace this highly toxic compound, having a low plant tolerance, led in 1915 to 3-chloro-4-hydroxymercury(II) hydroxide (Uspulun), the first industrially produced fungicide. This was followed by other alkyl- and arylmercury compounds (Ceresane, 1930), which still have not been surpassed in safety and width of biological activity as seed-dressing agents.

The fungicidal properties of dithiocarbamates and thiuram disulfides were discovered in 1933—1935, but only the metal salts of alkylene-bis(dithiocarbamates) found universal application in orchards, vineyards, and the potato and hop fields (1941). The trichloromethylsulfenyl derivatives of dicarboxylic acid imides set a new standard in the fight against numerous diseases of the green parts of plants (1951), and have made it possible to reduce greatly the use of copper and dithiocarbamate preparations in orchards and vineyards.

After it had thus been found that some broad-spectrum fungicides can be found among the metal-free and purely organic compounds, systematic research led to the discovery of many new useful groups of compounds. Showing a greater variety in morphology, pathogenesis, and site of infection, fungi have to be fought with a greater variety of agents than insects, and therefore more fungicides than insecticides will be needed.

Systemic fungicides were discovered only in the last few years; while the conventional fungicides are purely protective, these systemic fungicides—derivatives of benzimidazole and pyrimidine—confer on plants internal prophylaxis, which is independent of the stability of the surface residues. Some of them, namely oxathiine derivatives, enable one for the first time to combat some plant diseases, such as rust and loose smut of cereals.

3.3. Herbicides

Weed killing in cultivated fields is a difficult form of plant protection, because it calls for substances capable of selecting weeds from the not much more highly evolved useful plants. Neither nature nor early chemistry knew such a substance. Besides, weed-induced damage must have long been underestimated, for it was not thought to be worth any extra cost: until the middle nineteen-forties cheap inorganic compounds available in large amounts were practically the only ones in use as herbicides, the main examples being iron(II) sulfate (since 1900), sulfuric acid (since 1910), ammonium sulfate, and—since 1942—ammonium sulfamate, arsenic(III) oxide, and sodium arsenite. Sodium chlorate and sodium borate were first tried in 1900 and 1930, respectively; they have to be applied in large amounts and have several other disadvantages, but are still used for total weed killing. Sodium 4,6-dinitro-2-methylphenoxide was the first organic herbicide to gain practical application in 1932.

As a result of a systematic search for selective herbicides, starting toward the end of the last war, there were in 1945, 1956, 1963, and 1971 respectively about four, forty, ninety, and over a hundred commercial herbicides with various mechanisms and spectra of action. The main impetus came with the discovery of aryloxy fatty acids in the USA and Britain in 1942—44. These phytohormone-type herbicides kill virtually only dicotyledons, and can therefore be used on cereals; they are still the most important herbicides. Some chlorobenzoic acids and chlorophenylacetic acids also behave like phytohormones.

Herbicides that inhibit photosynthesis form another important group. Since all higher plants rely on photosynthesis for their energy supply and metabolism, these herbicides can, when used in sufficient concentration, terminate plant growth and thus obviously fully eradicate weeds. The surprising fact is that many cultivated plants tolerate some of these herbicides. The most important photosynthesis inhibitors are *N*-aryl-*N'*-alkylureas, diamino-*s*-triazines, carboxylic acid anilides, uracils, and pyrazines.

Differential herbicidal action is exerted against graminaceous plants by *N*-arylcarbamates, *N,N*-dialkylthiolcarbamates, and chloroacetamides. Quaternary bipyridyls interfere with electron transfer during photosynthesis and cause H_2O_2 to accumulate, which destroys the green parts of plants. Increasing economic importance is attached to herbicides of the nitrodiaryl ether type (for rice) and of the type of *N,N*-dialkylanilines carrying three electronegative substituents (for cotton).

It can be said in conclusion that systematic target-oriented research and screening of readily accessible organic compounds have given—and no doubt will continue giving—numerous biologically active agents for the protection of useful plants.

4. Tasks of Chemical Plant Protection for the Near Future

The future development of chemical plant protection depends mainly on the market and the price of produce, and on the overall profile of the substances used for plant protection. The market depends upon the significance of the various plants on the one hand and upon the specific protection problems involved on the other. Most sources of damage can now be combated by quite efficient substances, and large-scale production lowers the production cost. A new agent will be commercially successful only if it has a favorable price/effect ratio, fills a gap on the market, or is particularly advantageous to use.

The trend, aimed at improving profitability and rationalization, will continue to be toward labor-saving measures and single-crop cultivation over large areas. Of crops cultivated over large areas, those with a high yield per unit area (*e.g.* corn) and those with a high-protein yield (*e.g.* soybean) will gain increasing importance. The changing problems of plant protection will call for special care in this field. The need for herbicides will increase, as it has in the past few years (the consumption in the German Federal Republic quadrupled between 1962 and 1969). Over half the money spent in the world on plant protection agents is already spent on herbicides.

There is a worldwide need for agents against parasites that could not previously be combated effectively or at all, examples being bacteria, viruses, and pathogens of systemic and wilt diseases. Furthermore, new agents will be needed in areas or countries where chemical crop protection has not yet started; this is because the existing agents are not always suitable for tackling the problem when one is confronted with different harmful species, their different associations, and different climatic and soil conditions.

Proliferation of certain species, the disturbance of the biological equilibrium, and similar phenomena may lead to such an upsurge of currently insignificant parasites as to call for special measures. The nature and the incidence of harmful species are certainly in constant state of change, mainly because of cultural measures (trend toward large single-crop farms, absence of crop rotation, and cultivation of high-yield varieties), and because most of the common plant-protection agents work toward the biological selection of the less sensitive harmful species, which are then further promoted by the removal of competition, leaving behind a pressure-free biotope. More and more resistant strains of some mites and insects—and sometimes also of parasitic fungi—are emerging and proliferating, which calls for new agents for their control. New agents will also be needed to replace those having disadvantages as regards toxicological properties and environmental pollution.

Expensive labor will promote harvesting aids, and defoliation—necessary before the machine harvesting of cotton—may in the future be extended to orchards and vineyards as soon as suitable chemicals are found for this purpose. Current research suggests that agricultural chemicals will be increasingly used to influence crops, *e.g.* by inhibiting or accelerating their growth, retarding or accelerating the ripening of sap and fruit, reducing or increasing the fruit yield, raising the protein and sugar content of the produce, raising the yield, and improving frost resistance.

5. Biological (Nonchemical) Methods of Plant Protection

It has often been asked, especially recently, whether chemicals could be fully replaced by biological means of plant protection, including all suitable cultural measures such as the choice of the right location, soil treatment, breeding, and crop rotation[6], the breeding of disease-resistant varieties having been particularly successful. In other biological measures, aimed directly at the parasites[7–9], the natural enemies of the harmful species that are present in the locality are promoted, or such enemies of a new type are introduced. The use of specific predatory insects, insect-pathogenic fungi, and bacteria has had some success against certain species of harmful insects, and a virus preparation has been released in the US for restricted use in this field. There is understandable doubt, however, whether these natural agents are entirely harmless to man in the numbers in which they need to be used. Besides, it is difficult to estimate the consequences of disturbing the biological equilibrium in this way.

Other insecticideless methods devised before or under development include sterilization with γ-rays or chemicals and the use of attractants, repellants, antifeedants, and hormones, but only the sterilization of insects has shown any practical success. These methods are efficient only when used on a large scale, and they need extensive organization and management by the government. The release of innumerable additional insects is bound to increase temporarily the damage to cultivated plants. In use over small areas, possibly with toxicologically faultless chemicals, the results are uncertain and take a long time.

Two hormones responsible for insect metamorphosis, namely the molting hormone ecdysone and the juvenile hormone, have recently been isolated and their structure has been elucidated[10–12]. However, attempts to control the reproduction of insects on a large scale through these natural substances or their synthetic analogs have not yet been successful.

An objective assessment of all these methods indicates that today chemical plant-protection agents cannot be fully replaced. However, any feasible method should be fully investigated in view of the emergence of resistance, the problem of chemical residues, the environmental pollution, and the protection of useful species.

In the best combination of chemical and biological means, known as integrated plant protection, the idea is to rely primarily on biological means and to combat the still persisting damage with such chemical means, used in such quantities, that an optimal balance between harmful and useful species is set up. For this purpose the farmer must adopt a systematic and flexible approach, and he must be provided with various crop-specific agents for single-crop systems. Such agents are still rare at the present time. An associated question still to be answered concerns the emergence of resistance when chemicals are deliberately used in subthreshold doses.

6. The Toxicology of Plant Protection Agents

Contrary to a widely held view, plant protection agents are not merely biocides or poisons: most of the modern agents act on one metabolic process, vital only to certain groups of life-forms. Data for what are probably the twenty most commonly used insecticides, fungicides, and herbicides show that only a few—all insecticides—have a high acute oral toxicity for warm-blooded animals (Table 5), *Maier-Bode*[13], and only about 1% of cultivated land is treated with agents belonging to the poison class I. Furthermore, since the most toxic insecticides are quite rapidly decomposed, the user himself is virtually the only person at risk. Though the modern farmer can be familiar with toxic chemicals, it is desirable to replace the highly toxic insecticides by less toxic ones, and much has been done in this direction in the past few years.

Table 5. Acute oral toxicity in rats, of what are probably the 20 most commonly used agents among insecticides, fungicides, and herbicides (some of these substances have other trade names as well).

LD_{50}, mg/kg	20 insecticides	20 fungicides	20 herbicides
up to 20	6 [a]		
21— 100	6 [b]	1 [c]	2 [d]
101— 500	4 [e]	3 [f]	3 [g]
501—1000	2		2
>1000	2	16	13

[a] Azinphos, Disulfoton, Methyl-Parathion, Parathion, Mevinphos, Phosphamidon.
[b] Aldrin, Dichlorphos, Dieldrin, Endosulfan, Methyldemeton, Lindan.
[c] Phenylmercury acetate.
[d] Dinoseb, DNOC.
[e] DDT, Diazinon, Dimethoat, Fenthion.
[f] Nabam, Fentin acetate, trichlorodinitrobenzene.
[g] Diquat, Paraquat, 2,4-D.

A very important question concerns the contamination of food by chemical plant-protection agents and the magnitude of the resulting health hazard. Though we still do not know many of the thousands of substances that make up our food, and of which only relatively few are involved in the energy supply and the body's metabolism, many of them can be assumed to be dangerous in larger amounts. Other substances finding their way to our food come from animal husbandry (hormones, antibiotics, drugs, and other feed additives), preservatives, refining agents, artificial colors and flavoring substances, and possibly also packaging materials.

Improving the quality of the produce obviously must not involve any new health hazard, and this is in fact guaranteed with almost 100% certainty by the tests needed for registering new chemical food additives and by effective observation and control of the safety period and the instructions for use.

The produce rarely comes into contact with plant-protection agents that are applied to the seeds, the soil, or the green parts before fruit formation. The agents are gradually decomposed by chemical and physical action, but the amount left behind on or in the produce in the form of residues or their decomposition products is decisive. The permissible maximum amount of plant-protection agents that is considered safe (tolerance) is fixed by law in many countries (cf. the maximal quantity decree of November 30, 1966, Federal German Food Laws). Tolerances are not toxicological limits whose violation would necessarily damage health; they are values established by law to prevent the abuse of plant-protection agents. They are based on the toxicological tolerance, calculated with a certain safety margin from the maximal nontoxic dose found in chronic toxicity tests on animals. Regrettably, the legally defined tolerances vary quite considerably from country to country, which makes matters difficult for exports and imports.

The stage of chronic toxicity tests is nowadays the costliest part of developing a new plant protection agent: long-term feeding trials with the optimal doses on at least two species of mammals must continue for two years, *i.e.* for almost the whole of the animals' lifetime when rats are used. Only compounds entirely beyond suspicion as to carcinogenic and teratogenic action, embryo toxicity, and damage to organs can be considered safe. According to this criterion, many earlier agents are unsafe, and the law gives their permissible amounts in food at zero (zero tolerance). In Germany at present the law governs four groups of compounds in this field (arsenic compounds, fluoroacetic acid and its derivatives, mercury compounds (except for seed treatment), and selenium compounds), and ten individual agents, including eight chlorocarbon insecticides.

7. The Problem of the Environment

The lack of information about the health aspect of contaminants in air, drinking water, foods, drinks, and tobacco has recently led to widespread anxiety and uncertainty. The great progress in hygiene and public health has been paralleled by a great increase in waste materials, influenced by the growth of the population, rising standard of living, and

increased mechanization; nature's own physical, chemical, and biological purification mechanisms are in some cases already overloaded as a result.

A distinction must be made between acute local side effects and the large-scale spread and accumulation of certain agents in the soil, water, and the food chain. Acute local effects of plant-protection agents on wildlife (*e.g.* deer, birds, and fish) have occurred from time to time, though fewer cases have been really due to these agents than is generally supposed. Such cases are generally caused by rodenticides and insecticides with a high toxicity but short-lived stability. However, they are not direct and inevitable consequences of these agents, but instead are mostly attributable to incorrect use, lack of care, or unfortunate circumstances. The resulting damage to wildlife is local and is soon compensated. Though plant protection agents are used more and more, the number of roes and red deer in the Federal Republic of Germany has increased by a factor of 5—10 since the last world war.

The stability of plant-protection agents and their metabolites requires considerable attention. Except for short-term insecticides, the agents must be stable on plants or in the soil for a considerable time in order to fulfil their function against *e.g.* weeds or fungal diseases. On the other hand, natural decomposition of the agents is desirable in order to minimize residues in food, avoid any unknown long-term effect on the soil, and prevent contamination of the rivers and the ground water.

Of the pollutant metals and metalloids, only mercury, used in seed-dressing preparations, is of general importance here, but even that is used in a small amount in this sector in comparison with the total quantity of mercury used, the amount of mercury used in agriculture in the Federal Republic of Germany in 1969 being only 27 tons or 3.6% of the total 760 tons. Recent work shows that the quantity of mercury thus introduced into the environment is insignificant in comparison with that passing into the atmosphere from other sources and depositing from there. The danger is greater in connection with the seed treated with mercury compounds itself when it is irresponsibly used for feeding livestock. The mercury reaching the food chain *via* fish definitely does not come from plant protection.

The accumulation of plant-protection agents in the soil is dangerous if they cannot be sufficiently decomposed by atmospheric forces or microorganisms. However, this generally causes only local problems, but the use of such agents over large areas and for a long time can admittedly lead to wider environmental pollution, assisted by air, water, and the food chain, which spread them beyond the area of actual use.

The problem of environmental pollution by plant protection agents first arose in connection with DDT. It has since been found that part of the contamination originally blamed on DDT has been due to polychlorobiphenylene, which has been used for various technical purposes for over 40 years, but it cannot be denied that DDT is now present everywhere, partly because it has a high persistence (half-life about 30 months), and partly because large amounts of DDT can be stored by microorganisms (including plankton) and the fatty tissues of higher animals. However, extensive investigations[14] have shown that, apart from a few local exceptions, the present overall DDT concentration need not be feared as a cause of physiological damage in man and wildlife. Nevertheless, health and environment authorities in several countries have banned DDT, except for certain applications, on the grounds of the possibility of unforeseeable damage. The ban has been extended to the other relatively persistent chlorinated hydrocarbon insecticides, for the same reason. To eliminate any new persistent agents at the start, data on the degradability must now be submitted when applying for registration.

8. Future Outlook

Plant-protection agents and growth-regulating agents are at present indispensable if intensive agriculture is to provide enough food. However desirable this might be, it seems that chemical agents cannot be basically replaced by non-chemical and economically feasible methods of plant protection. The nature and the amount of these chemicals should be so chosen as not to damage human health or pollute the environment. For this purpose the users must adhere to guidelines and instructions and be aware of their responsibilities toward their fellow men and nature. They must choose the best agent for each purpose, favor selective agents, minimize the dosage, observe the safety periods, and avoid the use of persistent agents over large areas. No purpose is served by quoting isolated cases—highly regrettable but insignificant within the overall picture—to suggest to the public that people are gradually being poisoned by plant-protection agents. According to the present state of knowledge, the existing laws and the means of their implementation are sufficient to ensure wholesome food.

The development and the use of plant-protection agents are no longer the sole concern of industry and agriculture, and it would be commendable if the cooperation already existing in several areas between industry, the universities, and government bodies were further extended and developed.

The worldwide trade in agricultural produce and the protection of the environment call for international laws on plant-protection agents, based on the relevant national laws. A promising start has been made with the international residue tolerances recommended by the FAO in conjunction with the World Health Organization.

Received: June 11, 1971 [A 862 IE]
German version: Angew. Chem. *84*, 271 (1972)
Translated by Express Translation Service, London

[1] *G. B. Orlob*, Pflanzenschutz-Nachrichten „Bayer" *17*, 185 (1964).

[2] *H. H. Cramer*, Pflanzenschutz-Nachrichten „Bayer" *20*, 1 (1967).

[3] *W. Bartels* and *H. H. Cramer*, Pflanzenschutz-Nachrichten „Bayer" *19*, 129 (1966).

[4] *W. Forsyth*: Über die Krankheiten und Schäden der Obst- und Forstbäume, nebst der Beschreibung eines von ihm erfundenen und bewährten Hilfsmittels, 1791.

[5] *Anonymous*: Erfahrungsmässige Anweisung zur richtigen Kenntnis der Krankheiten der Wald- und Gartenbäume, der Getreidearten,

Futterkräuter, Küchengewürze, Blumen, nebst den bewährten Mitteln dagegen, 1795.

[6] *F. Sprau*, Arch. Pflanzenschutz *6*, 225 (1970).

[7] *H. L. Sweetman*: The principles of biological control—Interrelation of hosts and pests and utilization in regulation of animal and plant populations, Wm. C. Brown Comp., Dubuque, Iowa, 1958.

[8] *J. M. Franz* in: Handbuch der Pflanzenkrankheiten. Vol. 6, 2nd Edit., 3rd Part, Paul Parey, Berlin 1961, pp. 1 ff.

[9] *W. W. Kilgore* and *R. L. Doutt*: Pest Control, Biological, Physical and Selected Chemical Methods. Academic Press, New York 1967.

[10] *V. V. Wigglesworth*, Endeavour *24*, 21 (1965).

[11] *H. Hoffmeister*, Chem. Unserer Zeit *3*, 140 (1969).

[12] *C. E. Berkoff*, Quart. Rev. Chem. Soc. *23*, 372 (1969).

[13] *H. Maier-Bode*, Z. Praeventivmed. *10*, 285 (1965).

[14] See, *e.g., D. A. Spencer*: An Ecologist views the Environment. National Agricultural Chemicals Association, Washington 1970.

Structure of Porous Adsorbents

By Klaus Unger[*]

Porous solids are gaining in importance as adsorbents and catalysts both for scientific investigations and for industrial applications. Adsorbents having predetermined pore structure can be prepared by specific synthesis. This pore structure can be described in detail and comprehensively by specific parameters, which can be determined by gas adsorption measurements and by other means. Information concerning the bonding state and the concentration of the functional groups on the surface is obtainable by the use of chemical and physical methods of investigation. Other functional groups can be attached to the surface by chemical reactions. It is possible in this way to prepare selective adsorbents.

1. Introduction

Porous adsorbents differ from other solids in that they have a pore structure. The shape and the width of the pores range from macroscopic depressions and cracks having a diameter of about 1 μm to pores with widths of the order of magnitude of molecular dimensions. The large internal surface is responsible for the excellent adsorption properties of porous adsorbents toward gases, vapors, and solutes.

The ability to adsorb substances on the surface is thus the reason for the use of porous adsorbents in various fields, *e.g.* as material for the separation of mixtures on the analytical, preparative, or industrial scale, as catalysts or catalyst supports for chemical reactions, or as materials for the production of a vacuum (adsorption pumps).

Special interest is being shown at present in two problems:

1. the use of porous solids having selective adsorption properties to prevent the pollution of air and of water;

2. the use of porous adsorbents for the storage of biologically active substances.

Adsorbents with specific properties are required for the successful study of these problems. The most important of these properties are the parameters of the pore structure and the chemical composition of the framework and its surface, and also in a wider sense the mechanical properties such as strength, compressibility, and the shape and size distribution of the porous particles.

[*] Prof. Dr. K. Unger
Eduard-Zintl-Institut für Anorganische und Physikalische Chemie der Technischen Hochschule
61 Darmstadt, Hochschulstrasse 2 (Germany)

Porous substances having variable properties were first prepared on a purely empirical basis. It is only during the last decade that systematic investigations have been carried out on certain systems of substances. These investigations were concentrated on the following three aspects:

1. elucidation of the steps in the synthesis of an adsorbent that lead to the formation of its pore structure. If these processes and the quantities that they affect are known, the parameters of the pore structure can be systematically varied;

2. critical examination of known methods and development of new methods for the description of the pore structure of porous adsorbents in order to obtain more detailed information than has hitherto been available;

3. physical and chemical investigations on the bonding state and the reactivity of the functional groups on the surface of an adsorbent; execution of chemical reactions on the surface to effect a systematic modification of the adsorption properties.

The present progress report reviews this development with the aid of some selected examples. It will also show the degree to which scientific problems provide a link between the most diverse disciplines of natural science.

2. Description of the Pore Structure of Porous Adsorbents

For a porous adsorbent, the most important of the properties mentioned above is the pore structure. The width of

the pores determines the rate at which matter is transported to the active centers of the surface. The adsorption and desorption processes take place on the pore walls.

It is usual to characterize the pore structure of porous substances, irrespective of their chemical composition, by the following parameters:

geometric extension of the pore wall surfaces per gram of adsorbent = *specific surface area* s ($m^2.g^{-1}$);

total volume of pores per gram of adsorbent = *specific pore volume* v_p (ml of liquid taken up per gram);

average pore diameter $\bar{d}_p$ (Å);

distribution function $dv_p/d\bar{d}_p = f(\bar{d}_p)$ = *pore size distribution.*

Values for these parameters are obtained mainly from gas adsorption and desorption measurements[1,2]. The adsorptives used are mainly nitrogen, as well as argon and other inert gases and hydrocarbons. The result is an adsorption isotherm, which shows the quantity x_a of gas adsorbed (moles per gram of adsorbent) as a function of the relative pressure p/p_0 in the range $0 < p/p_0 \lesssim 1$ (p = equilibrium vapor pressure of the adsorbate during adsorption, p_0 = saturation vapor pressure of the pure liquid adsorptive).

The experimental results can be evaluated by several methods. These make assumptions either about the process of adsorption or about the state of the adsorbed material, and yield equations that show good agreement with the course of the isotherms in certain regions. They also provide a relation between the quantities actually measured (x_a, p/p_0) and the parameters s, v_p, $\bar{d}_p$ to be determined. The real pore structure is approximated by pore models.

Methods for the measurement of gas adsorption have been greatly improved from the experimental standpoint over the past ten years, and the underlying phenomena of adsorption and capillary condensation have been critically examined with regard to their physical significance to porous solids. The influence of the chemical nature of the surfaces of porous substances on their adsorption properties has also been studied in detail with adsorptives having various polarities[3]. Other methods of characterizing the pore structure of porous substances, which are not based on gas adsorption data, have also been developed; these include small angle X-ray scattering, electron microscopy, permeability measurements with gases, penetration measurements with liquid metals, and radiochemical methods. Consequently, the description of the pore structure of porous solids has been refined and differentiated to a greater degree than was previously possible.

2.1. The Average Pore Diameter as a Classifying Parameter of the Pore Structure

The decisive criterion in the adsorption of gases and vapors on porous solids is the value of the average pore diameter $\bar{d}_p$ and its relation to the size of the adsorptive molecule.

The diameters of the gas molecules used range between 3 and 7 ångström units (nitrogen ≈ 3.0 Å, argon ≈ 3.8 Å, methane ≈ 5.0 Å, benzene ≈ 7.0 Å). If we consider the ratio of the pore diameter to the molecular diameter, we can distinguish two limiting cases:

1. the average pore diameter $\bar{d}_p$ is several orders of magnitude greater than the diameter of the adsorptive molecule. Because of the large pore diameter, the pore wall surface may be regarded, to a first approximation, as a planar surface;

2. the average pore diameter $\bar{d}_p$ is of the same order of magnitude as the diameter of the adsorptive molecule, and therefore lies within the range of dispersion forces.

We may therefore expect that the process of adsorption will proceed differently in the two cases.

In the first case, we have very large pores with a small specific surface area (average pore diameter $\bar{d}_p > 2000$ Å, specific surface area $s < 2\ m^2.g^{-1}$). The adsorptive can diffuse very readily into the pores, and the adsorption equilibrium is established very rapidly. At very low pressures, adsorption occurs first on the most active centers of the surface. With increasing pressure p, the less active centers also become occupied, and a polymolecular adsorption layer is formed. We obtain an adsorption isotherm as illustrated in Figure 1c. It is similar to the isotherm of a non-porous substance (type II of the BDDT classification[4]).

Whereas the activation energy of diffusion is very low in the case of adsorbents with very large pores, a much higher activation energy is required for adsorption in micropores (second case)[5]. The adsorption rate is also strongly dependent on the size of the adsorptive molecule. In such a narrow pore, the gas molecule interacts simultaneously with several surface atoms of opposite pore walls. In contrast with the situation in large pores, we have here an adsorption space instead of an adsorption surface. This

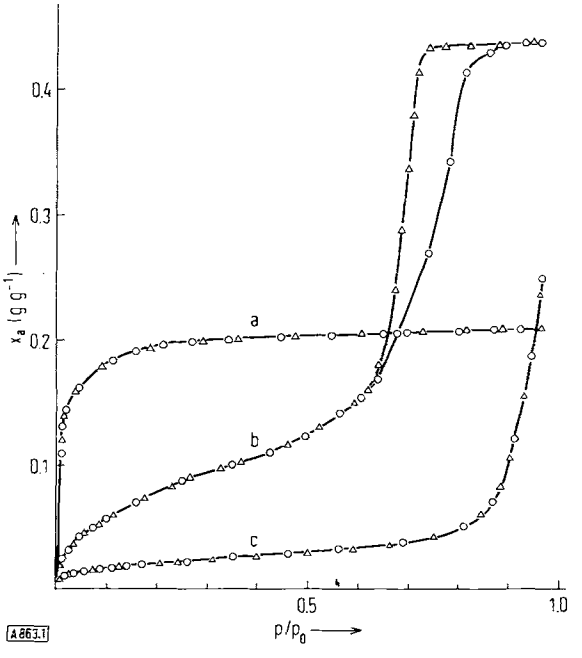


Fig. 1. Adsorption isotherm of an adsorbent with micropores (a), with intermediate pores (b), and with macropores (c). Adsorbent: porous silica; adsorptive: nitrogen; method: gravimetric determination with a Sartorius 4102 electronic vacuum microbalance. ○ = adsorption, △ = desorption.

cavity becomes increasingly packed with adsorbate with increasing pressure p. Once the adsorption space has been saturated, the quantity of gas adsorbed remains constant when the pressure is increased further. Figure 1a shows the corresponding adsorption isotherm (type I of the BDDT classification, Langmuir type). A characteristic of this type is the steep ascent at low p/p_0 values and the almost horizontal course at higher p/p_0 values.

Consideration of the adsorption process on the basis of the relationships discussed necessarily leads to a classification of adsorbents into those with narrow pores (micropores, average pore diameter $\bar{d}_p < 30$ Å) and those with very large pores (macropores, average pore diameter $\bar{d}_p > 2000$ Å)[6]. Adsorbents are then described as microporous or macroporous if the porous solid contains only pores of one of the two sizes. The limiting values indicated for the average pore diameter should not be regarded as rigid limits, but are intended merely as an indication of the order of magnitude.

In the case of microporous adsorbents, the shape of the pores must also be considered. If the micropores have constrictions (ink-bottle pores), they must be characterized by two parameters, *i.e.* the diameter of the narrow neck of the pore and the diameter of the wide body.

In the classification of porous adsorbents according to the average pore diameter, consideration must also be given to the range $30 < \bar{d}_p < 2000$ Å. Pores of this size are known as intermediate pores or mesopores. Adsorbents in which all the pores have diameters in this range are described as intermediate porous adsorbents.

Like microporous and macroporous adsorbents, adsorbents with intermediate pores also exhibit a phenomenon that leads to a characteristic shape for the adsorption isotherm. Intermediate-porous adsorbents are characterized by a hysteresis loop between the adsorption and desorption branch of the isotherm (see Fig. 1d). This can best be explained by the phenomenon of capillary condensation on the basis of the Kelvin equation[1, 7].

$$\log p/p_0 = -\frac{4\sigma V \cos\Theta}{2.3\,RT\,d_K}$$

σ = surface tension of the liquid adsorptive (dyne.cm^{-1})
V = molar volume of the liquid adsorptive (ml.mole^{-1})
Θ = angle of contact between the liquid and the pore walls
d_K = Kelvin diameter (pore diameter) (Å) on the assumption of open cylindrical pores

On adsorption at the beginning of the hysteresis loop, it is assumed that the gas condenses in the pores to form a liquid on the polymolecular adsorption layer already present. At the end of the hysteresis loop and in the subsequent horizontal part of the isotherm, all intermediate pores are filled with capillary-condensed liquid. On desorption (along the upper part of the isotherm in Fig. 1b from higher to lower values of p/p_0) the pores are emptied apart from a polymolecular layer, whose thickness t depends on the value of p/p_0.

The hysteresis between the adsorption and desorption branch of the isotherm is explained by a difference in the mechanism of the filling and emptying of the pores as a function of their shape[7]. No hysteresis is observed with microporous adsorbents.

For macroporous adsorbents, capillary condensation corresponding to the Kelvin equation occurs only at p/p_0 values close to unity. The equilibrium is also established very slowly in this range. For these reasons, capillary condensation in macropores can be determined only with very large errors, if at all.

The classification into microporous, intermediate porous, and macroporous adsorbents was proposed by *Dubinin*[6]. It is a useful classification, since characteristic differences are found in the shape of the adsorption isotherm for the three pore size ranges. With such an approach, however, instead of characterizing the pores present in an adsorbent by the specific total surface area and the specific total pore volume, one must give the characteristic parameters s, v_p, and $\bar{d}_p$ for the pore size range in question.

The knowledge of these specific structural parameters is sometimes important when porous substances are used in adsorption processes. The macropores play only a minor part in adsorption. However, they often provide access to the smaller pores. The rate of diffusion of a gas into the interior of a porous core is therefore decisively influenced by the geometry of the macropores.

The majority of synthetically produced adsorbents have pores with diameters that cover two, and often even all three ranges of pore sizes. The pore size distribution is least often homogeneous. Frequency maxima occur at various pore sizes in many cases. Gas adsorption measurements alone are not enough to characterize the pore system of such adsorbents. They must be supplemented by other methods, such as mercury porosimetry[1, 8, 9] or electron microscopy[10].

The ways in which the specific structure parameters of the three types of adsorbents and the total specific pore volume and the total specific surface area can be determined are briefly described below.

2.2. Determination of the Parameters of the Pore Structure

2.2.1. Determination of the Specific Surface Area

For adsorbents whose pores belong to one one of the three size ranges, we find the following surface area values[6]:

microporous adsorbents	$s > 500$ m^2.g^{-1}
intermediate-porous adsorbents	$10 < s < 500$ m^2.g^{-1}
macroporous adsorbents	$s < 10$ m^2.g^{-1}

Figure 2 presents a brief survey of some methods for the determination of the specific surface area by gas adsorption measurements[11–16]. The most important of these will be briefly described here.

BET Method[11, 17] (Fig. 2a): The specific monolayer capacity x_m of the adsorbent (mole.g^{-1}) is determined with the aid of the BET equation from the region ($0.05 < p/p_0 < 0.35$) of the isotherm of a gas (usually nitrogen). x_m multiplied by a_m (Å^2/molecule), the area of the gas molecule

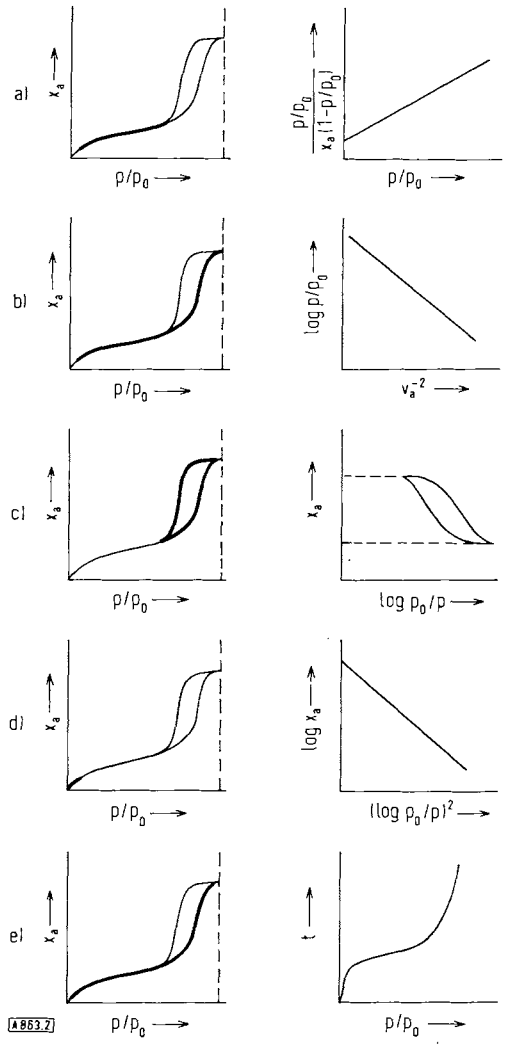


Fig. 2. Survey of methods for the determination of the specific surface of porous adsorbents. The region of the isotherm that is used is given on the left, and the equations of the isotherms are plotted as graphs on the right.

a) BET method [11, 17]:

$$\frac{p/p_0}{x_a(1-p/p_0)} = \frac{1}{x_m \cdot C} + \frac{C-1}{x_m} p/p_0$$

$$s_{BET} = x_m a_m N_L \times 10^{-20}\ (m^2 g^{-1})$$

b) Method of *Harkins* and *Jura* [12]:

$$\log p/p_0 = B - A v_a^{-2}$$

$$s_{HI} = k A^{1/2} \quad k = 4.06 \text{ (for } N_2)$$

c) *Kiselev*'s Method [13, 14]:

$$s' = \frac{2.3\,RT}{\sigma} \int_{x_{a_1}}^{x_{a_2}} \log(p_0/p)\,dx_a$$

d) *Kaganer*'s Method [15]:

$$\log x_a = \log x_m - D\,(\log p_0/p)^2$$

$$D = 2.3\,k R^2 T^2$$

$$s_K = x_m a_m N_L \times 10^{-20}\ (m^2 g^{-1})$$

(valid for the range $1 \times 10^{-5} < p/p_0 < 0.03$)

e) Method of *Lippens* and *de Boer* (*t* method) [16]:

$$t = \frac{v_a}{v_m}\delta = f(p/p_0)$$

$$s_t = 15.47\, v_a/t \text{ (for } N_2)$$

x_a = quantity adsorbed (mole.g^{-1})
x_m = specific monolayer capacity (mole.g^{-1})
v_a = quantity adsorbed (ml of gas.g^{-1})
v_m = specific monolayer capacity (ml of gas.g^{-1})
a_m = molecular cross-sectional area of a gas molecule (Å^2/molecule)
δ = thickness of a monomolecular adsorption layer (Å)
t = statistical thickness of the adsorption layer
For further abbreviations see text.

in a complete monolayer and the factor 6.02×10^3 gives the specific surface area (m^2.g^{-1}).

The two-parameter BET equation used[17] describes the interaction of a gas with a planar surface of the pore walls. Consequently, only the surface of macroporous adsorbents and to a first approximation that of intermediate porous adsorbents can be determined with the aid of this equation. On mathematical consideration of the BET equation, moreover, it is found that the isotherm of the adsorbent used for the evaluation must be concave with respect to the pressure axis, or the value C in the BET equation must be greater than two[17–19].

Purely microporous adsorbents usually give isotherms of the Langmuir type. If the course of the isotherm corresponds to the Langmuir equation, the specific monolayer capacity x_m can be obtained from the following function

$$\frac{p}{x_a} = \frac{1}{B x_m} + \frac{p}{x_m}$$

B = constant of the Langmuir equation

The determination of the specific surface area by the method of *Harkins* and *Jura*[12] (Fig. 2b) will not be discussed here.

Determination of the Specific Surface Area s' of the Adsorption Layer from the Isotherm: According to *Kiselev*[13, 14] (Fig. 2c), the specific surface area s' of the adsorption layer can be determined, on the basis of thermodynamic considerations, with the aid of the following equation:

$$s' = \frac{2.3\,RT}{\sigma} \int_{x_{a_1}}^{x_{a_2}} \log \frac{p_0}{p}\,dx_a$$

σ = surface tension of the pure liquid adsorptive (dyne.cm^{-1})
x_{a_1} = quantity adsorbed (mole.g^{-1}) at the beginning of the hysteresis loop
x_{a_2} = quantity adsorbed (mole.g^{-1}) at the end of the hysteresis loop.

The value of the integral is determined both for the desorption branch and for the adsorption branch of the isotherm from the function

$$x_a = f(\log p_0/p)$$

and the two values are then averaged. It is assumed that at the beginning of the hysteresis loop, corresponding to the lower integration limit x_{a_1}, the adsorbate is present as a condensed liquid phase, and that at the end of the hysteresis loop, corresponding to the upper integration limit x_{a_2}, the pores are filled with capillary-condensed liquid. An indication that these assumptions are permissible was provided by the agreement of the values of s' found for an intermediate porous silica with various adsorptives. The values also agree with the BET surfaces[14].

It can be seen that this method can be used for the determination of the specific surface areas only of adsorbents with intermediate pores, since only these exhibit hysteresis. Unlike the BET method, this method requires accurate determination of the entire isotherm.

Determination of the Specific Surface Area after Kaganer[15] (see Fig. 2d): On the basis of *Dubinin*'s potential theory[1], *Kaganer*[15] derived an equation that represents the course of the isotherm of a porous substance in the monolayer adsorption range ($1 \times 10^{-5} < p/p_0 < 0.03$):

$$\log x_a = \log x_m - D\,(\log p_0/p)^2$$

It differs from the Dubinin-Raduschkewitsch equation (see Section 2.2.2) in the constant and in the replacement of the term $\log W_0/V$ by $\log x_m$. x_m is obtained by extrapolation of the straight line to the value $(\log p_0/p)^2 = 0$. The specific surface area can be calculated with the aid of x_m as follows:

$$s_K = x_m N_L a_m \times 10^{-20}\ (m^2 g^{-1})$$

Determination of the Specific Surface Area after Lippens and de Boer (t Method)[16] (see Fig. 2e): The *t* method developed by *Lippens* and *de Boer*[16] is not an independent method for the determination of the specific surface. When the correct *t* curve is used ($t = f(p/p_0)$), the value of s_t must agree with the specific surface area according to the BET method.

Specific Surface Area from Mercury Penetration Measurements: According to *Rootare* and *Prenzlow*[20], the specific surface area of an adsorbent can be determined from mercury penetration measurements with the aid of the following equation:

$$s = -\frac{1}{\sigma \cos\Theta} \int_{v_0}^{v_{max.}} p\,dv$$

σ = surface tension of mercury (dyne.cm^{-1})
Θ = contact angle between liquid mercury and the pore walls
v = volume of mercury forced into the pores of the adsorbent with increasing pressure
v_0 = volume of mercury at $p = 1$ atm (v assumed to be 0)
v_{max} = volume of mercury forced in at p_{max}

The value of the integral is determined graphically from the experimentally obtained function $p = f(v_p)$. No assumptions are made about the shape of the pores. Measurements on various adsorbents have shown that the surface values obtained in this way agree with the BET values at $s < 100$ m^2.g^{-1}.

2.2.2. Determination of the Specific Pore Volume

The specific pore volume can be determined from adsorption measurements only for adsorbents with micropores and intermediate pores. The specific pore volume of macroporous and intermediate-porous adsorbents can be determined independently by mercury penetration measurements[1, 8, 9].

The total pore volume is determined by mercury and helium permeametry[21], in which the apparent densities ρ_{Hg} (density with respect to mercury) and ρ_{He} (density with respect to helium) of the porous adsorbent are determined in two separate experiments. The reciprocal $1/\rho_{Hg}$ corresponds to the specific volume of the skeletal substance plus the specific volume of pores having $\bar{d}_p < 12$ µm, while $1/\rho_{He}$ corresponds only to the specific volume of the skeletal substance. The difference $1/\rho_{Hg} - 1/\rho_{He}$ is thus equal to the specific total pore volume.

Determination of the Specific Pore Volume from Gas Adsorption Measurements; Gurwitsch Rule: The Gurwitsch rule[1, 22] is based on the assumption that when the isotherm of a gas is parallel to the abscissa in the range $0.95 < p/p_0 \lessapprox 1$, all the pores of an adsorbent are completely filled with liquid adsorbate. In this way, the pore volume of microporous and intermediate-porous adsorbents is found from the equation

$$v_p = x_a \cdot V\ (ml\,g^{-1})$$

x_a = quantity adsorbed (mole.g^{-1}) at $0.95 < p/p_0 \lessapprox 1$
V = molar volume of the liquid adsorptive at the experimental temperature (ml.mole^{-1})

It was found from numerous adsorption experiments with gases and vapors on a wide range of adsorbents (at various temperatures) that the pore volume determined from the Gurwitsch rule is practically independent of the adsorptive used[1].

Determination of the Specific Pore Volume after Dubinin-Raduschkewitsch[1, 6, 24, 25]: On the basis of *Polanyi*'s potential theory[23], *Dubinin et al.* derived a theory of the adsorption of gases in micropores (theory of volume filling of micropores). The result is an equation that represents the course of the adsorption isotherm in the range $1 \times 10^{-5} < p/p_0 < 0.2$:

$$\log x_a = \log \frac{W_0}{V} - B'T^2 (\log p_0/p)^2$$

x_a = quantity of gas adsorbed (mole.g^{-1})
W_0 = total volume of the adsorption space (= specific pore volume v_p) (ml.g^{-1})
V = molar volume of the liquid adsorptive (ml.mole^{-1})
B' = constant ($= 2.3 \times k' R^2 T^2$)

A plot of $\log x_a$ against $(\log p_0/p)^2$ gives a straight line whose intercept on the ordinate corresponds to the ratio W_0/V.

Below the boiling point of the adsorptive, V is equal to the molar volume of the liquid, to a first approximation. For higher temperatures, *Dubinin et al.* describe a method for the calculation of the molar volume[6]. W_0, which corresponds to the micropore volume of the adsorbent in question, can thus be calculated.

2.2.3. Determination of the Pore Size Distribution

The function $dv_p/dd_p = f(\bar{d}_p)$ of a porous adsorbent can be determined experimentally from gas adsorption measurements and from mercury penetration measurements[1]. Gas adsorption measurements yield information only on the pore size distribution in the micropore and intermediate pore range, while mercury penetration measurements give the distribution in the macropore and intermediate pore range provided that $p_{max} \approx 4000$ atm. In the subsequent calculation, the real pore structure is approximated by models[26], or a ratio dv_p/ds is given without assumption of a model[27, 38].

Brunauer[27, 28] described a method by which the pore size distribution of microporous adsorbents can be calculated. In this method, in addition to the measured adsorption isotherm, it is necessary to know the t curve[29, 30], which shows the dependence of the thickness t of the adsorbed layer on the relative pressure p/p_0 on a non-porous adsorbent of the same chemical composition (Fig. 2e).

For adsorbents with intermediate pores, the pore size distribution is calculated from the isotherm in the hysteresis region with the aid of the Kelvin equation[1]. It is assumed that the differences in the shape of the hysteresis are determined by the pore shape. For some pore models, the course of the desorption and adsorption isotherms can be given theoretically[26, 31]. Depending on the model chosen, therefore, the adsorption branch, the desorption branch, or both branches of the isotherm are used. The evaluation can be carried out by various calculation methods, in which the thickness t of the adsorbed layer is assumed to be constant or its dependence on p/p_0 is taken into account[32–38].

The mercury penetration measurements are evaluated on the basis of *Washburn*'s equation[8, 9, 39]

$$p = -\frac{4\sigma\cos\Theta}{d_p}$$

σ = surface tension of mercury (dyne.cm^{-1})
Θ = contact angle between liquid mercury and the pore walls
p = equilibrium pressure

This equation is valid for cylindrical pores. Comparison of the pore size distributions found for porous adsorbents by the mercury penetration method and by gas adsorption measurements shows good agreement in the intermediate pore range[40, 41].

3. Preparation of Porous Adsorbents with Variable Parameters of the Pore Structure by Specific Synthesis

In naturally occurring porous adsorbents, such as kieselgur and kaolin, the pore structure is fixed by geochemical processes spanning millions of years. Most of the adsorbents used today, however, are either prepared synthetically or obtained from natural products by special treatment (examples: active charcoal, cellulose).

Two types of methods can be distinguished in synthesis. In one type, the pore structure is formed directly as a result of consecutive or simultaneous chemical and physical processes, while in the other it may arise indirectly from the removal of one component from a solid having an inhomogeneous composition (example: porous glass).

The direct synthesis is the more interesting method from the standpoint of preparative chemistry. Its object is to produce porous adsorbents having a specific pore structure by variation of the preparation conditions. This requires a knowledge of the processes that lead to the formation of the pore structure of a porous substance, and of the factors that influence them. Systematic studies of this nature have been successfully carried out on only a few substances.

Depending on the average pore diameter of the adsorbent, moreover, quite different processes are responsible for the formation of the pore structure. Micropore formation involves processes that take place in the range of atomic dimensions and lead *e.g.* to a different linkage of atoms or groups of atoms. The pore structure in the range of intermediate pores may result *e.g.* from the packing together of non-porous particles (colloidally dissolved or highly dispersed particles). Macropores, on the other hand, are formed from interstices between aggregated crystallites or arise from cracks and dislocations of crystals.

From the many porous adsorbents, two are selected here for the discussion of the formation of their pore structure and its variation. Example 1 consists of the synthetic zeolites, which have a pronounced micropore structure. Their main importance is in industry, *e.g.* in the separation and refining of hydrocarbon mixtures[42, 43]. Example 2 is porous silica (silica gel). Its average pore diameter can be varied over a much wider range than that of the zeolites. The main use of this adsorbent is in chromatography[44].

3.1. Preparation of Synthetic Zeolites

Zeolites are crystalline aluminosilicates[45, 46] having the chemical composition $M_{2/m}\cdot Al_2O_3\cdot nSiO_2\cdot xH_2O$. The aluminosilicate framework consists of $[SiO_4]$ and $[AlO_4]$ tetrahedra linked to one another by the oxygen atoms. The negative excess charge resulting from the replacement of silicon by aluminum is neutralized by alkali metal and/or alkaline earth metal ions. Fibrous, lamellar, and infinite three-dimensionally crosslinked structures are found[42].

Only the infinite three-dimensionally crosslinked zeolites are suitable for use as adsorbents. Their structure can be imagined as consisting of polyhedra formed from $[SiO_4]$ and $[AlO_4]$ tetrahedra. Linkage of these polyhedra by four-membered, six-membered, eight-membered, or even twelve-membered oxygen rings gives cavities that extend throughout the entire zeolite crystal. In the unactivated state, the cavities are filled with water.

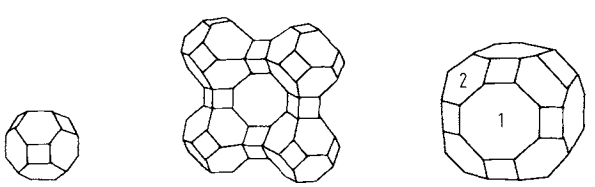


Fig. 3. Formation of the cavity structure in zeolite A by linkage of octahedra (schematic). a) Truncated octahedra. b) Part of the model of the unit cell. c) Large cavity of b (magnified). For 1 and 2 see text.

As an example, Figure 3 shows schematically the formation of the cavity structure in the synthetic zeolite A (faujasite type)[47, 48], which has a cubic crystal structure. The cavity is formed by linkage of truncated octahedra by four-membered rings of oxygen atoms (Fig. 3b). We distinguish a larger cavity (Fig. 3c) bounded by eight truncated octahedra and having a diameter of 11 Å. This cavity is accessible *via* six openings (corresponding to the surfaces such as 1),

each of which is formed from eight oxygen atoms. The diameter of such an eight-membered ring is 4 Å. In each of the eight truncated octahedra, there is also a smaller cavity having a diameter of 7 Å. Each of these smaller cavities is linked to the larger cavity by a six-membered ring of oxygen atoms (diameter 2 Å, corresponding to the surfaces such as 2). It must be pointed out that on adsorption, the entrances to the smaller cavities of the synthetic zeolite A are too narrow for molecules, so that these pass into the cavity only through the larger openings[5].

These cavities are connected to other cavities with the same dimensions by the six-membered and eight-membered openings (corresponding to the surfaces 2 and 1 respectively) to give a system of cavities having extremely regular dimensions. This structure is described as a micropore structure, since the diameters of the cavities (pores) are of the order of magnitude of molecular dimensions.

The micropores of zeolites are characterized by two parameters, *i.e.* the diameter of the entrance to the cavity and the diameter of the cavity. Values for these parameters can be estimated from X-ray structural data. Adsorption measurements give only the total volume of the pores.

What has been said about zeolite A is also applicable to the other synthetic zeolites[49] which differ from zeolite A only in the manner in which the polyhedra are linked, *i.e.* in the lattice constants of the unit cell. In this way one obtains porous solids having cavities with definite diameters, depending on their structure. The diameter of the entrances can be additionally varied by ion exchange[50, 51]. According to *Barrer*[52], the synthetic zeolites can be divided into five types according to the diameter of the entrances leading to the cavities, *i.e.* type 3A (3 Å), 4A (4 Å), 5A (5 Å), 10X (8 Å), and 13X (10 Å).

It can be seen from the above discussions that the pore structure of zeolites is determined by their crystal structure. To obtain reproducible values for the pore structure, it is necessary to adhere exactly to the synthesis conditions that lead to zeolites having definite compositions and crystal structures.

The natural zeolites were formed millions of years ago by the action of basic mineral salt solutions on rocks at 100 to 300 °C under pressure. The conditions of this hydrothermal synthesis have been simulated in the preparation of synthetic zeolites.

The starting materials are aqueous solutions of sodium aluminate and sodium silicate and of sodium hydroxide. When the solutions are mixed, they form a gel, which is then heated under pressure at 50—350 °C. This leads to recrystallization of the amorphous gel. The microcrystalline precipitate is separated from the mother liquor, washed, and dried.

Reproducibility of the composition and crystal structure of the synthetic zeolites can be achieved through the conditions of the hydrothermal synthesis. The most important factors are the molar ratio $SiO_2:Al_2O_3$, the content of alkali metal and/or alkaline earth metal ions, and the crystallization temperature. The influence of these parameters on the crystal structure of the zeolites has been studied in detail by *Barrer*[53] and by *Shdanov*[54].

The zeolites are formed in the synthesis as a microcrystalline powder (range of particle diameters 0.1—10 μm). For industrial use, the zeolite crystals are mixed with a binder (*e.g.* clay) and the material is then pressed into small rods or spheres. This process results in an additional pore structure, which is determined by the size of the crystallites and the molding pressure. The resulting pores are macropores having $\bar{d}_p > 2000$ Å[5].

3.2. Preparation of Porous Silica

In the synthetic zeolites, the parameters of the cavity structure are determined by the crystal structure, *i.e.* by the linkage of the atoms and the distances between them. Porous silica, on the other hand, is an amorphous substance having the composition $SiO_2 \cdot xH_2O$. The framework consists of infinite three-dimensionally crosslinked $[SiO_4]$ tetrahedra. On its surface, porous silica has polar hydroxyl groups and adsorbed water[55].

Because of its amorphous character, we cannot expect such a homogeneous pore structure as in the case of the zeolites. However, the special advantage of porous silica is that samples with highly variable average pore diameters (range $10 < d_p < 10000$ Å) can be prepared. Its properties can thus be adjusted to suit a wide range of applications.

The pore structure of porous silica arises in an entirely different manner from that of the zeolites, and the processes involved in its formation are much more complicated. They will be illustrated by the example of preparation from sodium silicate[55].

On acidification of a sodium silicate solution, the silicate ions are converted into silicic acids, which condense, according to the pH, to give polysilicic acids. The submicroscopic polysilicic acid particles grow into larger particles, which are non-porous, and which are spherical. Their diameter is approximately 100 Å. They are in colloidal solution (polysilicic acid sol). The subsequent aggregation of the polysilicic acid particles finally leads to the formation of a polysilicic acid gel. The reason for the aggregation is the dehydration of surface hydroxyl groups of neighboring polysilicic acid particles. The polysilicic acid gel is an infinite three-dimensionally crosslinked packing of spherical polysilicic acid particles, which still contains immobilized water. The water is removed by subsequent heating, and the dehydration thus proceeds further. The final product is a hard, porous xerogel (silica gel). The walls of the pores are formed by the surfaces of the spherical polysilicic acid particles. Depending on the size and packing density of the particles, we obtain pores of various sizes. The formation of small and large pores is shown schematically in Figure 4.

The parameters of the pore structure are thus determined by the dimensions of the polysilicic acid particles and by their packing density[56]. To obtain given values of these parameters, the size and the growth of the polysilicic acid particles and the gel formation must be controlled. The influence of the preparation conditions in the steps polysilicic acid sol → polysilicic acid gel → xerogel on both processes have been systematically studied in numerous investigations[57-65].

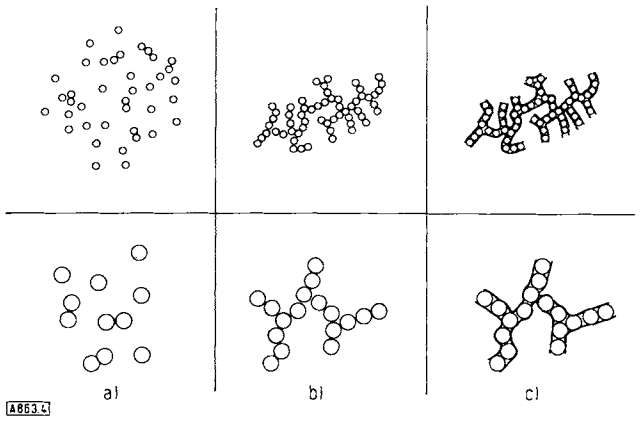


Fig. 4. Development of large and small pores on formation of porous silica (schematic). a) Colloidal solution of polysilicic acid particles, top: small particles, bottom: large particles. b) Aqueous polysilicic acid gel, top: many contact points for small particles, bottom: few contact points for large particles. c) Hard, porous xerogel, top: many small pores and correspondingly large surface area for the small particles, bottom: few large pores and correspondingly small surface area for the large particles.

The growth of the polysilicic acid particles can be inhibited as follows: by a pH of <7 in the polysilicic acid sol[57, 59]; by treatment of the polysilicic acid gel with dilute acids[60, 61, 64]; by replacement of the immobilized water with organic solvents[65]. A pH of >5 in the polysilicic acid sol, on the other hand, favors the growth of the polysilicic acid particles and accelerates the gel formation[59, 60, 63]. The same effect is achieved if the polysilicic acid gel is treated with alkaline solutions or with strong sulfuric acid solutions[62]. The hydrothermal treatment of the polysilicic acid gel at high temperatures in an autoclave is particularly effective[66–68]. Because of the higher solubility of the smaller polysilicic acid particles, larger particles are formed with rising temperature and with increasing treatment time.

Porous silica is generally obtained in the form of hard, irregularly shaped particles, which are crushed and sieved or classified to obtain the desired grain size fraction. However, spherical porous silicon dioxide particles are required for many purposes, *e.g.* for use as stationary phase material in column chromatography[69] or as a catalyst support in moving bed or fluidized bed reactors.

As an example, a new method for the preparation of spherical silica particles is described below[70, 71]. The starting material is a tetraalkoxysilane, *e.g.* tetraethoxysilane. The tetraethoxysilane is dissolved in a solvent, and a slight amount of water containing small quantities of a catalyst is added. A hydrolytic polycondensation now occurs in the homogeneous phase with formation of a high molecular weight polyethoxysiloxane, which still contains ethoxy groups. The polyethoxysiloxane is freed from solvent and from monomer. Its viscosity can be varied by adjustment of the hydrolysis conditions.

In a further reaction, the condensation of the polyethoxysiloxane is completed in a heterogeneous phase by addition of solvent and an excess of water containing a catalyst. This reaction is carried out with stirring. The stirring leads to the emulsification of the polyethoxysiloxane, and the resulting droplets subsequently harden. The spherical particles obtained are porous. Figure 5 shows a photomicrograph of such a product.

The parameters of the pore structure can be systematically varied over a wide range in this method by variation of the nature and concentration of the catalyst in the hydrolytic polycondensation reaction (Table 1). Another advantage

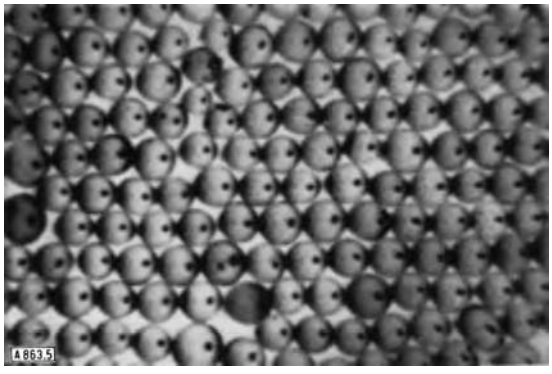


Fig. 5. Photomicrograph of a porous silica consisting of spherical particles (magnification 1:40).

is that very pure silica preparations can be obtained. The droplet size of the polyethoxysiloxane and hence the diameter of the resulting spherical particles, can be varied within wide limits (range about 1—1000 μm) by variation of the viscosity of the polyethoxysiloxane and of the stirring rate during the emulsification.

Table 1. Examples of the variation of the parameters of the pore structure of porous silica prepared from tetraethoxysilane. s_{BET} = specific surface according to BET method, v_p = specific pore volume, $\bar{d}_p$ = average pore diameter.

Sample	s_{BET} ($m^2\,g^{-1}$)	v_p ($ml\,g^{-1}$)	$\bar{d}_p$ (Å)
1	563	0.30	20
2	630	0.63	40
3	311	0.78	100
4	178	0.88	200
5	220	2.20	400
6	215	4.19	800

4. Chemical Modification of the Surface of Porous Adsorbents

Examples of the preparation of porous substances with variable parameters of the pore structures were given in the last section. The adsorption properties of a porous substance are determined not only by the geometry of the pore system but also by the nature and structure of the surface atoms or groups of atoms[3]. This can be seen *e.g.* in the adsorption behavior to different polar gases or vapors.

Methods by which one type of functional group on the surface of an adsorbent can be replaced by others to obtain selective adsorbents are therefore of interest. This is possible by reactions of the existing surface groups with suitable

reactants to form new functional groups, which in turn are chemically bonded to the surface. For such surface reactions to occur, the existing functional groups of an adsorbent must be sufficiently reactive. Moreover, the reactions should be carried out under conditions that give a dense monomolecular surface layer that eliminates as far as possible the influence of the original surface on the adsorption process.

These reactions on the surface of porous solids must be distinguished from chemisorption processes *e.g.* on metal surfaces[72,73]. The latter are carried out with gases such as oxygen, hydrogen, and carbon monoxide on clean, definite surfaces under ultra-high vacuum conditions. Their purpose is to elucidate the elementary steps in the adsorption and the bonding between the adsorbate and the adsorbent. The investigation methods used include field electron and field ion microscopy, mass spectrometry, IR spectroscopy, and low energy electron diffraction (LEED method).

Porous adsorbents have a specific surface area several orders of magnitude greater than that of metals. The effects in surface reactions on porous adsorbents are consequently greater. Moreover, their surface is often contaminated with traces of adsorbed water or oxygen, since the samples are heated at high temperatures before the reaction only in a high vacuum, and not in an ultra-high vacuum. The surfaces before the reaction are therefore not usually clean in the physico-chemical sense. Furthermore, most porous adsorbents have an energetically heterogeneous surface. These facts impose limits regarding the interpretation of such reactions. Their theoretical description is further hindered by the fact that the diffusion and adsorption of the reactants in the pore system is very complicated[5].

The importance of surface reactions on porous adsorbents lies in the preparation of new adsorbents and in their wide practical application. Numerous reactions on adsorbents have already been investigated, *e.g.* on graphite[74,75], synthetic zeolites[45], and oxide adsorbents[70,74]. The problem of surface reactions will be illustrated for an oxide adsorbent, *i.e.* porous silica. This is particularly suitable for use as a model substance, on the one hand because of the possibility to vary the parameter of its pore structure, and on the other because its polar hydroxyl groups allow numerous reactions. Promising reactions are those in which an Si—C bond is formed on the surface. The favorable solid-state properties of porous silica are combined in this way with the many synthetic possibilities of organic chemistry. The attachment of Si-aryl groups to the surface, for example, changes the polarity of the surface, and further reactions are also possible on the aryl groups[76].

4.1. Chemical Structure of the Surface of Amorphous Silica

The surface of both amorphous and of crystalline silica is hydrated[74,77]. Weakly acidic hydroxyl groups attached to silicon atoms are distinguished from siloxane groups on the surface. The concentration of hydroxyl groups can be determined *e.g.* by the following chemical and physical methods: reaction with methyllithium or Grignard compounds followed by quantitative determination of the methane formed[78,79], heterogeneous isotope exchange with D_2O and subsequent mass-spectrometric analysis[80,81], and heterogeneous isotope exchange with tritium-labeled water[79]. The maximum concentration of hydroxyl groups α_{OH} on porous silica at an activation temperature of 200 °C is 8.0—9.0 μmole.m^{-2}[78,82]. α_{OH} is a function of the temperature (Fig. 6). With rising temperature, condensation leads in an increasing degree to the formation of siloxane groups.

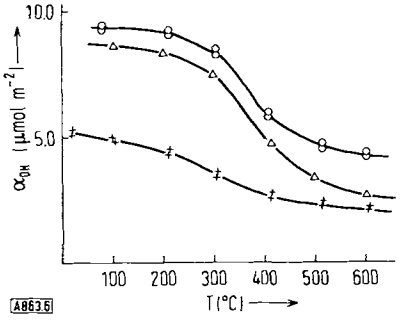


Fig. 6. Dependence of the hydroxyl group concentration α_{OH} (μmole.m^{-2}) of porous and non-porous silica samples on the activation temperature with simultaneous vacuum treatment. ○ = silica gel, $s_{BET} = 35$ m^2.g^{-1}, $\bar{d}_p = 1200$ Å; △ = silica gel, $s_{BET} = 330$ m^2.g^{-1}, $\bar{d}_p = 200$ Å; + = Aerosil, $s_{BET} = 200$ m^2.g^{-1}. Determination method: reaction with methyllithium, followed by determination of methane.

It can be concluded from the course of the curve (Fig. 6) that the hydroxyl groups are bonded in different ways. Further information is provided by IR-spectroscopic studies (transmission measurements, disks)[78,83-85]. Both non-porous and porous silica give a sharp band at 3750 cm^{-1}, which is assigned to the stretching vibration of free hydroxyl groups. A further broad, indistinct band appears in the vicinity of 3550 cm^{-1}, and this is assigned to the stretching vibration of hydroxyl groups which are bonded to one another by hydrogen bonds.

Numerous models have been developed for the bonding of hydroxyl groups on the surface of porous silica. The two most important are:

1. *Concept of free and bound hydroxyl groups:* On a silica surface, one can distinguish free and bound hydroxyl groups. According to *Kiselev*[86], at a total concentration of $\alpha_{OH} = 8.0$ μmole.m^{-2}, 4.3 μmole.m^{-2} is the concentration of free hydroxyl groups and 3.7 μmole.m^{-2} is the concentration of bound hydroxyl groups. *Armistead et al.*[87] give a concentration of 2.5 μmole.m^{-2} of free and 5.2 μmole.m^{-2} of bound or paired hydroxyl groups for a total concentration of 7.7 μmole.m^{-2}.

2. *Concept of paired hydroxyl groups:* According to *Peri*[88], a silica surface has mainly paired (geminal and vicinal) hydroxyl groups, together with isolated free hydroxyl groups. The concentration of each of these species can be calculated as a function of the total concentration.

The course of the curve in Figure 6 can be interpreted as follows on the basis of these models. The hydroxyl group concentration initially decreases slightly as a result of desorption of adsorbed water[78]. At about 300 °C, the con-

centration of adsorbed water is negligibly small in relation to that of the hydroxyl groups. The pronounced decrease in α_{OH} between 300 and 500 °C is attributed to the condensation of bound or paired hydroxyl groups. The condensation of free hydroxyl groups occurs only above 600 °C. The course of the curve differs slightly for each porous silica sample, depending on its preparation.

It is interesting in this connection to note that two sharp, symmetrical IR bands have been found at 3657 cm^{-1} and 3636 cm^{-1} for crystalline quartz (ATR Technique, powder)[89]. These bands are assigned to the stretching vibration of free and relatively free hydroxyl groups. It can be concluded from the results that the surface of crystalline silicon dioxide resembles those of crystalline titanium dioxide (anatase) and of γ-aluminum oxide more than that of amorphous silica.

4.2. Formation of an Si—C_{aryl} Bond on the Surface of Porous Silica[76]

As an example, we shall describe the formation of a surface Si—C_{aryl} bond. The following two methods are possible[90–94]:

1. Reaction of silica with arylchlorosilanes. A siloxane linkage is formed with elimination of hydrogen chloride. The Si—C bond in this case is already present in the reactant.

2. Reaction of silica with silicon tetrachloride or thionyl chloride followed by a reaction of the chlorosilylated or chlorinated products with aryllithium compounds. In the first reaction, a very reactive group is formed on the surface, and in the second, an Si—C bond is formed directly with elimination of lithium chloride.

The kinetics of the reaction and the influence of the reaction temperature on the conversion was investigated first for the reaction of porous silica with the homologs phenyltrichlorosilane, diphenyldichlorosilane, and triphenylchlorosilane[91,92,94]. Because of the diffusion of the reactants into the pores, the times required to reach a constant conversion were very long. The conversion also increased with rising temperature. Above 200 °C, however, no further increase could be achieved. This was taken as evidence that maximum coverage had been reached under these conditions (see Table 2).

On the basis of these results, porous silica was allowed to react under the same conditions with silicon tetrachloride or thionyl chloride[93]. In the subsequent reaction of these modified products with solutions of phenyllithium, α-naphthyllithium, or trityllithium in ether, heating was possible only up to a maximum of 35 °C; however, the aryllithium compounds were used in large excess[93]. The following analytical studies were carried out on the modified derivatives and on the starting materials: elementary analysis for chlorine, carbon, silicon (increase on modification with $SiCl_4$), determination of the hydroxyl group concentration, IR spectroscopic studies (transmission measurements, disks). Results are shown in Table 2.

The values in Table 2 show that the maximum coverage with aryl groups is a function of the size of the molecule offered for reaction. Both with the homologous phenylchlorosilanes and with the aryllithium compounds, the maximum conversion under given conditions decreases with increasing molecular size. This is due to the increasing cross-sectional area of the molecules.

4.3. Influence of the Surface Reaction on the Parameters of the Pore Structure[95]

A surface reaction can cause a total of three effects that can alter the parameters of the pore structure:

1. The reaction leads to a specific increase in weight in relation to the starting material. The specific surface and the specific pore volume of the modified products must therefore be corrected by a corresponding amount.

2. The reaction leads to a change in the polarity of the surface. Since the parameters of the pore structure are determined from adsorption and desorption measurements

Table 2. Maximum surface concentration of Si-aryl groups on porous silica samples (hydroxyl group concentration of the starting material $\alpha_{OH} = 8.0$ μmole · m^{-2}).

Sample modified with	Surface functional groups	Maximum surface concentration (μmol m^{-2})
	—OH	8.0
Phenyltrichlorosilane	$>Si(Cl)C_6H_5$	3.6
Diphenyldichlorosilane	$—Si(Cl)(C_6H_5)_2$	2.6
Triphenylchlorosilane	$—Si(C_6H_5)_3$	1.9
Benzyltrichlorosilane	$>Si(Cl)CH_2C_6H_5$	4.1
Silicon tetrachloride	$—SiCl_3$, $>SiCl_2$	2.3; 2.9
Thionyl chloride	—Cl	6.8
Silicon tetrachloride + Phenyllithium	$\geqslant Si—C_6H_5$	5.4
+ α-Naphthyllithium	$\geqslant Si—C_{10}H_7$	3.4
+ Trityllithium	$\geqslant Si—C(C_6H_5)_3$	1.9

with nitrogen, this can lead to a decrease in the quantity adsorbed and hence to a decrease in s and v_p.

3. The reaction results in the deposition of a layer of thickness t on the original surface. The average pore diameter consequently decreases by $\Delta\bar{d}_p = 2t$. This decrease may lead to a more or less large decrease in the specific surface area s and in the specific pore volume v_p, depending on the $\bar{d}_p$ value of the starting material.

In macroporous silica samples, these effects are negligible, and the parameters s, v_p and $\bar{d}_p$ are not affected. In purely microporous samples, the reactions mentioned lead to total blockage of the pores, since the size of the reacting molecules is of the same order of magnitude as the diameter of the pores. The resulting products are non-porous. In silica samples with intermediate pores, s and v_p were found to decrease by an amount which depends on the size of the reacting molecule. Also the mean pore diameter $\bar{d}_p$ of the modified samples becomes smaller than that of the starting material. These effects are still being investigated.

4.4. Influence of the Chemical Modification of the Surface of Porous Silica on Its Adsorption Properties[94]

On replacement of the acidic protons of the hydroxyl groups by Si-aryl groups, the hydrophilic character of silica largely disappears. The resulting products are hydrophobic, and can no longer be wetted with water. A quantitative measure of the change in the adsorption properties is provided by the heats of adsorption of the modified products for various polar gases (Table 3).

Table 3. Isosteric heats of adsorption ($q_{isost.}$) of benzene and methanol on various modified porous silica samples and the starting material ($s_{BET} = 35\ m^2 \cdot g^{-1}$, $\bar{d}_p = 960$ Å). Determination method: gas chromatography at 190°C.

Surface functional groups	$q_{isost.}$ (kcal mol^{-1}) Benzene	Methanol
—OH	6.9 ± 0.5	12.1 ± 0.5
>Si(OH)C_6H_5	4.6	9.3
—Si(OH)$(C_6H_5)_2$	4.4	7.2
—Si$(C_6H_5)_3$	1.3	1.7
—Si$(CH_3)_3$	1.6	2.2

The heat of adsorption of benzene or methanol, as expected, is highest for the starting material and lowest for the silica modified with triphenylchlorosilane. The latter corresponds in its hydrophobic character to a product obtained by reaction with trimethylchlorosilane. A gradation is found between the two values, the heat of adsorption decreasing with the number of phenyl groups bonded to the silicon atom. The differences are more pronounced in the case of the polar methanol than in the case of benzene. The results also confirm the composition of the surface, which was obtained from analytical data independently of adsorption measurements.

Substitution reactions can be carried out on the surface aryl groups. In this way, it is possible to synthesize porous silica samples having acidic or basic functional groups[96].

5. Closing Remarks

Porous silica and synthetic zeolites have been used as examples to illustrate a number of general lines of development that are currently of interest in the field of adsorbents. The most important aspects are their preparation and the use of chemical and physical methods to describe the geometry of their pore system and the chemical structure of their surface. It is only with the aid of this knowledge that adsorbents having desired properties can be prepared and their mode of action interpreted.

Received: May 19, 1971 [A 863 IE]
German version: Angew. Chem. *84*, 331 (1972)
Translated by Express Translation Service, London

[1] *S. J. Gregg* and *K. S. W. Sing*: Adsorption, Surface Area and Porosity. Academic Press, New York 1967.

[2] For a review of equipment used, see: *E. Robens*, Archiv für Technisches Messen (ATM), March/April issue 1968, Sartorius-Werke, Göttingen (Germany).

[3] *A. V. Kiselev*, Zh. Fiz. Khim. *38*, 1501 (1964); *41*, 1338 (1967); Gas Chromatogr. Proc. Symp. *5*, 238 (1964).

[4] *S. Brunauer, L. S. Deming, W. S. Deming*, and *E. Teller*, J. Amer. Chem. Soc. *62*, 1723 (1940).

[5] *D. P. Timofejew*: Adsorptionskinetik. VEB Deutscher Verlag für Grundstoffindustrie, Leipzig 1967.

[6] *M. M. Dubinin*, J. Colloid Interface Sci. *23*, 487 (1967); Advan. Colloid Interface Sci. *2*, 217 (1968).

[7] *D. H. Everett* in *E. A. Flood*: The Solid-Gas Interface. M. Dekker, New York 1967, Vol. 2, p. 1055.

[8] *J. J. F. Scholten* in *R. L. Bond*: Porous Carbon Solids. Academic Press, New York 1967, p. 225.

[9] *N. M. Kamakin* and *T. G. Platschenow* in *M. M. Dubinin*: Methoden zur Strukturuntersuchung an hochdispersen und porösen Stoffen. Akademieverlag, Berlin 1961, pp. 73 and 88.

[10] *W. M. Lukjanowitsch* and *L. W. Raduschkewitsch* in *M. M. Dubinin*: Methoden zur Strukturuntersuchung an hochdispersen und porösen Stoffen. Akademieverlag, Berlin 1961, p. 57.

[11] *S. Brunauer, P. Emmet*, and *E. Teller*, J. Amer. Chem. Soc. *60*, 309 (1938).

[12] *W. D. Harkins* and *G. Jura*, J. Amer. Chem. Soc. *66*, 1366 (1944).

[13] *A. V. Kiselev*, Usp. Khim. *14*, 367 (1945).

[14] *A. V. Kiselev* in *M. M. Dubinin*: Methoden zur Strukturuntersuchung an hochdispersen und porösen Stoffen. Akademieverlag, Berlin 1961, p. 132.

[15] *M. G. Kaganer*, Zh. Fiz. Khim. *33*, 2202 (1959); *42*, 640 (1958); Doklady Akad. Nauk SSSR *138*, 405 (1961).

[16] *B. C. Lippens, B. G. Linsen*, and *J. H. de Boer*, J. Catalysis *3*, 32 (1964); *B. C. Lippens* and *J. H. de Boer*, *ibid. 4*, 319 (1965).

[17] *St. Brunauer, L. E. Copeland*, and *D. L. Kantro* in *E. A. Flood*: The Solid-Gas Interface. Dekker, New York 1967, Vol. 1, p. 77.

[18] *G. A. Nicolaon*, Bull. Soc. Chim. France *1969*, 91.

[19] *A. A. Isirikyan* and *A. V. Kiselev*, Zh. Fiz. Khim. *65*, 601 (1961); *66*, 210 (1962).

[20] *H. M. Rootare* and *C. F. Prenzlow*, J. phys. Chem. *71*, 2733 (1967).

[21] *D. H. T. Spencer* in *R. L. Bond*: Porous Carbon Solids. Academic Press, New York 1967, p. 87.

[22] *L. Gurwitsch*, J. Phys. Chem. Soc. (Russ.) *47*, 805 (1915).

[23] *M. Polanyi*, Verh. dtsch. physik. Ges. *16*, 1012 (1914).

[24] *B. P. Bering, M. M. Dubinin*, and *V. V. Serpinsky*, J. Colloid Interface Sci. *21*, 378 (1966).

[25] *M. M. Dubinin*, Chem. Rev. *60*, 235 (1960).

[26] *J. H. de Boer* in *D. H. Everett* and *F. S. Stone*: The Structure and Properties of Porous Materials. Butterworth, London 1958, p. 68.

[27] *St. Brunauer*, Z. phys. Chem. (N. F.) *64*, 54 (1969).

[28] *R. Sh. Mikhail, St. Brunauer*, and *E. E. Bodor*, J. Colloid Interface Sci. *26*, 45 (1968).

[29] *J. H. de Boer, B. C. Lippens, B. G. Linsen, J. C. P. Broekhoff, A. van Heuvel*, and *Th. J. Osinga*, J. Colloid Interface Sci. *21*, 405 (1966).

[30] *J. H. de Boer, B. G. Linsen*, and *Th. J. Osinga*, J. Catalysis *4*, 643 (1965).

[31] *B. G. Linsen* and *A. van Heuvel* in *E. A. Flood:* The Solid-Gas Interface. Dekker, New York 1967, Vol. 2, p. 1025.

[32] *S. P. Shdanov* in *M. M. Dubinin:* Methoden der Strukturforschung an hochdispersen und porösen Stoffen. Akademieverlag, Berlin 1961, p. 176.

[33] *J. W. Sutherland* in *R. L. Bond:* Porous Carbon Solids. Academic Press, New York 1967, p. 1.

[34] *E. P. Barett, L. G. Joyner,* and *B. P. Halenda,* J. Amer. Chem. Soc. *73,* 373 (1951).

[35] *R. W. Cranston* and *F. A. Inkley,* Advan. Catalysis *9,* 143 (1957).

[36] *J. C. P. Broekhoff* and *J. H. de Boer,* J. Catalysis *9,* 8 (1967).

[37] *C. G. Shull,* J. Amer. Chem. Soc. *70,* 1405 (1948).

[38] *St. Brunauer, R. Sh. Mikhail,* and *E. E. Bodor,* J. Colloid Interface Sci. *24,* 451 (1967).

[39] *E. W. Washburn,* Phys. Rev. *17,* 273 (1921).

[40] *L. G. Joyner, E. P. Barett,* and *R. Skold,* J. Amer. Chem. Soc. *73,* 3155 (1951).

[41] *M. M. Dubinin,* Quart. Rev. (Chem. Soc.) *9,* 101 (1965).

[42] *R. M. Barrer,* Brennstoff-Chem. *35,* 325 (1954).

[43] *J. V. Habernickel,* Chemieanlagen und -verfahren, CAV, No. 10, p. 49 (1969); No. 11, p. 49 (1969).

[44] Cf. *H. W. Kohlschütter* and *K. Unger* in *E. Stahl:* Dünnschichtchromatographie. Springer, Berlin 1967, p. 1.

[45] *O. Grubner, P. Jiru,* and *M. Rálek:* Molekularsiebe. VEB Deutscher Verlag der Wissenschaften, Berlin 1968.

[46] *W. Eitel:* Silicate Science. Academic Press, New York 1966, Vol. IV, p. 461.

[47] *D. W. Breck, W. G. Eversole, R. M. Milton, T. B. Reed,* and *T. L. Thomas,* J. Amer. Chem. Soc. *78,* 5963 (1956).

[48] *T. B. Reed* and *D. W. Breck,* J. Amer. Chem. Soc. *78,* 5972 (1956).

[49] *R. M. Barrer,* Ber. Bunsenges. Phys. Chem. *69,* 786 (1965).

[50] *R. M. Barrer,* J. Chem. Soc. *1950,* 2342.

[51] *R. M. Barrer* and *D. W. Riley,* Trans. Faraday Soc. *46,* 853 (1950).

[52] *R. M. Barrer,* Brit. Chem. Engng. *1959,* 436.

[53] *R. M. Barrer, J. W. Baynham, F. W. Bultitude,* and *W. M. Meier,* J. Chem. Soc. *1959,* 195.

[54] *S. P. Shdanov,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1965,* 950.

[55] *R. K. Iler:* The Colloid Chemistry of Silica and Silicates. Cornell University Press, Ithaca 1965.

[56] *R. Yu. Sheinfain* and *J. E. Neimark,* Kinetika i Kataliz *8,* 433 (1967).

[57] *K. Gärtner* and *R. Griessbach,* Kolloid-Z. *160,* 21 (1958).

[58] *K. C. Sen* and *B. N. Ghosh,* J. Indian Chem. Soc. *31,* 803 (1954).

[59] *J. D. Madeley* and *K. S. W. Sing,* J. Appl. Chem. *4,* 365 (1954); *11,* 313 (1961); *12,* 494 (1962).

[60] *J. E. Neimark* and *J. B. Slinjakova,* Kolloidnyi Zh. *18,* 219 (1956).

[61] *R. Yu. Sheinfain,* Kolloidnyi Zh. *23,* 756 (1961).

[62] *J. E. Neimark* and *J. B. Slinjakova,* Kolloidnyi Zh. *19,* 706 (1957).

[63] *J. E. Neimark, M. A. Piontorskaja,* and *J. B. Slinjakova,* Kolloidnyi Zh. *18,* 61 (1956).

[64] *D. Dollimore* and *G. R. Heal,* J. Appl. Chem. *12,* 445 (1962).

[65] *O. P. Stas, R. Yu. Sheinfain,* and *J. E. Neimark,* Kolloidnyi Zh. *29,* 256 (1967).

[66] *A. V. Kiselev, V. M. Lukyanovich, Yu. S. Nikitin, E. B. Oganesyan,* and *A. J. Sarakhov,* Kolloidnyi Zh. *31,* 388 (1969).

[67] *A. V. Kiselev, Yu. S. Nikitin,* and *E. B. Oganesyan,* Kolloidnyi Zh. *31,* 525 (1969).

[68] *A. V. Kiselev, Yu. S. Nikitin, A. J. Sarakhov,* and *E. B. Oganesyan,* Kolloidnyi Zh. *30,* 842 (1968).

[69] *A. J. de Vries, M. le Page, R. Beau,* and *C. L. Guillemin,* Anal. Chem. *39,* 935 (1967).

[70] *H. W. Kohlschütter* and *U. Mihm,* Kolloid-Z., Z. Polymere *243,* 148 (1971).

[71] *K. Unger* and *J. Schick-Kalb,* unpublished.

[72] *W. M. H. Sachtler,* Angew. Chem. *80,* 673 (1968); Angew. Chem. internat. Edit. *7,* 668 (1968).

[73] *D. Menzel,* Angew. Chem. *82,* 263 (1970); Angew. Chem. internat. Edit. *9,* 255 (1970).

[74] *H. P. Boehm,* Angew. Chem. *78,* 617 (1966); Angew. Chem. internat. Edit. *5,* 533 (1966).

[75] *H. P. Boehm, E. Diehl, W. Heck,* and *R. Sappock,* Angew. Chem. *76,* 742 (1964); Angew. Chem. internat. Edit. *3,* 669 (1964).

[76] *K. Unger,* Habilitationsschrift, Technische Hochschule Darmstadt 1969.

[77] *V. F. Kiselev,* Z. Chem. *7,* 369 (1969).

[78] *J. J. Fripiat* and *J. Uytterhoeven,* J. Phys. Chem. *66,* 800 (1962).

[79] *K. Unger* and *E. Gallei,* Kolloid-Z., Z. Polymere *237,* 358 (1970).

[80] *L. T. Zhuravlev, A. V. Kiselev, V. P. Naidina,* and *A. L. Polyakov,* Zh. Fiz. Khim. *37,* 1113, 1216 (1963).

[81] *L. T. Zhuravlev* and *A. V. Kiselev,* Kolloidnyi Zh. *24,* 22 (1962).

[82] *L. T. Zhuravlev* and *A. V. Kiselev,* Zh. Fiz. Khim. *39,* 236 (1965).

[83] *V. Ya. Davydov, A. V. Kiselev,* and *L. T. Zhuravlev,* Trans. Faraday Soc. *60,* 2254 (1964).

[84] *V. Ya. Davydov* and *A. V. Kiselev,* Zh. Fiz. Khim. *37,* 1404 (1963).

[85] *L. H. Little:* Infrared Spectra of Adsorbed Species. Academic Press, New York 1967.

[86] *V. Ya. Davydov, L. T. Zhuravlev,* and *A. V. Kiselev,* Zh. Fiz. Khim. *38,* 1108 (1964).

[87] *C. G. Armistead, A. J. Tyler, F. H. Hambleton, S. A. Mitchell,* and *J. A. Hockey,* J. Phys. Chem. *73,* 3947 (1969).

[88] *J. B. Peri* and *A. L. Hensley jr.,* J. Phys. Chem. *72,* 2926 (1968).

[89] *E. Gallei* and *G. A. Parks,* J. Colloid Interface Sci., in press.

[90] *J. E. Neimark,* Izv. Akad. Nauk Beloruss. SSR, Ser. Khim. Nauk *1966,* 102.

[91] *K. Unger, K. Berg,* and *E. Gallei,* Kolloid-Z., Z. Polymere *234,* 1108 (1969).

[92] *K. Berg* and *K. Unger,* Kolloid-Z., Z. Polymere, *246,* 682 (1971).

[93] *K. Unger, W. Thomas,* and *P. Adrian,* Kolloid-Z., Z. Polymere, in press.

[94] *K. Unger, K. Berg, E. Gallei,* and *G. Erdel,* Fortschr. Kolloide and Polymere *55,* 34 (1971).

[95] *G. Erdel,* Dissertation, Technische Hochschule Darmstadt, 1972.

[96] *K. Berg, K. Unger,* and *T. Lothe,* unpublished.

Advances in Acoustical Holography

By K. Preston, Jr.[*]

The most recent branch of holography, acoustical holography employing acoustical radiation, presents a variety of new and highly interesting possible applications: Thus objects can be imaged in a turbid liquid medium (marine research); the technique can be used for non-destructive investigations of the internal structure of objects that are opaque to light (testing of materials) and is possibly also a potential tool for the three-dimensional imaging of biological structures (biomedical diagnosis).

1. Introduction

Optical holography is familiar to all of us. It has opened a new and interesting area of technical endeavor. Although not every reader of this article may have seen holographic images with his own eyes, he will certainly have encountered numerous articles on the subject of holography.

The reader is probably less aware that holography has been used in an entirely different mode during the past five years—in a mode wherein the hologram is made by means of acoustical radiation. After recording an acoustical hologram a holographic image may be formed by means of light so that the image may be examined by the human eye. Images may also be formed from an acoustical hologram by means of a digital computer where the image is displayed using a cathode ray tube. It is the purpose of this article to review the state of the art in the field of acoustical holography and to illustrate the benefits a chemist may derive from use of the technique.

2. Fundamental Properties

Before continuing the discussion of acoustical holography, this article discusses some of the fundamentals of holography by using one or two illustrations from the world of optical holography. Either the optical or the acoustical hologram may be recorded in the form of a transparency which, when illuminated from a monochromatic point source, acts upon the illuminating radiation in such a way as to create a multiplicity of spherical wavefronts each corresponding in strength and apparent source position to all points in the original scene from which the hologram was made. This explains why holographic imaging has been called *wavefront reconstruction*[1]. There is no fundamental restriction in holography as to the particular radiation chosen to create the hologram nor on the radiation used for illuminating the hologram in performing wavefront reconstruction.

2.1. Forming the Hologram

Let us first set holography in perspective by considering the formation of the hologram itself. Construction of the hologram of an object requires that the object be illuminated with monochromatic radiation. To create the hologram, interference fringes are formed between the back-scattered waves of radiation from the object and another wavefront called the *reference*. In most holographic systems the reference is of the same frequency as the illuminating radiation.

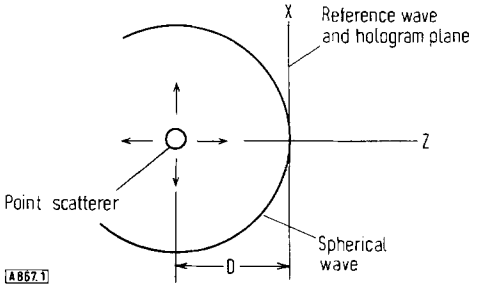


Fig. 1. Schematic diagram showing a spherical wave radiating from a point scatterer and impinging in the hologram plane with a planar reference wave.

The simplest hologram—and the one from which all other holograms may be derived—is the hologram of a point scatterer. Figure 1 shows the spherical wave reflected from a single point scatterer; the $x-y$ plane (perpendicular to this page) is chosen to be the *hologram plane*. It is in this plane that the interference pattern between the back-scattered wave and the reference wave is formed. For simplicity Figure 1 shows the hologram plane parallel to a coplanar reference wave. In this case the interference pattern which constitutes the hologram is the well known *Fresnel zone plate*[2] of classical optics (see Fig. 2). This hologram consists of alternately bright and dark concentric rings. This hologram is dark at the center when the reference wave and the back-scattered wave are out of phase. The rings occur because the reference wave and the back-scattered spherical wave go alternately in and out of phase. The rings are more closely spaced as the distance from the center increases because of the quadratic nature of the phase across a spherical surface.

If D is the distance from the point scatterer to the origin, it is, of course, the radius of the back-scattered wave. The distance from the point scatterer to the $x-y$ plane is given by

$$\sqrt{D^2 + r^2};\ r^2 = x^2 + y^2$$

[*] Dr. K. Preston, Jr.
Optical Group
The Perkin-Elmer Corporation
Norwalk, Conn. 06852 (USA)

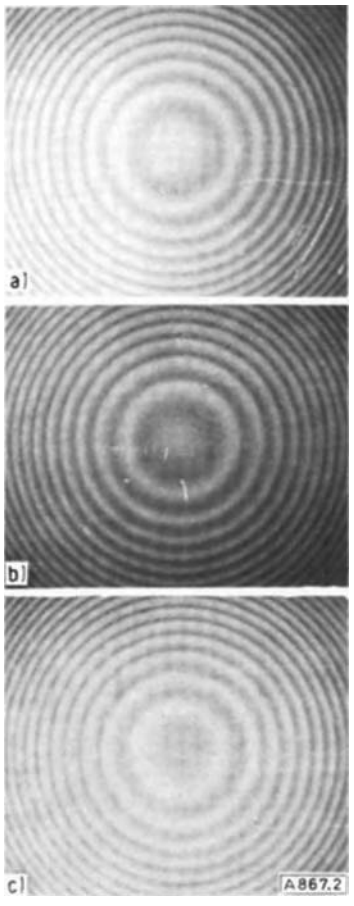


Fig. 2. Three holograms of a point scatterer showing, a) in-phase, b) intermediate phase, and c) out-of-phase conditions on the optical axis.

In order to determine whether the plane reference wave and the back-scattered wave are in or out of phase, we merely divide the difference between these two distances by the wavelength λ as follows:

$$\varphi(r) = \frac{2\pi}{\lambda}(\sqrt{D^2+r^2} - D)$$

If the above quantity is an integral multiple of π, then the difference between the two distances is an integral number of half wavelengths. If the integer is even, an in-phase condition exists yielding a bright ring in the hologram. If the integer is odd, the two waves are out-of-phase and a dark ring exists.

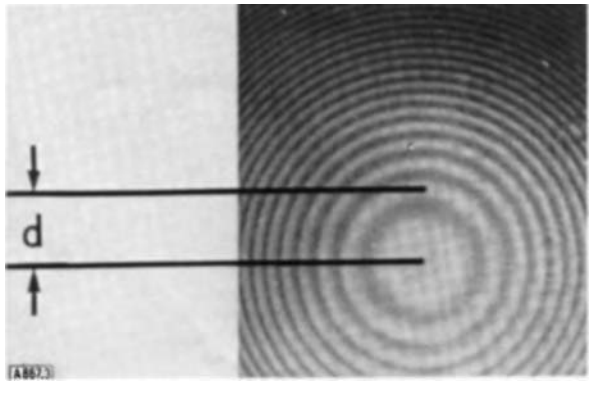


Fig. 3. Hologram of a point scatterer displaced a distance d from the optical axis.

A few simple variations on the Fresnel zone plate hologram will clarify the fundamentals of holography for the reader. For example, if the point scatterer shown in Figure 1 is moved a distance d along the y axis, the interference pattern created in the hologram plane merely shifts off-axis by an amount given by d; otherwise the pattern is unchanged (Fig. 3). It is clear that the position of the center of the hologram remains directly at the intersection of the normal to the reference wave which passes through the point scatterer.

Another example of interest occurs when the point scatterer is moved farther from the $x-y$ plane. Now, of course, the radius of the spherical wave is larger than before. The interference rings, therefore, will become more widely spaced since the quantity D in the above equation is larger. In other words there is less wavefront curvature and the back-scattered radiation goes in and out of phase more slowly as a function of x. The result is shown in Figure 4. Conversely, when the point scatterer is closer to the hologram plane, the interference rings in the hologram become more closely spaced. Thus the distance to the point scatterer is directly related to the spacing of the interference rings in the hologram.

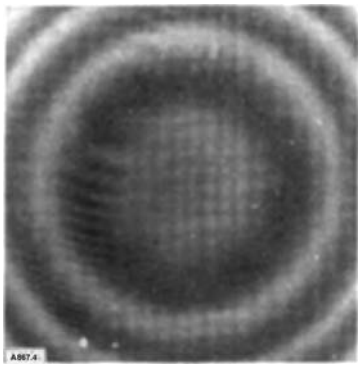


Fig. 4. Hologram of a point scatterer which is at an extreme distance from the hologram plane.

It is simple to extend the above concepts to more general holography. No matter what the configuration of the object being holographed, Huygens principle[3] tells us that it may be considered to consist of a multiplicity of point scatterers having different positions. Thus the hologram becomes a superposition of zone plates. Holograms of more general objects are discussed and illustrated in Sections 4 and 5.

2.2. Forming the Image

So far, this article has only treated the formation of a hologram and its general appearance. Next we discuss how the hologram may be used to produce an image. For simplicity consider the holographic image formed from a hologram created from a single point scatterer, *i.e.*, the Fresnel zone plate. In order to form an image using optical radiation a simple methodology is employed, as illustrated in Figure 5. The hologram is illuminated from a point source of optical radiation. The hologram of a

single point scatterer has the property that it focuses some of the radiation which passes through it to a point. This is because this simple hologram has the properties of a Fresnel lens[14]. The mechanism of focusing is the phenomenon called *diffraction*. Thus the image is formed.

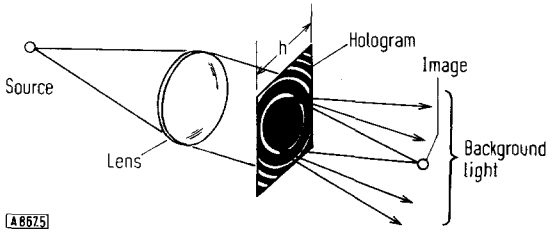


Fig. 5. An optical arrangement for producing an image of a point scatterer from its hologram.

However, this simple zone plate hologram also forms a virtual image. Furthermore it allows some of the illuminating radiation which passes through it to continue with its direction unaltered. Both the unaltered illumination and the radiation from the virtual image serve to corrupt the desired image. This is illustrated in Figure 6, which shows the real image formed from a zone plate hologram surrounded by a halo of illumination produced by the illuminating radiation whose direction is unaltered. Radiation from the virtual image is also present but is more dispersed. Several techniques may be used both in optical and acoustical holography to circumvent this type of image degradation (see Section 3).

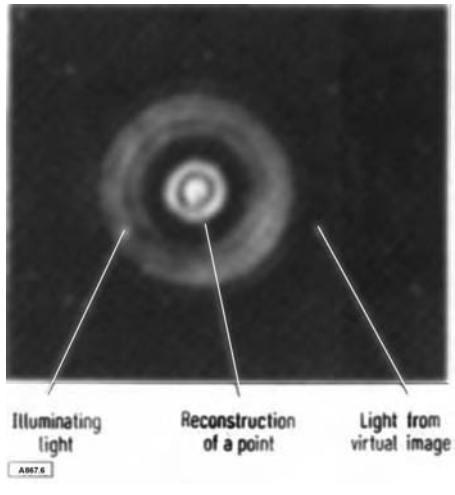


Fig. 6. Image formed from the hologram of a point scatterer showing the encircling halo produced by nondiffracted light from the illuminating source.

3. Methodology for Acoustical Holography

All of the above examples have been taken from optical holography. As we shall see, holograms made by acoustical techniques correspond directly to the holograms and holographic images shown above. The differences between acoustical and optical holography are primarily methodological ones.

The major difference between acoustical and optical holography is that the type of radiation used is sound rather than light. Another important difference is that there is no equivalent in acoustics to the silver halide emulsions used in recording optical holograms. A completely different method must be used for recording. In order to detect acoustical radiation over the hologram plane the user requires a material or device which is sensitive in some manner to acoustical radiation. In the early 1960's when the author was faced with the problem of how to record the acoustical hologram it was elected to scan the hologram plane with a small piezoelectric detector (see Fig. 7).

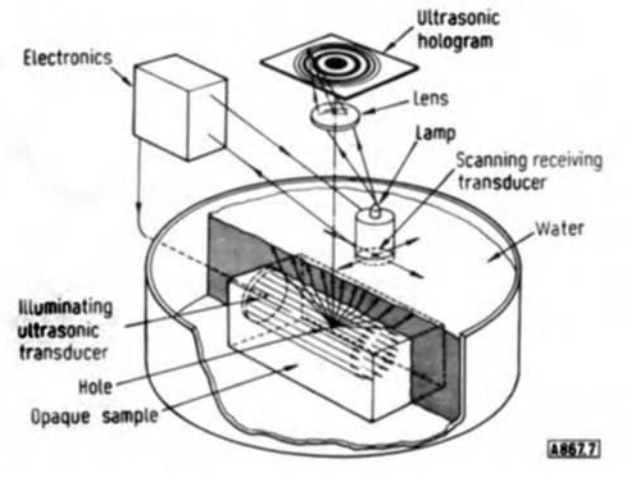


Fig. 7. Diagram of the arrangement utilized for producing an acoustic hologram by means of mechanical scanning.

The apparatus shown in Figure 7 was designed to utilize the fact that acoustical radiation propagates in many materials which are opaque to light. This permits the formation of acoustical holograms of point scatterers, *i.e.*, acoustic discontinuities within these materials. From these holograms images may be formed of the *internal structure* of these materials. In the apparatus shown the acoustical radiation is obtained by connecting a piezoelectric transducer to a block of the material to be examined. The block itself is placed in a tank of water so that there is good acoustical coupling between the back-scattered radiation and the transducer which scans the hologram plane.

The electronic system shown in Figure 7 serves three functions:

1) Generation of the excitation for the transmitting transducer.

2) Amplification and measurement of the back-scattered radiation detected by the scanning transducer.

3) Generation of signals to the lamp which is used to record the hologram.

The recording lamp is mechanically attached to the carrier which moves the scanning transducer. An image of the recording lamp is formed by means of a camera on photographic film.

The electronic system takes advantage of modern pulse techniques. Instead of being continuously energized, the

transmitting transducer is energized by short pulses. Also the acoustical radiation detected by the scanning transducer is amplified by a pulse amplifier. This approach has the advantage that the hologram which is recorded is only produced from acoustical radiation back-scattered from a volume in space selected by the length of the pulse utilized. This approach permits the elimination from the hologram of the effects of unwanted back-scattered radiation (such as that coming from exterior surfaces of the object being examined or from the surfaces of the tank itself). Those readers familiar with radar techniques will immediately see the analogy between this methodology and that used in pulsed radar.

3.1. A Simple Acoustical Hologram

A simple zone plate like those mentioned in Section 2 was formed using the apparatus shown in Figure 7. A small steel sphere was placed in the tank of water and ensonified by the transmitting transducer. The transmitting transducer was placed some distance from the sphere rather than being in contact with it. Thus the major source of back-scattered radiation was the surface of the sphere. The back-scattered radiation produced was picked up by the scanning transducer as it traversed the hologram plane. The resultant acoustical hologram was recorded on photographic film by means of the recording lamp and camera. The result is shown in Figure 8.

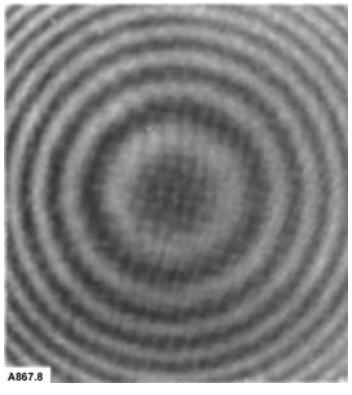


Fig. 8. Acoustic hologram of a point scatterer.

The complete parameters of this experiment are listed below:

Parameter	Value
Acoustical frequency	5 MHz
Pulse duration	100 μs
Pulse repetition frequency	1 kHz
Number of cycles in the transmitting pulse	500
Size of the hologram plane	20 × 20 cm
Distance of the sphere from the hologram plane	1.1 m
Number of scans across the hologram plane	256
Scanning velocity	4 cm s^{-1}
Number of pulses recorded	128 000
Size of hologram	1.0 × 1.0 cm
Recording medium	Eastman Kodak SO–243

3.2. Acoustical Holographic Imaging

To form an image from the acoustical hologram shown in Figure 8 the optical arrangement shown in Figure 9 was utilized. This arrangement differs from that shown in Figure 5 in that the image is no longer corrupted by the halo of illumination produced by light whose direction is unaltered as it passes through the hologram. This improvement is produced by two additional lenses which serve two functions. The first lens causes all illumination whose direction is unaltered by the hologram to impinge on what is called a "zero-order stop". This stop absorbs almost all of the illumination which would add a halo to the image. The second lens (in conjunction with the first one) relays the image formed by the hologram to a focal plane where it may be both observed and photographed. Light from the virtual image is widely dispersed in this focal plane and has essentially no effect on the image. The image itself is shown in Figure 10.

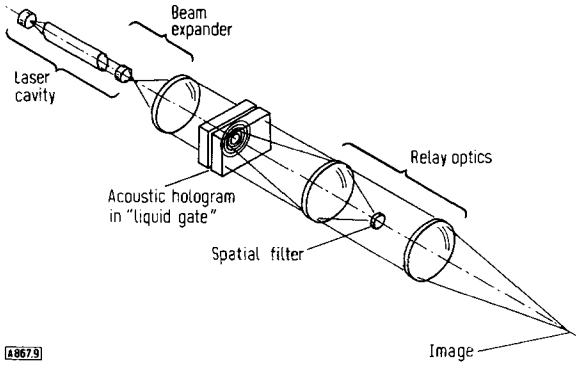


Fig. 9. Optical arrangement for use in producing acoustic holographic images wherein non-diffracted light is eliminated from the image.



Fig. 10. Image formed from the acoustic hologram of a point scatterer using the imaging system shown in Fig. 9.

Another method of forming the image from an acoustical hologram is to compute the image by means of a high speed digital computer. The results of the calculation may then be converted into either graphical or pictorial form. In order to do this the acoustical hologram must first be transferred into a format which is digital. The acoustical hologram shown in Figure 8 is a photographic transparency. An $x-y$ microdensitometer was utilized to read the point by point transmission values of the transparency. These transmission values were digitized and stored on magnetic tape which was then transferred to the computer.

The computer program required to calculate the image must perform the following four functions:

1) Compute a new set of transmission values from the values recorded which have zero mean. This operation is equivalent to the action of the zero-order stop mentioned above.

2) Compute a conjugate quadratic focusing function and apply it to the computed transmission values. This compensates for the focusing action of the hologram acting as a Fresnel lens. The proper focusing function is determined from geometrical considerations which take into account the original size of the hologram and the distance of the object holographed from the hologram plane.

3) Compute the two-dimensional Fourier transform of the resultant complete transmission values. This operation is equivalent to the function of the second lens in Figure 9[5].

4) Compute the intensity of the image by taking the square of the modulus of the resultant Fourier transform. This is the final step in the computational program.

A computer generated graph of the resulting calculation corresponding to the hologram shown in Figure 8 is provided in Figure 11. The z axis of this graph corresponds to the acoustical intensity while the $x-y$ plane is the final focal plane shown in Figure 9.

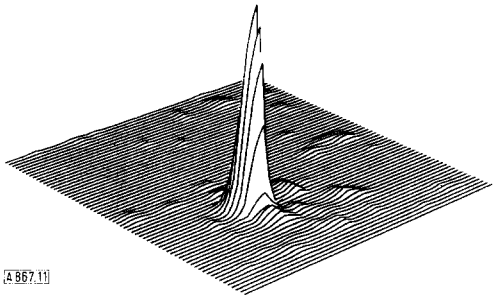


Fig. 11. Graph showing the computer generated acoustic intensity plot corresponding to the image shown in Fig. 10.

3.3. More Complex Holograms

Acoustical holograms have been made at Perkin-Elmer of more complicated structures than that of the simple sphere discussed above. One of the earliest acoustical holograms made is the now famous "bolt-hologram" recorded by *Kreuzer*[6] (Fig. 12). A conventional photograph of the bolt from which the hologram was made is shown in Figure 13. The bolt is approximately 13 mm in diameter with approximately 4 threads to the centimeter.

The acoustical hologram of the bolt has a highly complex structure. Upon observing the hologram it is possible to see a set of essentially parabolic rings which are due to the interference of the cylindrical wave reflected from the main body of the bolt. These rings are interrupted by a certain orthogonal fine structure which is due to the effect of sound back-scattered from the threads of the bolt. Using the optical image forming technique diagramed in Figure 9 the acoustical holographic image of the bolt was formed and photographed. The result is shown in Figure 14.

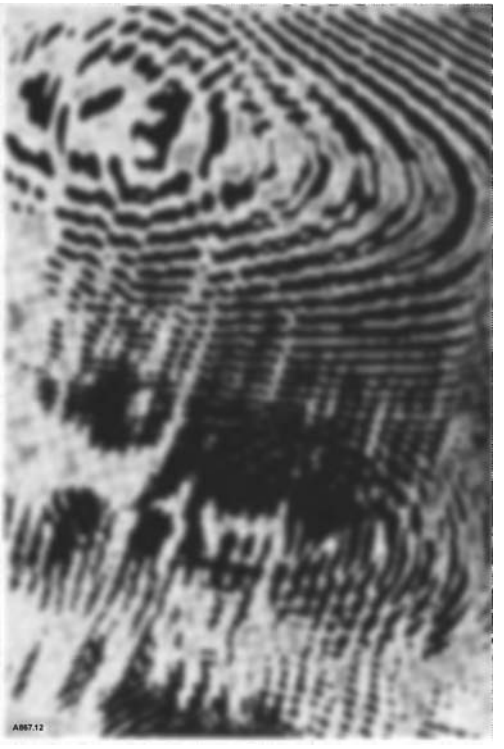


Fig. 12. Acoustic hologram of a 13 millimeter diameter bolt having two threads to the millimeter.

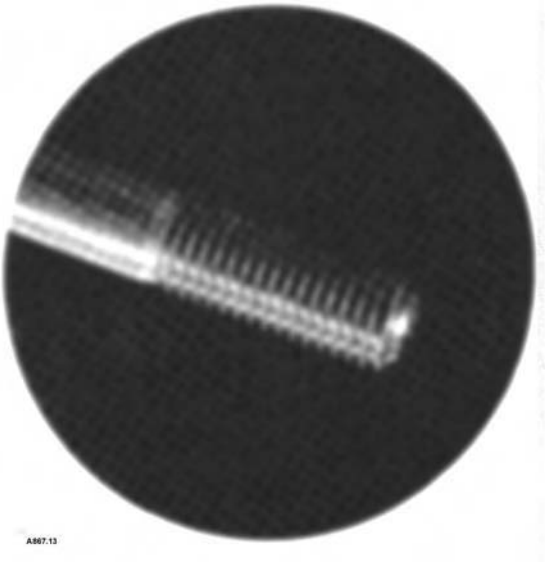


Fig. 13. Ordinary photograph of the bolt whose hologram is shown in Fig. 12.

The acoustic-holographic images shown in Figures 10 and 14 both correspond to objects lying in a plane. The holographic image of the entire object is in focus in this plane. When several objects are holographed, however, it is no longer possible to focus on all of them simultaneously and image interpretation becomes difficult.

Figure 15 shows a configuration of three objects which are at different distances from the hologram plane. The objects are all metal spheres and were simultaneously ensonified (in water) by the transmitting transducer. Two of the spheres shown in Figure 15 are approximately 13 mm in diameter and the third is approximately 25 mm

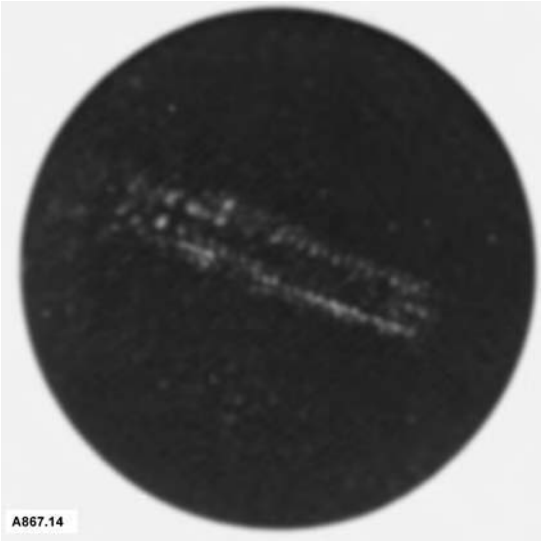


Fig. 14. Acoustic holographic image of the bolt shown in Fig. 13.

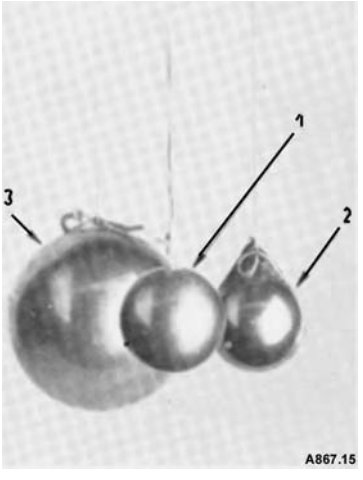


Fig. 15. Photograph of 3 steel spheres 25 mm, 13 mm, and 13 mm diameter placed 114, 118, and 122 cm from the hologram plane, respectively.

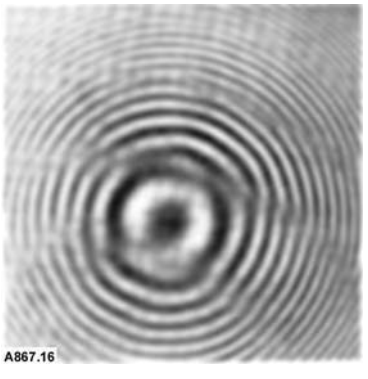


Fig. 16. Acoustic hologram of the three-sphere configuration shown in Fig. 15.

in diameter. Their distances to the hologram plane were 110, 114, and 118 cm, respectively. Using pulses of 5 MHz acoustic radiation having a duration of 150 microseconds a hologram was made of the entire volume containing the three spheres (Fig. 16). Because of the close lateral spacing of the spheres this hologram has the appearance of a single Fresnel zone plate. Close examination, however, shows a pattern of spherical moire fringes. These indicate, as expected, that the hologram consists of three superimposed zone plates. The moire fringes are circular because the three zone plates correspond to objects at different distances from the hologram plane. (Linear moire fringes would occur if the objects were all equidistant from the hologram and displaced laterally.)

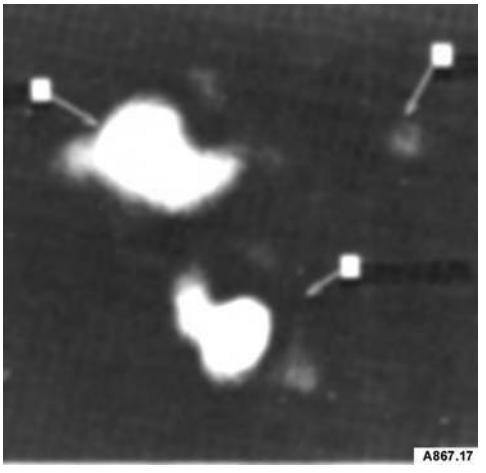


Fig. 17. Acoustic holographic image of the three spheres generated using the imaging arrangement shown in Fig. 9.

Figure 17 shows a holographic image formed from this hologram using the optical imaging arrangement shown in Figure 9. The image of the sphere nearest the hologram plane is in focus. The image of the sphere most distant from the hologram plane is strongly defocused. Surprisingly, the intermediate sphere is scarcely visible. Photometric measurements were made which showed that the in-focus intensity of the image of the intermediate sphere was less than 5% of the in-focus intensity of the other two spheres. This surprising result is assumed to be due to the fact that multiple reflections from the three spheres which arrive simultaneously in the hologram plane produced interference effects which suppressed the Fresnel zone plate corresponding to the intermediate sphere.

In order to confirm the results of optical imaging from the acoustical hologram the hologram shown in Figure 16 was scanned and its transmission values were recorded on

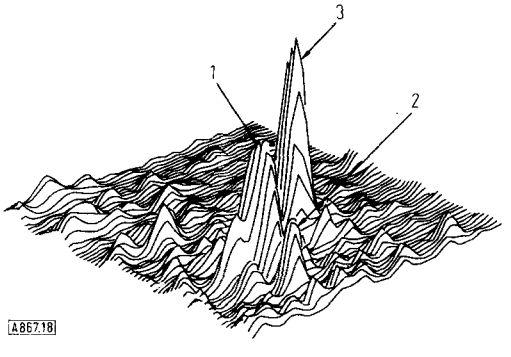


Fig. 18. Computer generated acoustic intensity graph corresponding to the acoustic holographic image shown in Fig. 17.

magnetic tape. The acoustic field intensity at a focal plane corresponding to the position of the intermediate sphere was calculated using the computer program described above. A graph-out of the result is shown in Figure 18. The low intensity of the image of the intermediate sphere is apparent thus confirming the previous results. This demonstrates that the formation of acoustical holograms of objects occupying a volume suffers from two rather serious problems:

1) It is impossible to focus on all portions of the volume simultaneously. The image of the portion of the object which is in focus is corrupted by defocused images of other portions of the object.

2) The true intensity of sound reflected from various portions of the object is not represented properly in the volume hologram due to interference effects.

3.4. Focus Equalization

Recently the author has worked out a method of circumventing most of the problems which are associated with the formation of images from holograms. The approach of holographing the entire volume was discarded. A new approach was taken where a multiplicity of holograms are made of different portions of the volume being holographed. The result is an image which is in focus throughout the volume. This new method is thus called *focus equalization*. Imaging is carried out entirely by computer.

Pulses of acoustical radiation are utilized which are only long enough to permit the production of a complete Fresnel zone plate from point scatterers in each region of the volume ensonified. The resultant computer generated image is then equalized for focus throughout the volume. Returning to the object configuration shown in Figure 15 (3 spheres) the resultant computer graph-out is shown in Figure 19. A comparison of Figure 19 with Figure 18 shows the enormous improvement in volume holographic imaging produced by this new technique of focus equalization.

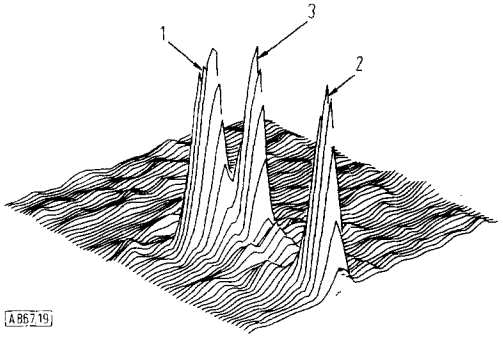


Fig. 19. Computer generated graph of the three-sphere image using focus equalization.

In order to take full advantage of focus equalization it is preferable to create a computer display which is readily interpretable when observed visually. It has already been mentioned in the introduction that it is possible to display images using a cathode ray tube. It is also possible to create photographic transparencies by means of the same technique. In order to record the graph-out shown in Figure 19 as an image on the face of a computer driven cathode ray tube, the electron beam is made to scan the face of the tube and the intensity of the electron beam is modulated according to the calculated values of acoustical intensity. Simultaneously the face of the tube is imaged on photographic film for recording purposes. The photographic transparency corresponding to Figure 19 is shown in Figure 20. This figure readily conveys to the human observer the fact that three objects exist in the volume holographed. This image is far superior to the optical acoustical holographic image shown in Figure 17. As can be seen, the image of each sphere is simultaneously in focus.

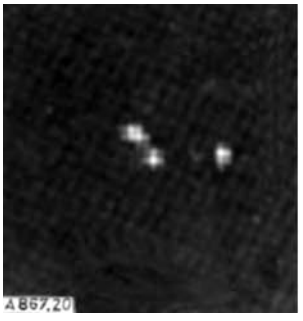


Fig. 20. Computer generated image of the three-sphere configuration using focus equalization.

The one draw-back of this display is that the human observer cannot tell that the three spheres shown are at different distances from the hologram plane. However, since distance information is included in the computer calculations, it may be added to the display. This has been done recently by the author with the result shown in Figure 21. Figure 21 is a stereo-pair which, when observed using both eyes in such a manner that the two images fuse, gives depth to the image. The right hand image of the pair is the same as that shown in Figure 20 while the left hand image was produced by translating the calculated values of acoustical intensity for different regions of the volume with respect to each other by the amount required to produce a left-eye view for an observer located halfway between the hologram plane and the three spheres.

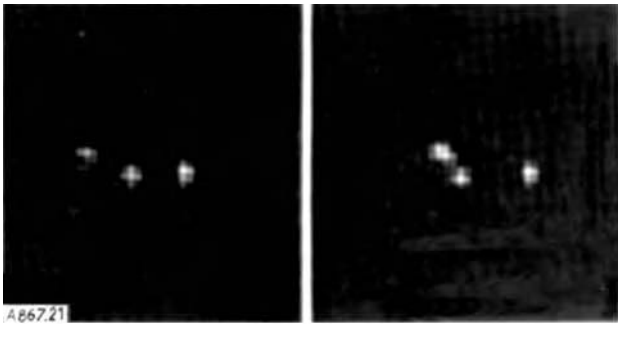


Fig. 21. Computer generated stereo pair of the three-sphere configuration shown in Fig. 15.

Observing the stereo-pair makes it possible for the viewer to ascertain that the central sphere is the nearest, the sphere on the left is the farthest, and that the sphere on the right is at an intermediate distance.

4. Views of Interior Structure

Acoustical holography may be used to form images of the interior structure of objects as well as of their exterior surfaces. Some preliminary experiments in this area were performed by *Kreuzer* in 1968. An example of a typical experiment is illustrated by Figure 22. This figure shows an aluminum block through which a slanted hole 3 mm in diameter has been drilled. In one of *Kreuzer*'s experiments this block was ensonified using a 5 cm diameter transmitting transducer affixed to one face of the block. The pulses of sound which were back-scattered by the hole were picked up by a scanning transducer moving in a horizontal hologram plane. The actual hologram formed is shown in Figure 23. This is a volume hologram where the duration of the pulses was sufficiently long to permit pulses scattered from all points along the hole to be received simultaneously

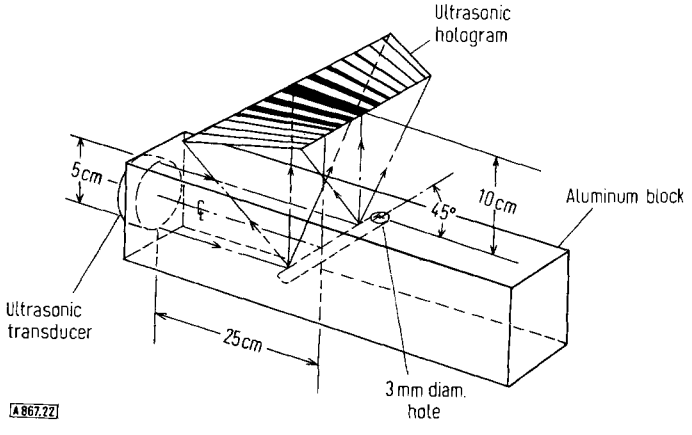


Fig. 22. Schematic diagram showing the arrangement used for creating an acoustic hologram of a hole in an aluminum block.

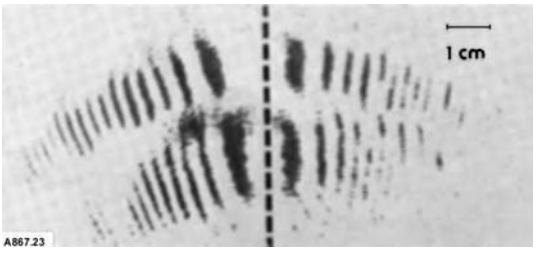


Fig. 23. Actual acoustic hologram of a hole (3 × 80 mm) in an aluminum block.

in the hologram plane by the scanning transducer. An acoustical frequency of 5 MHz produced a wavelength in the aluminum block of approximately 2 mm. The hole in the aluminum block had a diameter only somewhat greater than 1 acoustical wavelength. The hole was about 40 wavelengths long.

Images were formed from the hologram shown in Figure 23 using optical techniques. In this case two approaches were adopted to solve the problem of focusing optically throughout a volume. Figure 24a shows the image of the hole when the focal plane was adjusted to cause the upper end of the image of the hole to be in focus. Only a portion of the entire image of the hole can be seen as in focus. Most of the image is defocused to the point of being invisible. Since the image of the hole lies in a plane, the focusing problem may be solved by placing a tilted surface in the focal plane and by focusing upon this surface. The result is shown in Figure 24b. The result for this special case is quite satisfactory. This is only due to the fact that the hole lay in a plane. In order to completely solve the problem of volume holography for the interior structure of objects it is obvious that the focus equalization technique discussed above would be advantageous. This approach is now being pursued.

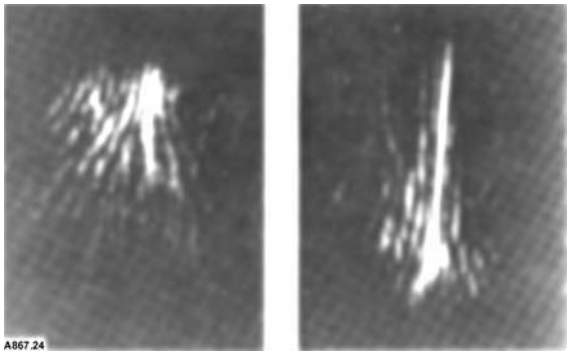


Fig. 24. Acoustic holographic images of the slanted hole shown in Fig. 22 taken a) end-on (left) and b) in the plane of the hole (right).

5. Summary

This paper has surveyed the relatively new field of acoustical holography[*] and has described methods for forming the hologram as well as both optical and digital-computer methods for forming acoustical holographic images. This new field is still in its developmental stages and should progress rapidly now that certain of the limitations which are fundamental to optical imaging from acoustical holograms have been removed by reverting to modern digital-computer methods for calculating and displaying images.

This field offers a technology which permits objects to be imaged in a liquid medium when ordinary photography is impossible. One example of such an application would be that of imaging objects in turbid water, *i.e.*, water filled with particulate matter. Acoustical holography is also of interest to workers in materials testing where it is necessary to observe the internal structure of objects which are opaque to light. The illustration provided where an image was formed of a long hole in an aluminum block gives a dramatic demonstration of this capability. Another

[*] In addition to the references cited in the main body of the article the reader who wishes a broad overview of the entire field should read the three volume survey edited by *Metherell* [9].

application may be in medicine where it might be possible to form three dimensional images of biological structures assuming that the problems associated with the transmission of sound in tissue can be solved.

The fact that systems for use in acoustical holography are rapidly becoming all-electronic (rather than electro-optical) makes instrumentation simpler and suggests that real-time imaging may soon be possible, particularly in view of recent advances in fast Fourier computation[7]. Also the single scanning receiving transducer may soon be replaced by transducer arrays taking advantage of well-known radar techniques in aperture synthesis[8]. The demonstration of stereo displays of acoustical holographic images where all portions of the volume are simultaneously in focus and where depth effects are readily apparent is the most recent advance. All of these innovations appear to be leading us towards extremely practical working systems for use in underwater exploration, materials testing, and perhaps, in biomedical diagnosis.

The author would like to acknowledge support from the US Army Materials and Mechanics Research Agency which permitted our early work to materialize. It should be noted that the first demonstration of acoustical holographic imaging at Perkin-Elmer was made by J. L. Kreuzer working under the direction of the author. Subsequent work, supported by Perkin-Elmer, has benefited from efforts by W. R. Arndt, J. R. Carvalko, and D. DeCava. F. Reizman has conducted the recent quantitative studies in evaluating the defects of optically forming acoustical holographic images. The computer generation of acoustical holographic images has been performed with the assistance of Jeanne Sand and D. Rosenzweig. Gennifer Austin is to be thanked for typing this manuscript and Grace Chew and J. Bannister for assistance with the illustrations.

Received: September 13, 1971 [A 867 IE]
German version: Angew. Chem. *84*, 280 (1972).

[1] *E. N. Leith*, J. Opt. Soc. Amer. *52*, 1123 (1962).

[2] *G. R. Fowles:* Introduction to Modern Optics. Holt, Rinehart, and Winston, New York 1968, Chapter 4.

[3] *G. Strong:* Concepts of Classical Optics. W. H. Freeman and Co., London 1958, Chapter 1.

[4] *L. Levi:* Applied Optics. Wiley, New York 1968, Chapter 9.

[5] *K. Preston, Jr.:* Use of the Fourier Transformable Property of Lenses in Signal Spectrum Analysis. MIT Press, Cambridge, Mass. 1965, Chapter 4.

[6] *K. Preston, Jr.* and *J. L. Kreuzer*, Appl. Phys. Lett. *10*, 150 (1967).

[7] *W. T. Cochran et al.*, Proc. IEEE *55*, 1664 (1967).

[8] *L. J. Cutrona et al.*, Proc. IEEE *54*, 1026 (1966).

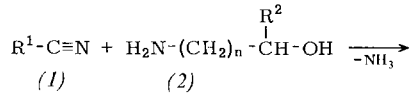
[9] *A. F. Metherell:* Acoustical Holography. Plenum Press, New York 1969, 1970, 1971, Vols. 1—3.

COMMUNICATIONS

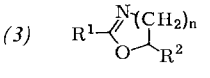
Simple Synthesis of 2-Substituted 2-Oxazolines and 5,6-Dihydro-4*H*-1,3-oxazines

By *Helmut Witte* and *Wolfgang Seeliger*[*]

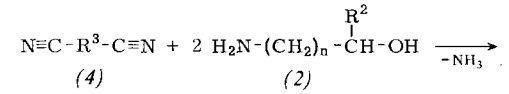
The methods for preparation of 2-oxazolines *(3a)* and 5,6-dihydro-4*H*-1,3-oxazines *(3b)* in the laboratory are rather cumbrous from the point of view of techniques or apparatus[2] or are limited to highly substituted derivatives[1,3].



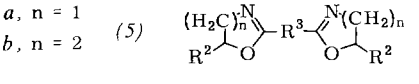
(1) *(2)*



(3)



(4) *(2)*



a, n = 1
b, n = 2 *(5)*

We have now found a single-stage synthesis in which heating nitriles *(1)* with α,β- *(2a)* or α,γ-amino alcohols *(2b)* gives, respectively, 2-oxazolines *(3a)* or 5,6-dihydro-4*H*-1,3-oxazines *(3b)* in good yield, provided that catalytic amounts of certain heavy-metal salts are present. Soluble zinc or cadmium salts have proved particularly suitable.

Additions of diamines or amino thiols to nitriles, however, yielding 2-imidazolines, 1,4,5,6-tetrahydropyrimidines, and 2-thiazolines, are known but proceed without metal catalysts[4].

Dinitriles *(4)* can be treated analogously with the amino alcohols *(2a)* and *(2b)*, giving bis(2-oxazolines) *(5a)* and bis(5,6-dihydro-4*H*-1,3-oxazines) *(5b)*, respectively. A selection of the compounds prepared is listed in Tables 1 and 2, where the yields refer to the amounts of nitrile used.

Table 1. Examples of compounds *(3a)* and *(3b)*.

R^1	R^2	*n*	Catalyst [a]	B.p. (°C/torr)	M.p. (°C)	Yield (%)
CH_3	H	1	A	110–112	—	73
cyclo-C_6H_{11}	H	1	B	85–90/9	—	62
n-$C_{11}H_{23}$	H	1	A	118–123/0.8	—	77
n-$C_{17}H_{35}$	H	1	A	—	51–53	77
C_6H_5	H	1	A	124–127/15	—	85
C_6H_5	CH_3	1	C	73–78/0.4	—	76
C_6H_5	H	2	C	75–80/0.2	—	72

[a] Catalysts: A, $Cd(CH_3COO)_2 \cdot 2H_2O$; B, $Zn(CH_3COO)_2 \cdot 2H_2O$; C, $ZnCl_2$.

[*] Dr. H. Witte and Dr. W. Seeliger
Forschungslaboratorien der Chemischen Werke Hüls AG
437 Marl (Germany)

Table 2. Examples of compounds *(5a)* and *(5b)*.

R^3	R^2	n	Catalyst [a]	B.p. (°C/torr)	M.p. (°C)	Yield (%)
$-(CH_2)_4-$	H	1	A	112–115/0.1	43–45	52
$-(CH_2)_{10}-$	H	1	A	175–180/0.3	62–65	73
p-C_6H_4	H	1	C	—	238–240	61
m-C_6H_4	H	1	C	—	143–146	52
p-C_6H_4	H	2	B	—	214–216	41
m-C_6H_4	CH_3	1	C	180–184/0.7	69–71	40

[a] See footnote [a] of Table 1.

General method:
1 mol of nitrile is heated with 1—1.5 mol of amino alcohol per nitrile group and 0.025 mol of catalyst for 25 h under reflux or at 100—130 °C, ammonia being driven off. When aromatic dinitriles are used, 500 ml of chlorobenzene is added as solvent. At the end of the reaction the product is distilled or, if necessary after removal of the solvent, recrystallized.

Received: December 29, 1971 [Z 593 IE]
German version: Angew. Chem. *84*, 343 (1972)

[1] *J. A. Frump*, Chem. Rev. *71*, 483 (1971) and literature cited therein.
[2] *W. Seeliger* and *W. Thier*, Liebigs Ann. Chem. *698*, 158 (1966).
[3] *W. Seeliger* and *W. Diepers*, Liebigs Ann. Chem. *697*, 171 (1966); *R. R. Schmidt*, Chem. Ber. *103*, 3242 (1970).
[4] *A. Marxer*, J. Amer. Chem. Soc. *79*, 467 (1957); *R. Kuhn* and *F. Drawert*, Chem. Ber. *88*, 55 (1955); Liebigs Ann. Chem. *590*, 55 (1954).

Thermal Formation of 1-Propenylketene from 2,4-Pentadienal[**]

By *Peter Schiess* and *Paul Radimerski*[*]

As has been recently reported[1], gas phase pyrolysis of 3,4-epoxycyclopentene *(1)* (14 torr/1 s) at 400 °C affords 2-*cis*-penta-2,4-dienal *(2)* and at 500 °C the *trans* isomer *(3)*. Compounds *(2)* and *(3)* were characterized as their dinitrophenylhydrazones[2] which were isolated in 8 and 10% yield, respectively.

We have now been able to show that the pyrolyzate of *(1)* contains not only the above aldehydes *(2)* and *(3)* but also up to 90% of the stereoisomeric propenylketenes *(4)* and *(5)*. When the pyrolysis products of *(1)* are trapped in methanol at −60 °C a mixture of *(2)*, *(3)*, and the stereoisomeric methyl 3-pentenoates *(6a)* and *(7a)*[3] results. Trapping in ethanol leads to the corresponding ethyl esters *(6b)* and *(7b)*[3] while use of an ethereal solution of aniline gives the two anilides *(6c)* and *(7c)* (eutectic mixture m.p. 64—66 °C)[3].

A solution of the products trapped at −80 °C in CS_2 exhibits an intense ketene band in the IR spectrum at 2180 cm^{-1}. In the NMR spectrum the signals of the aldehydes *(2)* and *(3)* (H^1 in *(2)*: 10.23 ppm d, $J = 8$ Hz; H^1 in *(3)*: 9.77 ppm d, $J = 8$ Hz) are accompanied by the signals of the ketenes *(4)* and *(5)*. Two characteristic doublets at 3.93 and 4.05 ppm ($J = 10$ Hz) correspond to the aldoketene H atoms in *(4)* and in *(5)*[4].

[*] Priv.-Doz. Dr. P. Schiess and P. Radimerski
Institut für Organische Chemie der Universität
CH-4056 Basel, St. Johanns-Ring 19 (Switzerland)

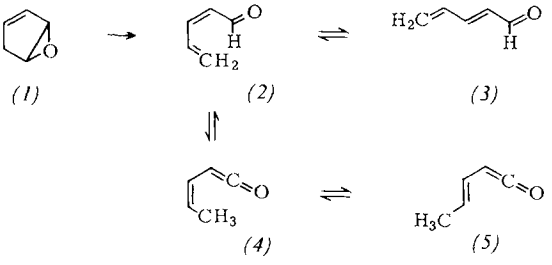
[**] This work was supported by the Schweizerischer Nationalfonds (Project No. 2.396.70) and by a contribution from Ciba-Geigy.

It may be seen from the Table that the *cis*-aldehyde *(2)* is formed as primary product on pyrolysis of *(1)* (1 torr/0.1 s) above about 300 °C. Ketene formation starts slightly above 300 °C, the proportion of *cis* isomer *(4)* initially predominating. The product mixture obtained at 600 °C corresponds to equilibration between the isomers *(2)*—*(5)* for at this temperature a product of approximately equal composition is obtained, irrespectively of whether one starts with epoxide *(1)*, *trans*-2,4-pentadienal *(3)*, or *trans*-3-pentenoyl chloride *(7d)*[5]. On the basis of the order in which the compounds *(2)*—*(5)* are found in the pyrolyzate with increasing temperature, it can be assumed that *(4)* is formed from *(2)* and that the *cis*, *trans* equilibria *(2)* ⇌ *(3)* and *(4)* ⇌ *(5)* are established at elevated temperature (see formula scheme).

Table. Composition of the product mixture formed on gas phase pyrolysis (1 torr/0.1 s) [a].

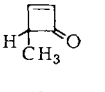
Cpd.	Pyrolysis temp. (°C)	*(1)*	*(2)*	*(3)*	*(4)*+*(5)*	Ratio *(4)*:*(5)* [b]
(1)	290	99	1	—	—	—
	320	91	3	—	6	7:1
	350	78	4	—	17	3:1
	405	25	7	1	65	2:1
	490	—	7	3	90	1:1
	565	—	6	11	83	1:1
	600	—	5	17	78	1:1
(3)	600	—	4	22	74	1:1
(7d)	600	—	4	17	78	1:1

[a] Percentages, determined from the NMR spectrum of the pyrolyzate trapped in methanol; [b] determined by gas chromatography of the methyl esters *(6a)* and *(7a)* (capillary column 0.2 mm, 50 m, Castorwax; 60 °C).



CH_3-CH=CH-CH_2-CO-R

cis: (6) *(a)*, R = OCH_3; *(b)*, R = OC_2H_5
trans: (7) *(c)*, R = NHC_6H_5; *(d)*, R = Cl



(8)

Formation of *(4)* from *(2)* can be regarded as a sigmatropic [1,5]shift of the aldehydic proton in *(2)*. We have previously observed a similar reaction on irradiation of a substituted pentadienaldehyde[6]. Reversible [1,5]hydrogen shifts have recently been invoked in the interpretation of thermal isomerization reactions of unsaturated aldehydes[7]. However, as far as we know the present case is the first example of *directly observed* thermal ketene formation from an acyclic unsaturated aldehyde.

The interconversion *(4)* ⇌ *(5)* could possibly proceed *via* 4-methylcyclobutenone *(8)* as an intermediate[8]. However, no cyclobutenone could be detected by spectroscopy in the pyrolysis mixture at −60 °C[9]; nor is any formed

from *(4)* or *(5)* on heating to room temperature—instead complete polymerization of the ketene occurs.

Received: November 2, 1971 [Z 558 IE]
German version: Angew. Chem. *84*, 345 (1972)

[1] *P. Schiess* and *H. L. Chia*, Helv. Chim. Acta *53*, 485 (1970).

[2] *E. E. Boehm* and *M. C. Whiting*, J. Chem. Soc. *1963*, 2541.

[3] Identified by comparison with authentic *trans*-3-pentenoic acid derivative *(7)* and by catalytic reduction to the valeric acid derivative.

[4] *G. Quinkert, B. Bronstert, P. Michaelis*, and *U. Krüger*, Angew. Chem. *82*, 221 (1970); Angew. Chem. internat. Edit. *9*, 240 (1970); *O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen*, and *H. E. Wright*, J. Amer. Chem. Soc. *91*, 6856 (1969).

[5] The mixture of esters isolated after pyrolysis of *(7d)* at 600 °C is formed *via (4)* and *(5)*, as was shown by incorporation of deuterium on trapping in CH_3OD.

[6] *P. Schiess* and *Chr. Suter*, Helv. Chim. Acta *54*, 2636 (1971).

[7] *P. W. Schiess* and *M. Wisson*, Tetrahedron Lett. *1971*, 2389; *W. H. Pirkle, H. Seto*, and *W. V. Turner*, J. Amer. Chem. Soc. *92*, 6985 (1970).

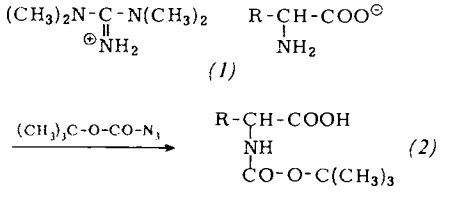
[8] *E. F. Jenny* and *J. D. Roberts*, J. Amer. Chem. Soc. *78*, 2005 (1956); *E. F. Silversmith, Y. Kitahara*, and *J. D. Roberts*, *ibid. 80*, 4088 (1958).

[9] *J. B. Sieja*, J. Amer. Chem. Soc. *93*, 2481 (1971).

Simple Method for the Synthesis of Some Boc-Amino Acids[1][**]

By *Akhtar Ali, Falk Fahrenholz*, and *Boris Weinstein*[*]

tert-Butyloxycarbonyl (Boc) amino acids are frequently employed as intermediates in the synthesis of peptides, and there are several methods available for their preparation[2]. We have now found that Boc amino acids are also formed in the reaction of 1,1,3,3-tetramethylguanidinium salts of some amino acids *(1)* with *tert*-butyloxycarbonyl azide[3] in dimethylformamide as solvent. The simple procedure outlined here provides a convenient method for the synthesis of a series of Boc amino acids in excellent yields (Table). In the case of Boc derivatives of Ala, Asp, Asn, Glu, and Tyr, the yields are only moderate.



(1)

(2)

Compound	Yield (%)	M.p. (°C) of crude product
Boc-Ala-OCH_3	80	33–34
Boc-Arg(NO_2)	82	122–124
Boc-Cys[*p*-OCH_3(Bzl)]-DCHA [a]	90	132
Boc-Glu(OBzl)-DCHA	87	139–140
Boc-Leu	94	oil [c]
Boc-Lys(Z)-DCHA [b]	82	154–155
Boc-Met	100	syrup
Boc-Phe	78	85–86
Boc-Pro	93	134–135
Boc-Ser(C_4H_9)	100	oil [c]

[a] Bzl = benzyl, DCHA = dicyclohexylammonium.
[b] Z = benzyloxycarbonyl.
[c] Solidifies after a few days.

[*] Dr. A. Ali, Dr. F. Fahrenholz, and Prof. Dr. B. Weinstein
Department of Chemistry
University of Washington
Seattle, Washington 98195 (USA)

[**] This work was supported by Grant GM-12616 of the National Institute of Health, U.S. Department of Health, Education and Welfare.

Experimental

tert-Butyloxycarbonyl azide (21.5 g, 0.15 mol) is added dropwise over a period of 30 minutes to a stirred suspension of proline (11.5 g, 0.1 mol) in dimethylformamide (220 ml) and 1,1,3,3-tetramethylguanidine (23 g, 0.2 mol) in an ice-bath. The resulting solution is stirred for three days at room temperature and then the solvent is removed by evaporation under vacuum. The residue is taken up in ethyl acetate (500 ml) and 20% citric acid solution (200 ml). The aqueous phase is removed and extracted once again with ethyl acetate (300 ml). The combined ethyl acetate extracts are then washed three times with water (200 ml), dried over magnesium sulfate, and finally concentrated by evaporation under vacuum. Crystallization of the residue from ethyl acetate/petroleum ether yielded 20.0 g (93%) of *N-tert*-butyloxycarbonyl-proline.

Received: November 3, 1971 [Z 564 IE]
German version: Angew. Chem. *84*, 259 (1972).

[1] Amino Acids and Peptides, Part 30.—Part 29: *D. Stevenson, R. M. Cook*, and *B. Weinstein*, Internat. J. Protein Res. IV, in press (1972).

[2] See *e.g. C. Birr* and *R. Frodl*, Synthesis *1970*, 474; *B. Rzeszotarska* and *S. Wiejak*, Liebigs Ann. Chem. *716*, 216 (1968); *E. Schnabel, H. Herzog, P. Hoffmann, E. Klauke*, and *I. Ugi*, *ibid. 716*, 175 (1968).

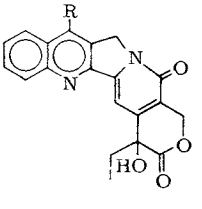
[3] *K. Sakai* and *J.-P. Anselme*, J. Org. Chem. *36*, 2387 (1971); *M. A. Insalaco* and *D. S. Tarbell*, Org. Synthesis *50*, 9 (1970); *L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza*, and *P. H. Terry*, *ibid. 44*, 15 (1964).

The Biogenetically Oriented Total Synthesis of Camptothecin and 7-Chlorocamptothecin[1]

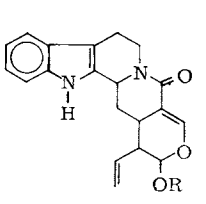
By *Ekkehard Winterfeldt, Tilman Korth, Dennis Pike*, and *Marlies Boch*[*]

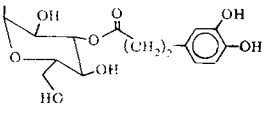
Camptothecin *(1a)* was first isolated by *Wall et al.* in 1966 from *Camptotheca acuminata*[2]; its structure was confirmed by X-ray structure analysis[3]. *Wenkert* has indicated the biogenetic connection between camptothecin and the indole alkaloids[4] and *Brown et al.* have recently announced the isolation and structural elucidation of an indole alkaloid *(2)* having a structure closely resembling that of camptothecin[5].

Since camptothecin was reported to have strong antileukemia and tumor-inhibiting activity, a synthetic route to this compound is of interest. Following a recent com-



(1), R = Cl
(1a), R = H



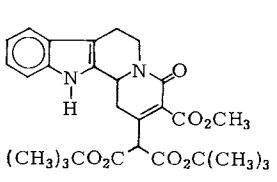


(2), R =

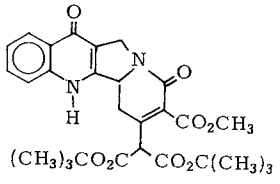
[*] Prof. Dr. E. Winterfeldt, Dr. T. Korth, Dr. D. Pike, and M. Boch
Organisch-Chemisches Institut der Technischen Universität
3 Hannover, Schneiderberg 1 B (Germany)

munication on a total synthesis[6] we now publish our results on a biogenetically oriented indole-camptothecin rearrangement.

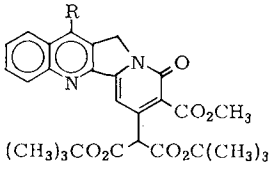
Using the easily accessible indolic compound *(3)*[7] as starting material, the indole-quinoline conversion could be carried out in two simple steps.



(3)



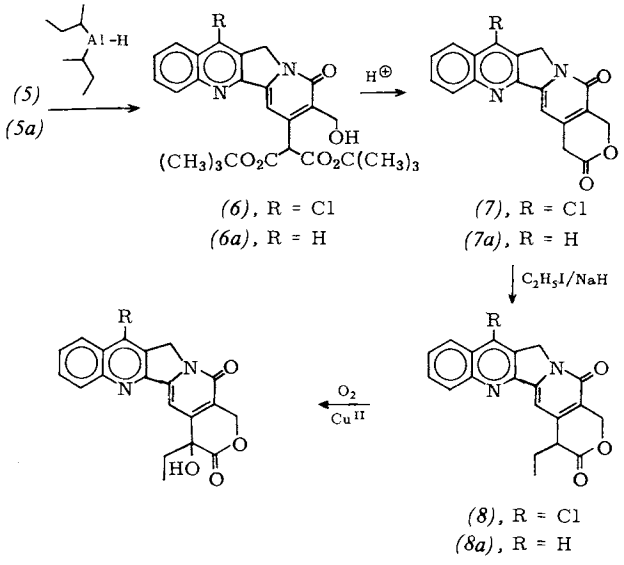
(4)



(5), R = Cl
(5a), R = H

Autoxidation[8] of *(3)* affords the quinolone *(4)*, which, on treatment with thionyl chloride in dimethylformamide, is converted into the chloroquinoline-pyridone *(5)*. Hydrogenation of *(5)* yields the chlorine-free derivative *(5a)*.

Selective reduction of *(5)* and *(5a)* with diisobutylaluminum hydride[9] affords the alcohols *(6)* and *(6a)*, which, on being allowed to stand at room temperature after addition of trifluoroacetic acid, are converted into the lactones *(7)* and *(7a)* respectively. Alkylation of *(7a)* and *(7)* with ethyl iodide in dimethylformamide yields deoxycamptothecin *(8a)* and the corresponding chloro compound *(8)*, which are converted into camptothecin *(1a)* and its 7-chloro derivative *(1)* respectively in high yields by passing oxygen through a dimethylformamide solution in the presence of copper(II) chloride. The natural product proved to be identical with a sample provided by Prof. *Wall*; all the other substances mentioned above have been characterized by elemental analysis, mass spectroscopy, and NMR spectroscopy.



(6), R = Cl
(6a), R = H

(7), R = Cl
(7a), R = H

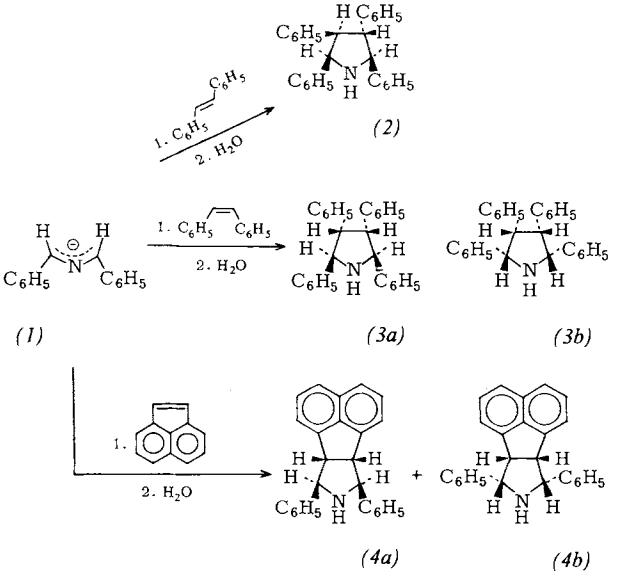
(8), R = Cl
(8a), R = H

Received: November 9, 1971 [Z 565 IE]
German version: Angew. Chem. *84*, 265 (1972)

Stereochemistry of the Cycloaddition of 1,3-Diphenyl-2-azaallyllithium to Alkenes at 0 °C[1][**]

By *Thomas Kauffmann* and *Edgar Köppelmann*[*]

1,3-Diphenyl-2-azaallyllithium[3], which was prepared by reaction of *N*-benzylidenebenzylamine with lithium diisopropylamide, was allowed to react under nitrogen in THF (deep red solution) at 0°C with *trans*-stilbene, with *cis*-stilbene, and with acenaphthylene (molar ratio 1:1 in each case) and the configuration of the pyrrolidines obtained by hydrolysis was determined by NMR spectroscopy[4]. The results are given in the following scheme and table.



(1) *(2)* *(3a)* *(3b)* *(4a)* *(4b)*

Reactant	Pyrrolidine formed	Yield (%)	M. p. (°C)
trans-Stilbene	*(2)*	83	110—111
cis-Stilbene	*(3a)* or *(3b)*	21 [a]	113—114
Acenaphthylene	*(4a)* + *(4b)*	40+40	176 and 194

[a] In the case of *cis*-stilbene, the greater part of which remained unreacted, a brown reaction flask was used owing to the light-sensitivity of the reactant.

[*] Prof. Dr. Th. Kauffmann and Dr. E. Köppelmann
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[2] *M. E. Wall, M. G. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail,* and *G. A. Sim*, J. Amer. Chem. Soc. *88*, 3888 (1966).

[3] *A. T. McPhail* and *G. A. Sim*, J. Chem. Soc. *B 1968*, 923.

[4] *E. Wenkert, K. G. Dave, R. G. Lewis,* and *P. W. Sprague*, J. Amer. Chem. Soc. *89*, 6741 (1967).

[5] *W. P. Blackstock* and *R. T. Brown*, Tetrahedron Lett. *1971*, 3727.

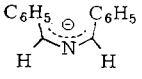
[6] *G. Stork* and *A. G. Schultz*, J. Amer. Chem. Soc. *93*, 4074 (1971).

[7] *E. Winterfeldt* and *H. Radunz*, Chem. Commun. *1971*, 374.

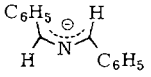
[8] *E. Winterfeldt*, Liebigs Ann. Chem. *745*, 25 (1971).

[9] We thank Schering AG, Berlin and Bergkamen for supplying the diisobutylaluminum hydride.

According to the above results the "alkene-created part" of the pyrrolidines obtained by [1,3]-anionic cycloaddition[2] always has the configuration of the alkene used in the reaction, thus indicating stereospecific *cis*-addition of the alkenes (no alternative in the case of acenaphthylene). In the "azaallyl-created part" the phenyl residues of the pyrrolidines always have *cis*-configuration, thus proving that the stereospecific addition always involves the same 1,3-diphenyl-2-azaallyl anion[5]. The findings are best interpreted in terms of a symmetry allowed one-step $[_{\pi}4_{s}+_{\pi}2_{s}]$-cycloaddition of 1,3-*(trans,trans)*- *(1)* or 1,3-*(cis,cis)*-diphenyl-2-azaallyl anion *(5)* according to the principle of conservation of orbital symmetry[7]. The *trans,-trans* configuration of the anion undergoing addition is thus much more probable since the anion of the comparable 1,3-diphenyl-allyllithium in THF at 0°C is always present in this configuration[5,6]. The *trans,trans* configuration of the 1,3-diphenyl-2-azaallyl anion at 0°C can also be deduced from the irreversible, and obviously quantitative configurational rearrangement of 1,3-*(cis,trans)*-diphenyl-2-azaallyl anion *(6)* on warming from −60°C to 0°C[8], since the thermodynamic stability should increase along the series *cis,cis* < *cis,trans* < *trans,trans* (completely coplanar, strain-free conformation is possible only in the case of *trans,trans*). However, confirmation of the *trans,-trans* conformation by direct NMR investigation has not, as yet, been reported.



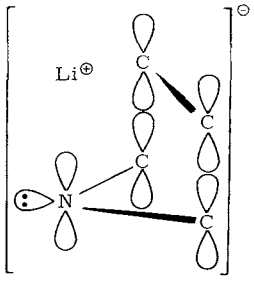
(5)



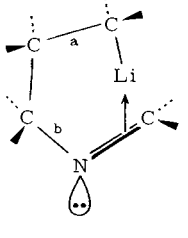
(6)

The pyrrolidines obtained from *cis*- and *trans*-stilbenes were free of detectable mutual contamination[9]. A decision between pyrrolidine structures *(3a)* and *(3b)* is still not possible. The pyrrolidines *(4a)* and *(4b)* (ratio *ca.* 1:1) obtained from acenaphthylene have configurations corresponding to those of *(3a)* and *(3b)*. The fact that—in contrast to experiments with *cis*-stilbenes—both possible isomers are formed in reactions with acenaphthylenes, may be due to slight differences in the grouping.

The orbital diagrams of the 2-azaallyl anions resemble those of 1,3-dipolar substances such as azomethine ylides or diazoalkanes. Hence, the MO considerations described



(7)



(8)

by *Huisgen et al.*[10] for 1,3-dipolar cycloadditions can be applied to the analogous reactions of 2-azaallyl anions. Since the cycloaddition processes in the reactions investigated here are one-step processes, they ought to proceed *via* a two-plane orientation complex *(7)*. However, a two-step process *via* an intermediate of type *(8)*, in which rotations about axes a and b are blocked by formation of a strong chelate bridge to the CN double bond or to the N atom, cannot, as yet, be ruled out[11].

Received: November 19, 1971 [Z 567a IE]
German version: Angew. Chem. *84*, 261 (1972)

[1] [1,3]-Anionic Cycloaddition, Part 5.—Part 4: Ref. [2].

[2] *Th. Kauffmann* and *R. Eidenschink*, Angew. Chem. *83*, 794 (1971); Angew. Chem. internat. Edit. *10*, 739 (1971).

[3] *Th. Kauffmann, H. Berg*, and *E. Köppelmann*, Angew. Chem. *82*, 396 (1970); Angew. Chem. internat. Edit. *9*, 380 (1970).

[4] *E. Köppelmann*, Dissertation, Universität Münster 1971.

[5] Since 1,3-diphenylallyllithium is extensively ionized in THF [6], it can be assumed that this is also the case with 1,3-diphenyl-2-azaallyllithium, since the N-atom in position 2 should not have any influence on the distribution of charge.

[6] *H. H. Freedmann, V. R. Sandel*, and *B. P. Thill*, J. Amer. Chem. Soc. *89*, 1762 (1967).

[7] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[8] *Th. Kauffmann, K. Habersaat*, and *E. Köppelmann*, Angew. Chem. *84*, 262 (1972); Angew. Chem. internat. Edit. *11*, 291 (1972).

[9] As control experiments have shown, an admixture with 6% of the other isomer would have been detectable in the NMR spectrum. Chromatographic tests were less sensitive because of the poor separation of the isomers.

[10] *A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey*, and *E. Spindler*, Chem. Ber. *100*, 2192 (1967).

[11] Reaction of 2-azaallyllithium compounds with ketones always leads to non-cyclic adducts; this is also possibly due to ring-opening of the anionic cycloadduct (*Th. Kauffmann, E. Köppelmann*, and *H. Berg*, Angew. Chem. *82*, 138 (1970); Angew. Chem. internat. Edit. *9*, 163 (1970)).

Ring-Opening of *N*-Lithio-2,3(*cis*)-diphenylaziridine to 1,3(*cis,trans*)-Diphenyl-2-azaallyllithium and Its Rearrangement to the *trans,trans*-Form[1][**]

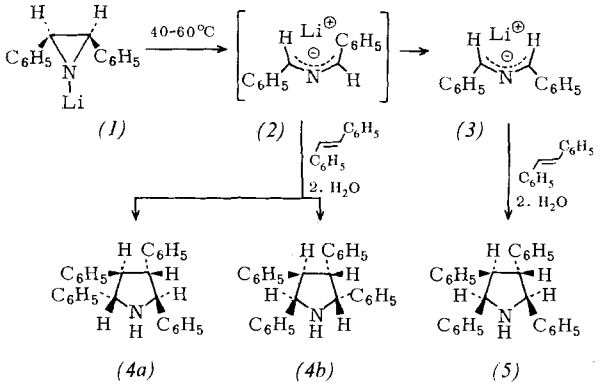
By *Thomas Kauffmann, Kai Habersaat*, and *Edgar Köppelmann*[*]

Some *N*-arylaziridines undergo conrotatory ring-opening with formation of azomethine ylides[3] when heated to *ca.* 100—110°C. We have now found a preparatively interesting analogous reaction, namely the ring opening *(1)* → *(2)*. The initially colorless THF solution turns red at temperatures as low as 40—60°C (nitrogen atmosphere) and the 1,3(*cis,trans*)-diphenyl-2-azaallyllithium *(2)* (regarding ionization cf.[2]) expected according to the principle of conservation of orbital symmetry[4] as intermediate, could be trapped when ring-opening was carried out in the presence of 1 mole of *trans*-stilbene. 2,3,4,5-Tetraphenylpyrrolidine (m.p. 138—140°C) having structure *(4a)* or *(4b)*—*i.e.* a cycloadduct with the two phenyl residues of the "2-azaallyl-created part" in the *trans* position (structural determination by NMR spectroscopy[6])—was formed to the extent of 73%[5]. 2,3,4,5-Tetraphenylpyrrolidine *(5)* (m.p. 110—111°C), which has the *cis*-configuration in the "2-azaallyl-created part" and which has already been reported in a previous communication, was formed as by-product (11%).

[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. K. Habersaat, and Dr. E. Köppelmann
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

When the product of the ring-opening reaction of *(1)* was cooled to 0 °C prior to treatment with 1 molar equivalent of *trans*-stilbene, the pyrrolidine *(5)* was the sole end product isolated. This indicates that the primary ring-opening product *(2)* is completely converted, either into the *trans,trans* form or the *cis,cis* form.—Evidence for the existence of the primary ring product in the *cis,trans* configuration by NMR spectroscopic investigation of the lithium compound is still pending.



(1) *(2)* *(3)* *(4a)* *(4b)* *(5)*

The 2,3,4,5-tetraphenylpyrrolidine *(4a)* or *(4b)*, m.p. 138—140 °C, is also formed (11%) as well as *(5)* (35%) when a solution of 1,3-diphenyl-2-azaallyllithium (prepared by reaction of 1 mole of lithium diisopropylamide with *N*-benzylidenebenzylamine) in THF is prepared at −60 °C and treated at this temperature with *trans*-stilbene. The lithiation of *N*-benzylidenebenzylamine leads, at least in part, to formation of the intermediate *(2)*. However, the *cis,trans* configuration is evidently destroyed on warming to 0 °C, since subsequent addition of *trans*-stilbene at this temperature leads to the pyrrolidine *(5)* having a *cis*-configuration in the "2-azaallyl-created part". From the irreversibility of the configurational rearrangement of *(2)* observed in control experiments it can be deduced that *(3)* is also formed. The ring-opening of *(1)* and its sodium analogs[7] provides an alternative route to the 2-azaallylmetal compounds. This method is of particular interest since it leads to solutions of 2-azaallylmetal compounds free of amine and metal amide and thus widens the scope of these organometallic compounds as reagents in organic synthesis[8].

Received: November 19, 1971 [Z 567b IE]
German version: Angew. Chem. *84*, 262 (1972)

[1] [1,3]-Anionic Cycloaddition, Part 6.—Part 5: [2]

[2] *Th. Kauffmann* and *E. Köppelmann*, Angew. Chem. *84*, 261 (1972); Angew. Chem. internat. Edit. *11*, 290 (1972).

[3] Cf. *R. Huisgen, W. Scheer*, and *H. Huber*, J. Amer. Chem. Soc. *89*, 1753 (1967); *H. W. Heine, P. Peavy*, and *A. J. Durbetaki*, J. Org. Chem. *31*, 3924 (1966).

[4] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[5] Yields based on aziridine.

[6] *E. Köppelmann*, Dissertation, Universität Münster 1971.

[7] *K. Habersaat*, Dissertation, Universität Münster, to be presented 1973.

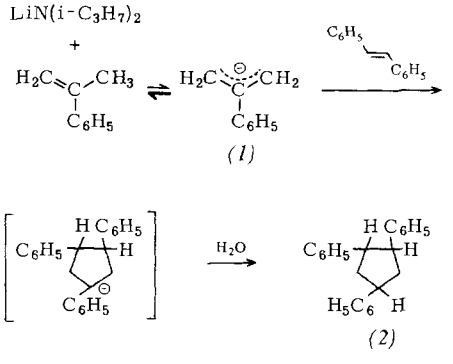
[8] The presence of diisopropylamine and lithium diisopropylamide (in equilibrium with 2-azaallyllithium compounds) interferes in reactions of 2-azaallyllithium compounds with substrates which, like phenyl isocyanates, oxiranes or alkyl halides are able to react with amides (*A. Busch*, Diplomarbeit, Universität Münster 1971; *R. Eidenschink*, Dissertation, Universität Münster, to be presented 1972).

Synthesis of Five-membered Carbocycles by [1,3]-Anionic Cycloaddition[1][**]

By *Rudolf Eidenschink* and *Thomas Kauffmann*[*]

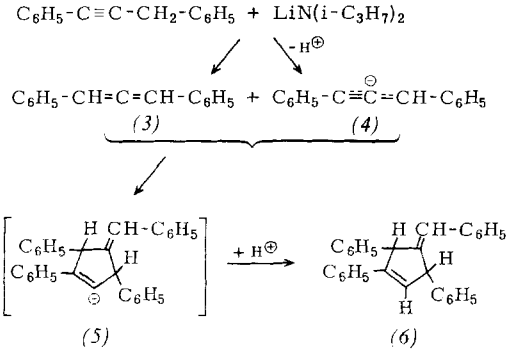
Appreciable driving force for the smooth cycloaddition of 2-azaallyl anions to multiple bonds is believed to lie in transfer of the negative charge from the peripheral C atoms of the 2-azaallyl system to the more strongly electronegative central N atom[2]. The cycloaddition of allyl anions[3] to multiple bonds should therefore be favored by anything that makes it easier for electrons to be taken up by the central C atom. A phenyl group on the central C atom or increase in the electronegativity of this atom by alteration of the degree of hybridization ($sp^2 \rightarrow sp$) should therefore be favorable. This has been tested.

After unsuccessful attempts to prepare the 2-phenylallyl anion *(1)* from α-methylstyrene by treatment with lithium diisopropylamide in THF[4], we brought α-methylstyrene into reaction with lithium diisopropylamide in the presence of one equivalent of stilbene in THF at 45 °C for 150 h. After hydrolysis by water we obtained a 41% yield of a hydrocarbon, m. p. 62 °C, to which the structure of a 1,2,4-triphenylcyclopentane *(2)* (configuration of the phenyl groups not yet determined[5]) is assigned on the basis of analytical values and spectra (IR, NMR, MS). Evidently small amounts of the 2-phenylallyl anion *(1)* are formed in an equilibrium reaction and this undergoes the expected cycloaddition to *trans*-stilbene and is continuously reformed[6].



(1) *(2)*

Further, we have warmed an *n*-hexane solution of equivalent amounts of lithium diisopropylamide, 1,3-diphenylpropyne, and tolan for 24h at 60 °C and, after hydrolysis by water, obtained, together with unchanged tolan (95%),



(3) *(4)* *(5)* *(6)*

[*] Dipl.-Chem. R. Eidenschink and Prof. Dr. Th. Kauffmann
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

a hydrocarbon of m.p. 129°C, apparently not hitherto described, which on the basis of analytical values and spectra (UV, IR, NMR, MS) possesses structure *(6)*. The configuration of the phenyl groups has not yet been determined.

We interpret this result as formation of 1,3-diphenylallene *(3)*[7] and the [1,3]-anion *(4)* together from the 1,3-diphenylpropyne and reaction of these products by a [1,3]-anionic cycloaddition (one- or two-stage process) to yield *(5)*. Since the tolan remains unchanged, *(4)* is evidently unable to add rapidly to the C—C triple bond flanked by phenyl groups.

Received: December 13, 1971 [Z 576 IE]
German version: Angew. Chem. *84*, 292 (1972)

[1] [1,3]-Anionic Cycloaddition, Part 7.—Part 6: *Th. Kauffmann, K. Habersaat,* and *E. Köppelmann,* Angew. Chem. *84*, 262 (1972); Angew. Chem. internat. Edit. *11*, 291 (1972).

[2] *Th. Kauffmann, D. Berger, B. Scheerer,* and *A. Woltermann,* Angew. Chem. *82*, 987 (1970); Angew. Chem. internat. Edit. *9*, 961 (1970).

[3] Cycloaddition of cyclic allyl anions to dehydrobenzene is known: *G. Wittig* and *E. Knauss,* Chem. Ber. *91*, 985 (1958); *C. F. Huebner* and *E. M. Donoghue,* J. Org. Chem. *33*, 1678 (1968); *W. T. Ford, R. Radue,* and *J. A. Walker,* Chem. Commun. *1970*, 966.

[4] A pale red color developed in the solution. No deuterium could be detected by NMR spectroscopy in the α-methylstyrene isolated after addition of D_2O.

[5] *F. H. Newman,* Liebigs Ann. Chem. *302*, 239 (1898), described a liquid 1,2,4-triphenylcyclopentane.

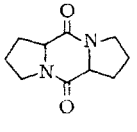
[6] Formation of a cyclic dimer on reaction of sodium with α-methylstyrene (*M. Kolobielski* and *H. Pines,* J. Amer. Chem. Soc. *79*, 5820 (1957)) presumably occurs analogously.

[7] Rearrangement of 1,3-diphenylpropyne to 1,3-diphenylallene under the influence of bases: *E. V. Dehmlow,* Chem. Ber. *100*, 3260 (1967), and references cited therein.

Side-Reactions Arising on Formation of Cyclodipeptides in Solid-Phase Peptide Synthesis[**]

By *Manfred Rothe* and *Jan Mazánek*[*]

During the solid-phase synthesis of oligo-L-prolines[1] we observed a considerable decrease in peptide yield (35—40% under usual condition[2]) in the step from diproline to triproline. From the filtrates of the neutralization reaction (with triethylamine/methylene chloride) after removal of the Boc protective group (with HCl/glacial acetic acid or trifluoroacetic acid/methylene chloride), from the washing operations, and from the coupling reaction with Boc-proline (with the aid of dicyclohexylcarbodiimide) we were able to isolate cyclodi-L-prolyl *(1)*



(1)

in a chromatographically pure state (TLC). Compound *(1)* was identified by melting point and mixed melting point determination (142—144°C), IR spectrum, optical rotation ($[\alpha]_D^{22} = -153.9°$, $c = 1$, H_2O), and mass spectrum ($M^+ = 194$). The amount of *(1)* formed increases on prolonged shaking in methylene chloride suspension of the polymer-bound diproline (90% after 24 h). The cyclization is catalyzed by tertiary amines.

This pronounced tendency to undergo ring closure was also found in the case of polymer-bound dipeptide esters of other *N*-alkyl amino acids, especially with disarcosine and L-prolylsarcosine (61% and 42%, respectively, of the cyclodipeptides [=diketopiperazines] isolated prior to the addition of carbodiimide). It is dependent upon the nature and the sequence of the amino acids; *e.g.* a value of 10% was found for sarcosylglycine, 5% for diglycine, and 2.5% for L-prolylglycine. Cyclodipeptide formation decreases with increasing bulk of the side chain and is hardly significant for most amino acids (cf. ref. [3]).

But even when only a few percent of the dipeptide cyclize, the reaction still represents a source of serious interference. The favorably placed hydroxymethyl groups formed on the polymer during the cyclization can undergo esterification in the subsequent coupling reactions with Boc-amino acids and carbodiimide and thus afford starting points for new peptide chains. For instance, during the synthesis of the antamanide sequence Phe-Phe-Val-Pro-Pro-Ala-Phe-Phe-Pro-Pro-polymer, small amounts of each of the Boc-amino acids used for chain lengthening were fixed to the resin by ester bonds (beginning with the tripeptide) and could be detected by TLC in samples cleaved from the carrier after each coupling step *(R. Pudill)*.

However, the amount of ester formation from *N*-protected amino acids and aliphatic alcohols with carbodiimides as condensing agent is only small in the absence of tertiary amines[4], as could be confirmed during solid-phase synthesis with hydroxymethyl resins[5]. In our own studies with a hydroxymethyl-polystyrene under the usual coupling conditions (reaction twice repeated with a threefold molar excess of Boc-proline, based on polymer-bound hydroxy groups) but for a prolonged reaction time (a total of 20 h) we found only 4% esterification.

Nevertheless, even very small amounts of amino acids bound in this way can possibly lead to peptide mixtures that are not further separable.

During the synthesis of oligoprolines this side-reaction hardly plays a significant role since the newly formed chain containing two proline residues less is removed again by cyclization as the cyclodipeptide at the diproline stage. Formation of hydroxy groups can be completely suppressed if the dipeptide stage is avoided in the synthesis, either by lengthening the prolyl polymer with, *e.g.* Boc-di- or Boc-triproline (no danger of racemization!), or by esterification of the chloromethyl polymer with Boc-triproline instead of Boc-proline.

Received: November 19, 1971 [Z 572 IE]
German version: Angew. Chem. *84*, 290 (1972)

[*] Prof. Dr. M. Rothe and Dipl.-Ing. J. Mazánek
Organisch-Chemisches Institut der Universität
65 Mainz, Johann-Joachim-Becher-Weg 18—20 (Germany)

[**] We are indebted to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and Farbwerke Hoechst AG (Karl Winnacker Fellowship granted to *M. R.*) for supporting this work.

[1] *M. Rothe, R. Theysohn, K.-D. Steffen, M. Kostrzewa,* and *M. Zamani:* Proc. 10th Europ. Peptide Sympos., Abano Terme 1969; North-Holland Publ. Co., Amsterdam 1971, p. 179; *M. Rothe, W. Dunkel, K.-D. Steffen, Hj. Schneider,* and *M. Zamani:* Angew. Chem. *80*, 413 (1968); Angew. Chem. internat. Edit. *7*, 399 (1968).

[2] *R. B. Merrifield,* Biochemistry *3*, 1385 (1964).

[3] *W. Lunkenheimer* and *H. Zahn,* Liebigs Ann. Chem. *740*, 1 (1970).

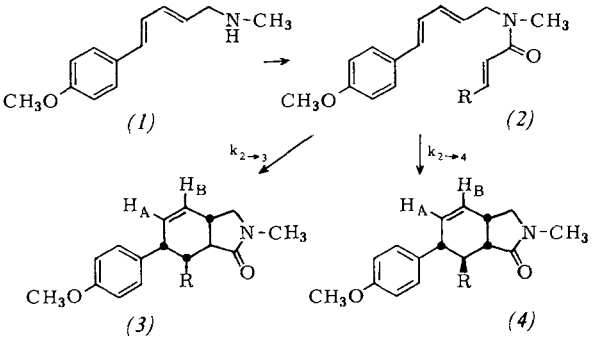
[4] *M. Rothe,* Collect. Czech. Chem. Commun. *24*, 28 (1959).

[5] *M. Bodanszky* and *J. T. Sheehan,* Chem. Ind. (London) *1966*, 1597; *H. C. Beyerman* and *R. A. In't Veld,* Recl. Trav. Chim. Pays-Bas *88*, 1019 (1969); *M. A. Tilak* and *C. S. Hollinden,* Tetrahedron Lett. *1968*, 1297.

Intramolecular $[_\pi 4 + _\pi 2]$-Cycloadditions: Preparative and Kinetic Aspects

By *Heinz W. Gschwend* and *Hans Peter Meier*[*]

The intramolecular version of the Diels-Alder reaction[1] represents an elegant high-yield method for the stereocontrolled synthesis of substituted carbo- and heterocyclic 5,6- and 6,6-ring systems. These intramolecular reactions not only proceed stereospecifically, with regard to the symmetry controlled $[_\pi 4_s + _\pi 2_s]$ process[2], and regiospecifically[3,4] (for geometrical reasons), but they also exhibit a much more favorable entropy factor than intermolecular Diels-Alder reactions. In the present communication we report the exceptionally ready formation of substituted isoindolines as well as the kinetic parameters of this reaction.



(a), R = $COOC_2H_5$; *(a')*, R = $COOCH_3$; *(b)*, R = C_6H_5

The reactive intermediate *(2a)* formed on acylation of the amine *(1)*[5] with the acyl chloride of monoethyl fumarate is not isolable at 0°C but gives the bicyclic lactam *(3a)* in 77% yield. The structure of *(3a)* and especially the relative configuration of the four centers of chirality appears to be confirmed by the NMR spectrum. Equilibration of *(3a)* in $CH_3OH/NaOCH_3$ leads cleanly to the thermodynamic product, the *cis*-fused lactam *(4a')*. With both epimerizable centers inverted, the stereochemistry of *(4a')* is identical to that of a kinetic product arising from an *exo*-addition *(4a)*[6].

If the amine *(1)* is acylated with a less reactive dienophile such as cinnamoyl chloride, then the intermediate *(2b)* can be isolated. This amide is an ideal substrate for the determination of the kinetic parameters of the intramolecular [4+2]-cycloaddition. Upon heating of a benzene solution of *(2b)* the *endo*- and *exo*-products *(3b)* and *(4b)* are formed (see Table 1). It may be deduced from the product ratio (15:2) of this kinetically controlled reaction that the activation energy for the *endo* transition state $[(2b) \rightarrow (3b)]$ lies about 1.4 kcal/mol below the *exo* transition state. The rate constants ($k = k_{2\rightarrow3} + k_{2\rightarrow4}$) were determined by NMR[7] and, more accurately, by UV spectroscopy[8] (Table 2).

Table 2. Kinetic data for the first order reaction $(2b) \rightarrow (3b) + (4b)$ [9], as calculated from UV measurements.

T (°C) (±0.1 °C)	k_{obs} (s^{-1})
70.0	0.897×10^{-5}
76.6	1.924×10^{-5}
85.3	3.914×10^{-5}
90.4	6.587×10^{-5}
log A =	9.80 s^{-1}
E_a =	23.3 ± 0.6 kcal/mol
$\Delta H^{\neq}$ =	22.6 ± 0.6 kcal/mol
$\Delta S^{\neq}$ =	−16.0 ± 1.5 e.u.

The most striking deviation from the kinetic data of bimolecular Diels-Alder reactions ($\Delta S^{\neq}$ varying between −30 to −40 e.u. and log A = 4.0 to 7.0)[10] is the higher value of the frequency factor and, accordingly, a significantly less negative entropy of activation. While the parameters of this intramolecular process reflect the increased degree of order of the substrate, the particular geometry of the transition state of this four-center reaction nevertheless manifests itself in a relatively large negative $\Delta S^{\neq}$. However, the value of −16 e.u. is found to be of the same order of magnitude as the entropy observed in the Cope rearrangement ($\Delta S^{\neq} = -11$ e.u. and E_a = 25.8 kcal/mol)[11], which

Table 1. Preparation and properties of the compounds *(3a)*, *(4a')*, *(2b)*, *(3b)*, and *(4b)*.

Cpd.	Conditions, yield	M.p. (°C)	IR (Nujol) (cm^{-1})	NMR ($CDCl_3$) or UV (CH_3OH) (ppm)
(3a)	0°C/CH_2Cl_2/Py 1 h 77%	114 ether	1718 1685	δ = 6.1 and 5.7, vinyl-H_A/H_B, br. q, J_{AB} = 10 Hz, $W_H(H_A)$ = 4 Hz $W_H(H_B)$ = 7.5 Hz
(4a')	$NaOCH_3/CH_3OH$ 19 h reflux 90%	127 ether	1735 1686	$\delta_{H_A} = \delta_{H_B}$ = 5.85, W_H = 2 Hz
(2b)	0°C/CH_2Cl_2/Py	78 ether	1646 1605	λ_{max} = 217 nm (29500) 223 nm (27100) 294 nm (51800)
(3b)	85°C/24 h/ benzene 79%	118 CH_2Cl_2/ hexane	1685	δ = 6.15 and 5.82, vinyl-H_A/H_B, br. q, J_{AB} = 10 Hz, $W_H(H_A)$ = 3 Hz $W_H(H_B)$ = 7 Hz
(4b)	10.5%	oil	1690 (CH_2Cl_2)	$\delta_{H_A} = \delta_{H_B}$ = 5.96

[*] Dr. H. W. Gschwend
Research Dept. CIBA-GEIGY Pharmaceuticals,
Division of CIBA-GEIGY Corporation
Summit, N.J. 07901 (USA)
Dr. H. P. Meier
Chemische Entwicklung, Division Pharma, CIBA-GEIGY A.G.
CH-4000 Basel (Switzerland)

is another intramolecular four-center reaction ([$_\pi$2+$_\sigma$2+$_\pi$2]-cycloaddition)[2].

Received: November 23, 1971 [Z 573 IE]
German version: Angew. Chem. *84*, 291 (1972)

[1] *Houben-Weyl-Müller:* Methoden der Organischen Chemie. Vol. VII 1c, Thieme-Verlag, Stuttgart 1970, p. 1113; *A. A. Krantz*, Doctoral Thesis, Yale University 1967; Chem. Abstr. *69*, 35526c (1968); *D. Bilović*, Croat. Chem. Acta *40*, 15 (1968); *A. L. Johnson* and *H. E. Simmons*, J. Org. Chem. *34*, 1139 (1969); *L. H. Klemm, R. A. Klemm, P. S. Santhanam*, and *D. V. White*, J. Org. Chem. *36*, 2169 (1971).

[2] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[3] *A. Hassner*, J. Org. Chem. *33*, 2684 (1968).

[4] Cf. also *W. Oppolzer*, J. Amer. Chem. Soc. *93*, 3833, 3834, 3836 (1971).

[5] Synthesized in 58% overall yield from *p*-methoxybenzaldehyde + a) Li—C≡C—CH=CHOCH$_3$, b) LiAlH$_4$, c) $H_3O^\oplus$, d) NH$_2$CH$_3$/Na$_2$SO$_4$, e) NaBH$_4$ (hydrochloride m.p. 190 °C).

[6] It was not established whether *(4a)*, which is present in small amounts in the mother liquor of *(3a)*, is a true primary product of an *exo*-addition or whether *(3a)* was equilibrated to *(4a)* under the reaction conditions (in pyridine).

[7] Measured at 70.0 and 85.0 °C in C_6D_6 by comparison of the areas under the N—CH$_3$ and OCH$_3$ peaks of reactant and product. The rate constants determined by this method were in good agreement with the values given above (greater error).

[8] Measured in decahydronaphthalene (spectro-grade, Aldrich) at four temperatures. The rate of disappearance of the substrate was determined by observing $\varepsilon_{294\,nm} = f(t)$.

[9] The kinetic data and their standard deviations were calculated on IBM computers (Models 1130 and 1108) using standard programs (*e.g.* ACTENG, compiled by *D. F. de Tar*, Florida State University).

[10] *J. Sauer, H. Wiest*, and *A. Mielert*, Chem. Ber. *97*, 3183 (1964); *J. Sauer, D. Lang*, and *A. Mielert*, Angew. Chem. *74*, 352 (1962); Angew. Chem. internat. Edit. *1*, 268 (1962); *R. Huisgen*, Angew. Chem. *75*, 742 (1963); Angew. Chem. internat. Edit. *2*, 633 (1963).

[11] *G. Foster, A. C. Cope*, and *F. Daniels*, J. Amer. Chem. Soc. *69*, 1893 (1947); *W. von E. Doering* and *W. R. Roth*, Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 115 (1963).

Oxidative Rearrangement of *C*-Sulfonylthioformamides

By *Nils Henning Nilsson* and *Alexander Senning*[*]

As previously reported[1], ozonolysis of the *C*-sulfonylthioformamide *(1)* leads to the *C*-sulfonylformamide *(2)*.

$$\underset{(1)}{4\text{-}CH_3C_6H_4\text{—}SO_2\text{—}CS\text{—}N(CH_3)_2} + O_3 \longrightarrow \underset{(2)}{4\text{-}CH_3C_6H_4\text{—}SO_2\text{—}CO\text{—}N(CH_3)_2} + SO_2$$

Meanwhile, further studies on the oxidation of *(1)* have shown that the ozonolysis represents a special case. With other oxidizing agents reaction proceeds *via* rearrangement to give *S*-sulfonylthiourethanes *(3)*.

$$(1) + IO_4^\ominus \longrightarrow \underset{(3)}{4\text{-}CH_3C_6H_4\text{—}SO_2\text{—}S\text{—}CO\text{—}N(CH_3)_2} + IO_3^\ominus$$

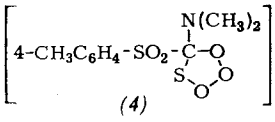
[*] Amanuensis cand. scient. N. H. Nilsson and Lektor fil. lic. A. Senning
Kemisk Institut
Aarhus Universitet
DK-8000 Århus C (Denmark)

The structure of *(3)* follows from the IR spectrum (in KBr; $\nu_{CO} = 1695\ cm^{-1}$, $\nu_{SO_2} = 1335$ and $1150\ cm^{-1}$), a barrier to rotation about the amide C—N bond as detected by NMR spectroscopy ($\Delta G^\neq = 15.6$ kcal mol^{-1}; the corresponding barrier for rotation about the S—N bond of the isomeric sulfenamide 4-CH$_3$C$_6$H$_4$—SO$_2$—CO—S—N(CH$_3$)$_2$ is expected from our experience with sulfenamides[2] to lie considerably lower), and cleavage with chlorine (in CCl_4 at 25 °C) to give *N,N*-dimethylcarbamoyl chloride and *p*-toluenesulfonyl chloride in quantitative amounts.

Oxidation of *(1)* to *(3)* is possible with hydrogen peroxide, peracetic acid, and *m*-chloroperbenzoic acid, as well as metaperiodate, but not with oxides of nitrogen.

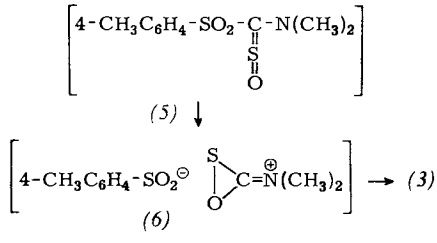
Preparative thin-layer chromatography (silica gel; ether/pet. ether) of the mixture obtained on ozonolysis of *(1)* (in $CHCl_3$ at 25 °C) showed it to contain not only *(2)* (13%) but also *(3)* (4%). Since *(3)* is not attacked by ozone, the reaction sequence *(1)* → *(3)* → *(2)* can be ruled out.

Our findings can be explained by assuming that the ozone attacks the carbon and the sulfur of the thiocarbonyl group simultaneously [*via* the intermediate *(4)* which subsequently decomposes to *(2)* and SO_2] while the other oxidations



(4)

proceed *via* the unstable *S*-oxide *(5)*. The ensuing isomerization of *(5)* to *(3)* can be regarded as a retro-Mannich condensation with subsequent recombination of the ion pair *(6)*. An analogous rearrangement occurs during the oxidation of thiuram sulfides[3].



(5) ↓

(6) → *(3)*

S-Tosyl-N,N-dimethylthiourethane (3)

To a stirred suspension of *(1)* (12.2 g, 0.05 mol) in glacial acetic acid (300 ml) and water (75 ml) is added, over a period of 1 hour, a solution of sodium metaperiodate (13.0 g, 0.06 mol) in water (75 ml). The resulting homogeneous solution is poured onto ice and the volume made up to 800 ml. The pale yellow precipitate of *(3)* is filtered off, washed with two 400-ml portions of water, and recrystallized twice from lukewarm ethanol. The last residue of iodine is washed out with a small volume of CCl_4. Yield: 4.2 g (32%) of *(3)*, m.p. 121—122 °C.

Received: August 26, 1971 [Z 574 IE]
German version: Angew. Chem. *84*, 293 (1972)
Publication delayed at authors' request

[1] *A. Senning, O. N. Sørensen*, and *C. Jacobsen*, Angew. Chem. *80*, 704 (1968); Angew. Chem. internat. Edit. *7*, 734 (1968).

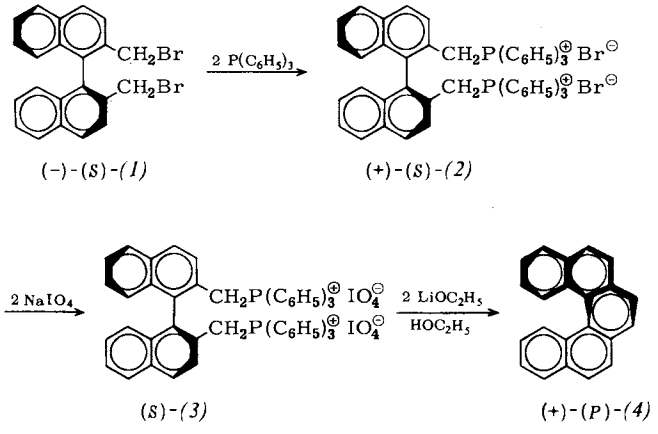
[2] *H. J. Jakobsen, A. Senning*, and *S. Kaae*, Acta Chem. Scand. *25*, 3031 (1971).

[3] *L. A. Brooks* and *R. T. O'Shaughnessy*, French Pat. 1 381 692 (1964), R. T. Vanderbilt Co.; Chem. Abstr. *62*, 9024 (1965); cf. *E. C. Cregg jr.*, J. Amer. Chem. Soc. *74*, 3691 (1952).

Determination of the Absolute Configuration of (+)-Pentahelicene

By *Hans Jürgen Bestmann* and *Wolfgang Both*[*]

Resolution of pentahelicene *(4)* was recently described[1]. We have now succeeded in the first allocation of absolute configuration to a helicene, namely to (+)-*(4)*.



(−)-(*S*)-*(1)* (+)-(*S*)-*(2)*

(*S*)-*(3)* (+)-(*P*)-*(4)*

The fundamental investigations of *Mislow et al.*[2], later confirmed by X-ray structure analysis[3], have shown that (−)-2,2′-bis(bromomethyl)-1,1′-binaphthyl *(1)* belongs to the (*S*)-series. The optically pure compound (−)-*(1)* with triphenylphosphane in molar ratio 1:2 afford the (+)-*(S)*-bisphosphonium salt *(2)* ($[\alpha]_{578}^{23} = +117.3°$, $[\alpha]_{546}^{23} = +138.7°$, $c = 5.48$ mg/cm³ in chloroform; m. p. 274—277 °C (dec.), m. p. (racemate) 289—290 °C (dec.)[4]), which is converted by $NaIO_4$ into the (*S*)-bisphosphonium periodate *(3)*. With lithium ethoxide at −5 to 0 °C[4], *(3)* gives the (+)-pentahelicene *(4)*, which has absolute conformation of the (*P*)-series[5] because of its preparation from (−)-(*S*)-*(1)*; it has $[\alpha]_{578}^{2} = 2260°$, $[\alpha]_{546}^{2} = 2730°$, $[\alpha]_{436}^{2} = 6820°$, $c = 2.90$ mg/cm³ in chloroform; $[\alpha]_{578}^{26} = -1670°$[1], $[\alpha]_{546}^{26} = -2025°$[1], $[\alpha]_{436}^{26} = -4950°$[1] in isooctane; m. p. 159 to 161 °C; the racemate has m. p. 176—177 °C[4]. Since we started from optically pure (−)-(*S*)-*(1)* and prepared *(4)* at 0 °C—a temperature at which no racemization of the compound can be observed—we assume that the (+)-(*P*)-pentahelicene formed is optically pure.

According to calculations partly based on CD measurements, (+)-hexahelicene[6, 7] and (+)-heptahelicene[7] also belong to the (*P*)-series[8]. We suspect that all (+)-helicenes belong to the (*P*)- and all (−)-helicenes to the (*M*)-conformation[9].

Received: December 13, 1971 [Z 575 IE]
German version: Angew. Chem. *84*, 293 (1972)

[*] Prof. Dr. H. J. Bestmann and Dipl.-Chem. W. Both
Institut für Organische Chemie der Universität Erlangen-Nürnberg
852 Erlangen, Henkestrasse 42 (Germany)

[1] *Ch. Goedicke* and *H. Stegemeyer*, Tetrahedron Lett. *1970*, 937.

[2] *D. D. Fitts, M. Siegel*, and *K. Mislow*, J. Amer. Chem. Soc. *80*, 480 (1958); *K. Mislow* and *F. A. McGinn, ibid. 80*, 6036 (1958); *K. Mislow, V. Prelog*, and *H. Scherrer*, Helv. Chim. Acta *41*, 1410 (1958); also the review by *K. Mislow*, Angew. Chem. *70*, 687 (1958).

[3] *H. Akimoto, T. Shioiri, Y. Jitaka*, and *S. Yamada*, Tetrahedron Lett. *1968*, 97.

[4] *H. J. Bestmann, R. Armsen*, and *H. Wagner*, Chem. Ber. *102*, 2259 (1969).

[5] For nomenclature of helicenes cf. *R. S. Cahn, Sir Ch. Ingold*, and *V. Prelog*, Angew. Chem. *78*, 413 (1966); Angew. Chem. internat. Edit. *5*, 385 (1966).

[6] *D. D. Fitts* and *I. G. Kirkwood*, J. Amer. Chem. Soc. *77*, 4940 (1955); *I. Tinoco* and *R. Woody*, J. Chem. Phys. *40*, 160 (1964); *J. H. Brewster*, Topics Stereochem. *2*, 40 (1967).

[7] *G. Wagnière* in: Aromaticity, Pseudoaromaticity, Antiaromaticity. The Jerusalem Symposium of Science, Jerusalem 1971.

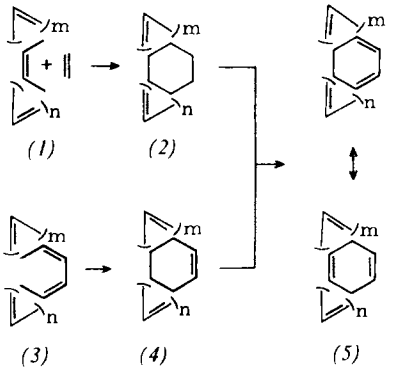
[8] The sole exception is recorded by *A. Moskowitz*, Dissertation, Harvard University 1957; Advan. Chem. Phys. *4*, 67 (1962).

[9] Cf. the agreement with thiaheterohelicenes: *M. B. Groen, G. Stuten, G. I. Visser*, and *H. Wynberg*, J. Amer. Chem. Soc. *92*, 7218 (1970).

Vinylogous Fulvalene: Synthesis and Electrocyclic Reaction[1][**]

By *Hubert Sauter* and *Horst Prinzbach*[*]

Angularly annelated indacenoid ring systems *(5)* have been the subject of several quantum-mechanical calculations[2] and the aim of preparative studies[3, 4]. We have sought the synthetic precursors *(2)* and *(4)* by α,ω-cycloadditions to the fulvalenes *(1)* (*m*=2, *n*=1; *m*=2, *n*=3; *m*=2, *n*=5)[3] and by electrocyclic ring closure of the vinylogous fulvalenes *(3)*. We report here the first example of the second of these synthetic routes[5]: we have been able to prepare compound *(4a)* (*m*=*n*=2) from *(3a)* (*m*=*n*=2).



(1) *(2)* *(3)* *(4)* *(5)*

1,2-Biscyclopentadienylideneethane *(3a)*, the vinylog of the extremely unstable fulvalene that has hitherto been obtained only in highly dilute solution[6], can be isolated in pure form as violet-red needles from pentane. For this purpose the deep red solution obtained when "glyoxal sulfate" *(6)* reacts with cyclopentadienylsodium (equivalent amounts, THF, −20 °C) in the presence of triethylamine, is chromatographed on Al_2O_3 (neutral, deactivated with 7% of H_2O) at −15 °C with pentane as eluant; *(3a)* crystallizes at −78 °C from the pure fraction (yield 3 to 5%)[7].

Crystalline *(3a)* is quite stable in an inert atmosphere at −20 °C but isomerizes rapidly and quantitatively in solution to tricyclo[7.3.0.0^{2,6}]dodeca-3,5,7,9,11-pentaene *(4a)*; its half-lifetime, determined by UV spectrometry (isosbestic points at 281, 362, 399 nm) in pentane at 30 °C amounts to *ca.* 20 min. Even under the influence of daylight the ring closure *(3a)* → *(4a)* is reversible. On base catalysis *(4a)* affords the known mixture of dihydro-*as*-indacenes obtain-

[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. H. Sauter
Lehrstuhl für Organische Chemie der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

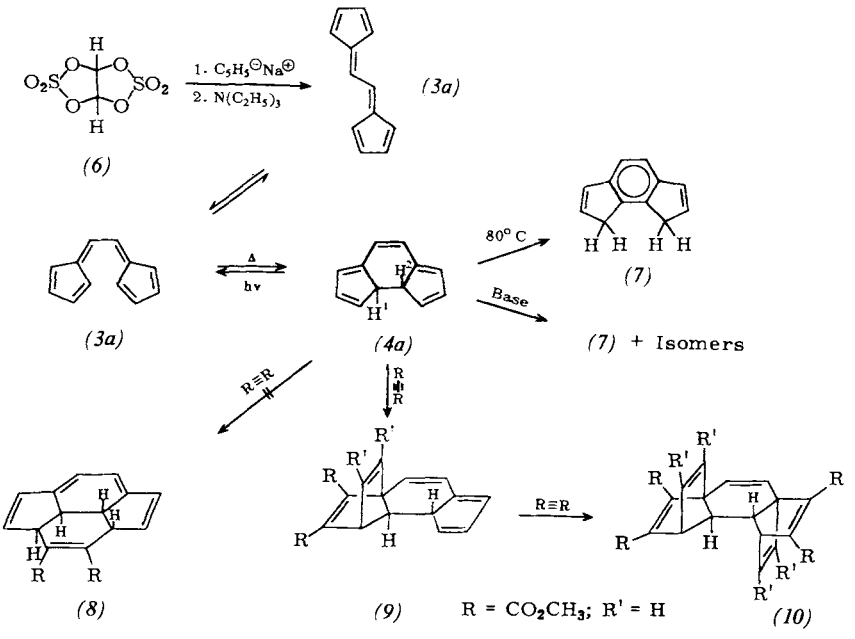


Table. Physical data for compounds *(3a)*, *(4a)*, *(7)*, *(9)*, and *(10)*.

Cpd. [a] M.p. (°C) MS (M^+)	UV λ_{max} (nm; ε)	NMR (τ)	
(3a)	310 (S, 16000)	2.72	(2/S)
77	324 (34500)	3.3 –3.6	(6/M)
154	339 (63000)	3.7 –3.9	(2/M)
[b]	357 (73500)		
	419 (490)		
	[c]		[d]
(4a)	355 (9800)	3.1 –3.6	(8/M)
	266 (12600)	7.52	(2/br.S)
	[e]		[f]
(7)	205 (35000)	2.73	(2/S)
51	226 (6800)	3.05–3.25	(2/M)
154	233 (6900)	3.45–3.65	(2/M)
	241 (5100)	6.6 –6.7	(4/M)
	276 (S, 12900)		
	286 (16000)		
	299 (10800)		
	304 (S, 6900)		
	[e]		[f]
(9)		2.9 –3.2	(2/M)
		3.3 –4.0	(5/M)
		5.9 –6.0	(1/M)
		6.24	(3/S)
		6.26	(3/S)
		6.6 –6.9	(1/M) J^{AB} = 12.7 Hz
		7.7 –8.0	(1/M)
			[f]
(10)	243 (6500)	3.2 –3.5	(4/M)
175	293 (S, 1700)	3.55	(2/br.S)
438		6.1 –6.3	(2/M)
		6.55	(6/S)
		6.63	(6/S)
		6.80	(2/br.S)
	[g]		[h]

[a] Satisfactory elemental analyses were obtained for all the compounds isolated. [b] Evaporation temperature below 60°C. [c] In pentane, 0°C. [d] In $CCl_4/CDCl_3$ 5:1, –15°C. [e] In pentane. [f] In $CCl_4/CDCl_3$ 5:1. [g] In ethanol. [h] In C_6D_6.

ed by another route[8], and on pyrolysis at 80°C gives exclusively the isomer *(7)*. On partial catalytic hydrogenation *(7)* and the tautomers are converted into hexahydro-*as*-indacene[9]. The spectroscopic data (Table) are in agreement with structures *(3a)* and *(4a)*.

In the case of *(3a)* special interest attaches to the allowed longest-wavelength π—π^* transition in connection with theoretical papers on the electronic spectra of bisdiphenylenepolyenes[10]. In qualitative agreement with improved HMO calculations the relevant absorption band (λ_{max} = 419 nm) is shifted slightly bathochromically with respect to that of fulvalene[11].

Ring closure of *(3a)*, which without doubt is not planar in the *s-cis*-conformation, should be conrotatory[12], leading to *(4a)* with *trans* geometry. The magnetically equivalent protons H^1, H^2 in *(4a)* would differ in the adduct *(9)*; the vicinal coupling of 12.7 Hz makes the *trans* arrangement probable but does not permit a final decision[13].

(4a) adds dimethyl acetylenedicarboxylate with satisfactory speed at 25°C, without notable isomerization to *(7)*. It thus affords *(9)* or *(10)* according to the reaction conditions[14]; compound *(8)*, the product of $[{}_{\pi}10_a + {}_{\pi}2_s]$-addition, was not found.

Received: December 14, 1971 [Z 577 IE]
German version: Angew. Chem. *84*, 297 (1972)

[1] Cyclic Cross-conjugated Bond Systems, Part 25.—Part 24: *H. Prinzbach* and *H.-J. Herr*, Angew. Chem. *84*, 117 (1972); Angew. Chem. internat. Edit. *11*, 135 (1972).

[2] *R. Zahradník*, Angew. Chem. *77*, 1097 (1965); Angew. Chem. internat. Edit. *4*, 1039 (1965); *G. Binsch* and *E. Heilbronner*, Tetrahedron *24*, 1215 (1968); *S. F. Wilcox jr.*, J. Amer. Chem. Soc. *91*, 2732 (1969).

[3] *H. Prinzbach*, Pure Appl. Chem. *28*, 281 (1971).

[4] *W. Grimme*, personal communication.

[5] Cf. the syntheses of linearly annelated systems: *K. Hafner*, Angew. Chem. *75*, 1041 (1963); Angew. Chem. internat. Edit. *3*, 165 (1964); *D. J. Bertelli*, J. Org. Chem. *30*, 891 (1965).

[6] *W. von E. Doering* in: Theoretical Organic Chemistry. Butterworths, London 1959, p. 35.

[7] The yield of crystalline *(3a)* depends strongly on the time taken for working up. The total yield, including that of the subsequent reaction products *(4a)* and *(7)* amounts to 15%.

[8] *T. J. Katz*, *V. Balogh*, and *J. Schulman*, J. Amer. Chem. Soc. *90*, 734 (1968).

[9] *H. Rapoport* and *G. Smolinsky*, J. Amer. Chem. Soc. *82*, 1171 (1960); *R. H. Wightman*, *R. J. Wain*, and *D. H. Lake*, Canad. J. Chem. *49*, 1360 (1971).

[10] *H. Stegemeyer*, Ber. Bunsenges. Phys. Chem. *73*, 612 (1969), where further literature is cited; cf. *B. Pullman* and *G. Berthier*, C. R. Acad. Sci. Paris *229*, 717 (1949).

[11] $\lambda_{max} = 416$ nm in pentane ($\varepsilon = 260$); *E. A. Matzner*, Dissertation, Yale University 1958; cf. [6].

[12] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[13] *L. M. Jackman* and *S. Sternhell*: Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press, Oxford, 2nd Edit. 1969, pp. 208 ff.

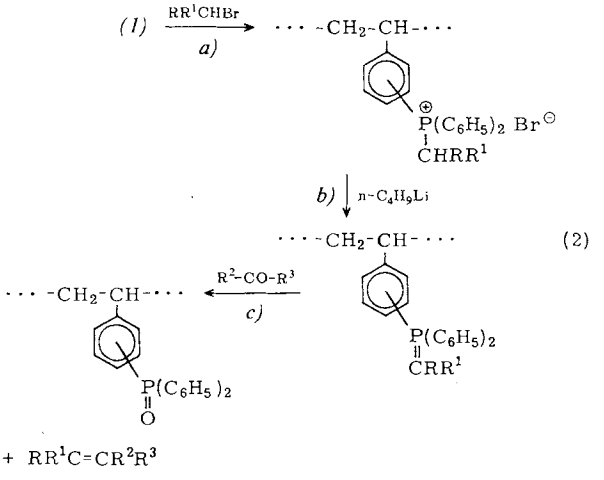
[14] The alternative structures with R = H and R′ = CO_2CH_3 are not excluded by the experimental data but are less probable on steric grounds. An X-ray structure analysis is projected (Dr. *W. Littke*).

Polymeric Wittig Reagents[1][**]

By *Walter Heitz* and *Rudolf Michels*[*]

"Polymeric reagents" are polymers that carry functional groups. Only those polymers are suitable that can quite easily be removed from a reaction mixture after reaction of their functional groups. Cross-linked polymers can be separated easily by filtration and can thus be used in large excess; linear polymers are in general unsuitable.

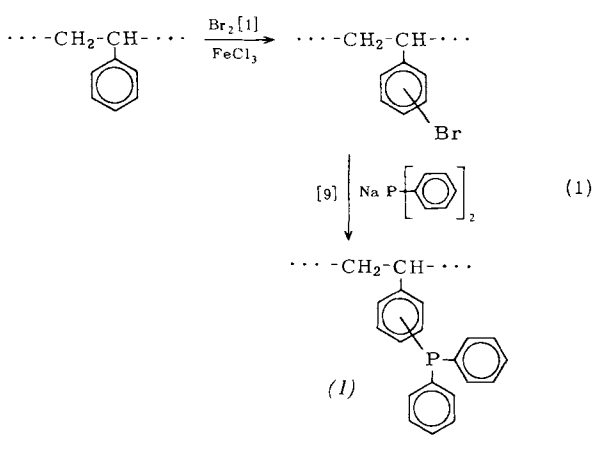
Polymeric reagents are especially advantageous when an excess of the analogous low-molecular reagent or its reaction product causes separation troubles or if a quantitative yield is sought; also the formation of by-products can be suppressed in some cases since intermediates, which are now more easily separated, can be removed.



taining 2.1—3.18 mequivalents of triphenylphosphane groups per g of polymer (6.5 or 9.9%, respectively, of P). (A polymer from pure vinyltriphenylphosphane would contain 3.47 mequivalents of triphenylphosphane groups per g of polymer.) The polymers containing triphenylphosphane groups can be used for *Wittig* olefination[2, 11].

Table. Comparison of yields in the conventional *Wittig* olefination and in the preparation of olefins by reaction with polystyrene cross-linked with 2% or 0.5% of divinylbenzene and containing triphenylphosphane groups.

RR′CHBr	Carbonyl compound	Yield (%) polymer 2%	polymer 0.5%	low-mol.	
Geranyl bromide	*p*-Chlorobenzaldehyde	11	48	49	(61 [4])
4-Benzoyl-1-bromobutane		32	26	22	(24 [5])
Ethyl bromide	9-Anthracenecarbaldehyde	—	66	7	(— [6])
Isopropyl bromide	9-Anthracenecarbaldehyde	10	—	16	(28 [6])
9-Fluorenyl bromide	Benzaldehyde	68	86	65	(84 [7])
Butyl bromide	Acetophenone	100	—	100	(100 [2, 8, 10])



According to eq. (1), reaction of polystyrene cross-linked with divinylbenzene affords a cross-linked polymer con-

In the reaction steps (2a) and (2b) the reagent (alkyl halide or butyllithium) can be added in excess, and the excess can be removed by filtration.

The reactions were carried out with polystyrenes cross-linked with 0.5 or 2.0 wt.-% of divinylbenzene. Gel-chromatographic studies[3] showed that only about 75% of the pore volume in a swollen polystyrene cross-linked with 2% of divinylbenzene is accessible to substances with molecular weights of 300—400. This percentage certainly decreases when the bulky triphenylphosphane groups have been introduced. Accordingly the yields obtained when working with the more strongly cross-linked copolymers are certainly considerably less than those obtained by conventional methods (Table). However, by starting with polystyrene cross-linked with only 0.5% of divinylbenzene we obtained at least as good yields as by the usual *Wittig* technique; examples are given in the Table.

In step (2b) the reaction of low-molecular reagents often causes formation of by-products that are not present after reaction of the polymeric reagents and removal of the base by filtration, as can be shown by gas chromatography; however, the by-products are formed even in these cases if the butyllithium is not carefully removed.

[*] Prof. Dr. W. Heitz and Dipl.-Chem. R. Michels
Institut für organische Chemie der Universität
65 Mainz, Johann-Joachim-Becher-Weg 18—20 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der chemischen Industrie, and the E. Merck company.

2-Phenyl-2-hexene

A copolymer (30 g) prepared according to eq. (1) from polystyrene cross-linked with 2% of divinylbenzene (7.3% of P, corresponding to 0.0705 mol of triphenylphosphane groups) was treated in THF (80 ml) with *n*-butyl bromide (11.6 g, 0.0841 mol). The suspension was stirred under reflux for 24 h, then the polymer was extracted with THF in a Soxhlet for 8 h and dried for 24 h at 40 °C in a vacuum. This afforded the polymeric *n*-butyltriphenylphosphonium bromide (39.0 g, 0.0657 mol of phosphonium groups).

The polymer (19 g), dried and loaded with N_2, was made into a slurry with anhydrous dioxane (40 ml), and 20% butyllithium solution (13 ml) was added at 20 °C. The Gilman test[12] was still positive after 30 min. The supernatant solvent was removed, anhydrous dioxane (30 ml) was added, then stirred and filtered again. The washing procedure was repeated until the Gilman test was negative.

The polymer thus obtained was suspended and vigorously stirred in dioxane (40 ml) at 20 °C and a solution of acetophenone (2.95 g, 0.0247 ml; freshly distilled) in dioxane (10 ml) was added. After 8 hours' stirring at 60 °C the reaction was stopped. The polymer was extracted with 1:1 aqueous THF in a Soxhlet for 12 h, after which the aqueous phase was separated from the eluate, and the residual solution was investigated by gas chromatography and IR spectroscopy (comparison with authentic olefin). Removal of the solvent left 4 g of extract from which distillation in a vacuum afforded pure 2-phenyl-2-hexene (3.85 g, 97%).

Received: December 6, 1971 [Z 578 IE]
German version: Angew. Chem. *84*, 296 (1972)

[1] Polymeric Reagents, Part 2. — Part 1: *W. Heitz* and *R. Michels*, Makromolekulare Chem. *148*, 9 (1971).

[2] *G. Wittig* and *U. Schöllkopf*, Chem. Ber. *87*, 1318 (1954).

[3] *W. Heitz, B. Bömer*, and *H. Ullner*, Makromolekulare Chem. *121*, 10 (1969).

[4] *F. Dallacker, F. Kornfeld*, and *M. Lipp*, Mh. Chem. *91*, 688 (1960).

[5] *T. J. Bieber* and *E. H. Eisman*, J. Org. Chem. *27*, 678 (1962).

[6] *E. G. E. Hawkins*, J. Chem. Soc. *1957*, 3858.

[7] *A. W. Johnson*, J. Org. Chem. *24*, 282 (1959).

[8] *G. Wittig* and *M. Schlosser*, Chem. Ber. *94*, 1373 (1961).

[9] *K. Issleib* and *D. W. Müller*, Chem. Ber. *92*, 3179 (1959).

[10] *U. Schöllkopf*, Angew. Chem. *71*, 260 (1959).

[11] *A. Maercker*, Org. Reactions *14*, 270 (1965).

[12] *Houben-Weyl-Müller*: Methoden der organischen Chemie. 4th Edit. Thieme-Verlag, Stuttgart 1970, Vol. XIII/1, p. 22.

Trifluoromethanesulfonic-Carboxylic Anhydrides, Highly Active Acylating Agents[1]

By *Franz Effenberger* and *Gerhard Epple*[*]

The trifluoromethanesulfonate anion has proved the best leaving group so far in solvolytic displacement reactions[2]. For acylation with carboxylic acid derivatives, however, a straightforward estimate of the influence of the leaving group on the reaction rate is impossible; depending on substrate and reaction conditions, there are several mechanistic pathways with a varying dependance on the nature of the leaving group[3]. Recent investigations have shown, though, that the acylation potential is higher for sulfonic-carboxylic than for carboxylic anhydrides[4, 5]. So, further increased reactivity may be expected with trifluoromethanesulfonic-carboxylic anhydrides *(3)*.

We have prepared the mixed anhydrides *(3)* by treating the silver salt *(1)* with acyl chlorides *(2)* (method A, Table 1); they are also formed, although in lower yields, by reaction of free trifluoromethanesulfonic acid with *(2)* (method B, Table 1).

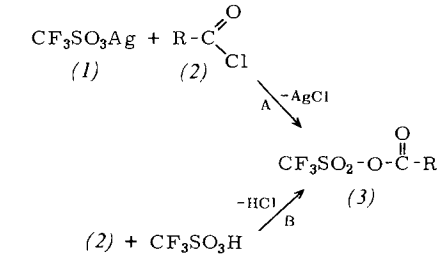
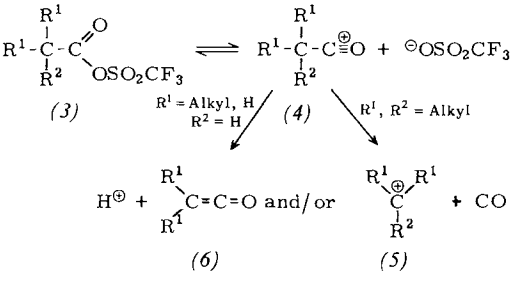


Table 1. Anhydrides *(3)* from *(2)* and *(1)* (method A) or from *(2)* and CF_3SO_3H (method B).

R	Method	B.p. (°C/torr)	Yield (%) [a]
C_6H_5	A	98–101/11	90
p-NO_2—C_6H_4	A	M.p. = 40–53 °C	80
p-CH_3—C_6H_4	A	62/0.3	94
p-Cl—C_6H_4	A	78/0.2	100
$(CH_3)_3C$	A	[b]	66
$(C_2H_5)_2CH$	A	54–58/0.1	36
C_6H_5	B	96–101/11	35
p-CH_3—C_6H_4	B	57–60/0.1	39
p-Cl—C_6H_4	B	73–75/0.1	63

[a] Crude yields are given in each case. Due to extreme sensitivity to water, elemental analyses of the anhydrides *(3)* often gives slightly inexact values. [b] Decomposes on distillation.

In the case of aromatic carboxylic acids [*(3)*, R = aryl], the anhydrides may be distilled without decomposition; the aliphatic members (R = alkyl) are thermolabile, and only a few do not decompose upon distillation. This instability can be rationalized in terms of a dissociation equilibrium of the anhydrides *(3)*: if R is an aliphatic group ($R = CR^1_2R^2$), the acylium cations *(4)* thus formed may either lose CO yielding carbonium ions *(5)* and/or be deprotonated to give ketenes *(6)*.



We have established that carbon monoxide is formed quantitatively in the decomposition of several aliphatic anhydrides; but ketenes have not been observed so far. When R = aryl, ketene formation is impossible, and decarbonylation appears rather unlikely because of the instability of the phenyl cations formed.

The anhydrides *(3)* are the most powerful acylating agents known so far. Whereas xylenes do not react with other

[*] Prof. Dr. F. Effenberger and Dipl.-Chem. G. Epple
Institut für Organische Chemie der Universität
7000 Stuttgart, Azenbergstrasse 14—18 (Germany)

sulfonic-carboxylic anhydrides even if heated for 24 h at 100 °C[5], non-activated arenes such as benzene are acylated smoothly by the mixed anhydrides *(3)*, without addition of Friedel-Crafts catalysts (Table 2). The trifluoromethanesulfonic acid can be recovered almost quantitatively as its barium salt.

Table 2. Acylation of aromatic compounds by anhydrides *(3)*.

Reactants *(3)*, R	Arene	Conditions T(°C)	t(h)	Product [b]	Yield (%)
C_6H_5	Benzene	−20	5	Benzophenone	5
C_6H_5	Benzene	+20	5	Benzophenone	52
C_6H_5	Benzene	+60	5	Benzophenone	90
C_6H_5	Anisole	+20	0.5	4-Methoxybenzophenone	77
C_6H_5	Chlorobenzene	+60	5	4-Chlorobenzophenone	67
p-NO_2—C_6H_4	Benzene	+80	1	4-Nitrobenzophenone	53
p-NO_2—C_6H_4	Anisole	+40	0.1	4-Methoxy-4′-nitrobenzophenone	84
CH_3	Anisole	−70	2 [a]	Acetophenone	66
$(CH_3)_2CH$	Anisole	+40	3.5 [a]	Isopropyl phenyl ketone	69

[a] The anhydride *(3)* was prepared in CH_2Cl_2 and allowed to react directly in this solution with the aromatic compound.
[b] The acylation products obtained were compared with authentic material.

Received: December 16, 1971 [Z 579a IE]
German version: Angew. Chem. *84*, 294 (1971)

[1] Electrophilic Substitution of Aromatic Compounds, Part 1. — This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[2] a) *R. L. Hansen*, J. Org. Chem. *30*, 4322 (1965); b) *A. Streitwieser jr., C. L. Wilkins*, and *E. Kielmann*, J. Amer. Chem. Soc. *90*, 1598 (1968); c) *Tah Mun Su, W. F. Sliwinski*, and *P. v. R. Schleyer*, *ibid. 91*, 5386 (1969).

[3] *J. March*: Advanced Organic Chemistry. Reactions, Mechanisms, and Structure. McGraw-Hill, New York 1968, p. 413 ff.

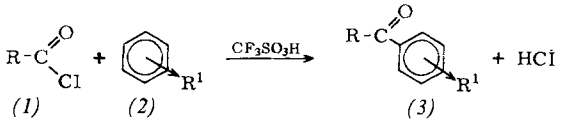
[4] a) *A. Baroni*, Atti Accad. Naz. Lincei, Mem., Cl. Sci. Fis., Mat. Natur. *17*, 1081 (1933); b) *C. G. Overberger* and *E. Sarlo*, J. Amer. Chem. Soc. *85*, 2446 (1963); c) *G. A. Olah* and *S. J. Kuhn*, J. Org. Chem. *27*, 2667 (1962); d) *H. Böhme* and *K.-H. Meyer-Dulhever*, Liebigs Ann. Chem. *688*, 78 (1965); e) *E. Sarlo* and *T. Lanigan*, Org. Prepar. and Proced. *1*, 157 (1969).

[5] *M. H. Karger* and *Y. Mazur*, J. Org. Chem. *36*, 528, 532, 540 (1971).

with strong Brønsted acids, though in poor yields[3]. However, the trifluoromethanesulfonic-carboxylic anhydrides obtainable from acyl chlorides and CF_3SO_3H do smoothly acylate aromatic compounds without addition of a catalyst[4]; in the course of the reaction, the sulfonic acid is set free again. Therefore, CF_3SO_3H-catalyzed acylation of aromatic compounds with acyl chlorides appeared a possibility.

If a catalytic amount (~1%) of CF_3SO_3H is added to a mixture of acyl chloride *(1)* and aromatic compound *(2)*, hydrogen chloride is evolved more or less violently, depending on the reactivity of the reactants, and aromatic ketones *(3)* (Table 1) are formed.

In many cases carboxylic anhydrides may be made to react under similar conditions, but the yields are then slightly lower.



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

Table 1. Formation of aromatic ketones by catalytic Friedel-Crafts acylation.

Reactants *(1)*, R	*(2)*	Conditions T (°C)	t (h)	Product	Yield (%)	*o*:*p*
C_6H_5	Benzene	80	8.5	Benzophenone	14	
C_6H_5	Chlorobenzene	132	5	2- and 4-Chlorobenzophenone	13	1:3
C_6H_5	Toluene	110	48	2- and 4-Methylbenzophenone	85	1:2
C_6H_5	*p*-Xylene	138	6	2,5-Dimethylbenzophenone	82	
p-NO_2—C_6H_4	Benzene	80	4	4-Nitrobenzophenone	82	
$(CH_3)_3C$	Anisole	154	12	*t*-Butyl *p*-methoxyphenyl ketone	54	
$(CH_3)_2CH$	Anisole	154	0.2	Isopropyl *p*-methoxyphenyl ketone	46	

Catalytic Friedel-Crafts Acylation of Aromatic Compounds[1]

By *Franz Effenberger* and *Gerhard Epple*[*]

For the synthesis of aryl ketones from aromatic compounds and acid chlorides or anhydrides at least one equivalent of Friedel-Crafts catalyst is required[2]. Highly activated arenes such as mesitylene or anisole may be acylated also

Trifluoromethanesulfonic-carboxylic anhydrides[4] formed as intermediates could be assumed to constitute the active acylating agent; on the other hand, the acylating potential of the acyl chlorides may also be increased sufficiently by protonation of the C=O group. We have therefore studied the catalytic efficiency of other strong Brønsted and Lewis acids. As shown in Table 2, catalytic acylation of arenes is possible in principle also with other acids; the yields, though, are of little preparative interest. Perchloric acid which has about the same acid strength as trifluoromethanesulfonic acid[5] is a considerably less effective catalyst. This finding supports our assumption that intermediate

[*] Prof. Dr. F. Effenberger and Dipl.-Chem. G. Epple
Institut für Organische Chemie der Universität
7000 Stuttgart, Azenbergstrasse 14—18 (Germany)

formation of mixed anhydrides is decisive for the catalytic influence of trifluoromethanesulfonic acid; a final decision, however, is not yet possible.

Table 2. Catalytic action of Brønsted and Lewis acids in the acylation of *p*-xylene by benzoyl chloride.

Catalyst	Amount (%)	Conditions T (°C)	t (h)	Yield (%)
CF_3SO_3H	1	138	6	82
FSO_3H	1	138	6	20
p-CH_3—C_6H_4—SO_3H	1	138	6	31
H_2SO_4	1	138	6	28
$HClO_4$	1	138	6	14
CF_3COOH	2.6	138	10	21
$HPOF_2$	3.1	138	10	4
$AlCl_3$	2	138	15	26
$SnCl_4$	2	138	15	30

2,5-Dimethylbenzophenone:

Benzoyl chloride (42 g) and *p*-xylene (95.5 g) are mixed and treated with trifluoromethanesulfonic acid (0.42 g), then heated for 6 h under reflux. After cooling, the reaction mixture is washed several times with water, dried over sodium sulfate and fractionated, yielding 82% (51.6 g) of 2,5-dimethylbenzophenone, b.p. 173—175 °C/12 torr. For recovery of the catalyst, the aqueous phases are neutralized with barium carbonate, and evaporated.

Received: December 16, 1971 [Z 579b IE]
German version: Angew. Chem. *84*, 295 (1972)

[1] Electrophilic Substitution of Aromatic Compounds, Part 2.—Part 1: [4].—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[2] See *G. A. Olah:* Friedel-Crafts and Related Reactions. Interscience, New York 1964, Vol. 3, pp. 8ff.

[3] a) *F. Unger*, Liebigs Ann. Chem. *504*, 267 (1933); b) *R. E. Foster*, US-Pat. 2496786 (1950), E.I. du Pont de Nemours; Chem. Abstr. *44*, 4930^b (1950); c) *G. N. Dorofeenko*, Zh. Obshch. Khim. *31*, 994 (1961).

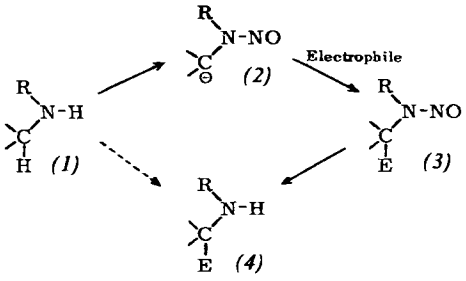
[4] *F. Effenberger* and *G. Epple*, Angew. Chem. *84*, 294 (1972); Angew. Chem. internat. Edit. *11*, 299 (1972).

[5] *Th. Gramsted*, Tidsskr. Kjemi, Bergvesen Met. *19*, 62 (1959); Chem. Abstr. *54*, 12739 (1960).

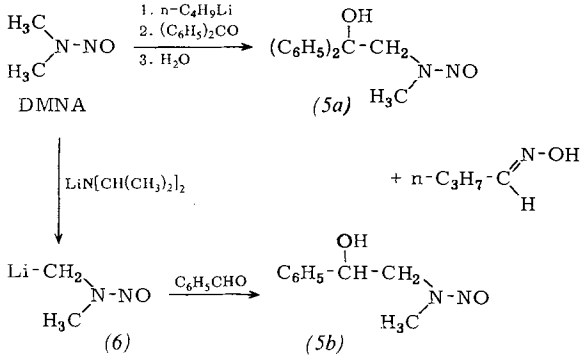
C—C-Bond Formation in the α-Position to Nitrogen in Secondary Amines. Lithiodimethylnitrosamine[**]

By *Dieter Seebach* and *Dieter Enders*[*]

In 1970 *Keefer* and *Fodor* published data showing that base-catalyzed H/D-exchange occurs in the α-position of nitrosamines[2]. The synthetic availability of corresponding anions *(2)* would offer a novel type of route to amine molecules. Thus, nitrosation of a secondary amine *(1)*, metalation to give a derivative of *(2)*, reaction with an electrophile to form *(3)*, and denitrosation[3] represent a way of carrying out the valuable electrophilic substitution *(1)* → *(4)* which is not feasible by known methods[4].



We were able to verify the sequence *(1)* → *(2)* → *(3)* using dimethylnitrosamine (DMNA) and a number of electrophiles; there are numerous examples in the literature[3] for the facile last step *(3)* → *(4)* in the above cycle.



In our first metalation experiments with DMNA it turned out that nucleophilic attack at the nitroso group and metalation at the methyl group of DMNA compete when organolithium compounds are employed: sequential addition of *n*-butyllithium and benzophenone to a solution of DMNA in THF at −80 °C furnished a mixture containing both the adduct *(5a)* and butyraldehyde oxime. Similarly, the highest yield of carbinol *(5b)* obtained

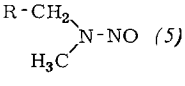


Table. Yields (not optimized), melting- and boiling points of nitrosamines *(5)* from DMNA [a] [the electrophiles were added 10 min after the solutions of DMNA and lithium diisopropylamide had been combined (total volume 40 ml THF/hexane 8:2 per 10 mmol); the mixtures were kept at −80 °C for 5—10 h].

Electrophile	*(5)*, R [a]	Yield [%]	M.p. (°C) or b.p. (°C/torr) [b]
Methyl iodide	CH_3	75	80/30 [c]
n-Butyl iodide	*n*-C_4H_9	75	100/10 [d]
Benzyl bromide	C_6H_5—CH_2	95	100/0.1 [e]
n-Butyraldehyde	*n*-C_3H_7—CHOH	80	120/1
Benzaldehyde	C_6H_5—CHOH	95	73
Cyclohexanone	1-hydroxycyclohexyl	90	63 (140/0.2)
2-Cyclohexen-1-one	1-hydroxy cyclohexenyl	75 [f]	140/0.5
Benzophenone	$(C_6H_5)_2COH$	70	113.5

[a] All new compounds gave correct elemental analyses and showed IR- [5a] and NMR spectra [5b] typical of nitrosamines.
[b] Bath temperature, short path distillation.
[c] B.p. 70 °C/35 torr [6].
[d] B.p. 96—98 °C/13 torr [6].
[e] B.p. 116 °C/2 torr [6].
[f] The spectra indicate the presence of little if any Michael adduct.

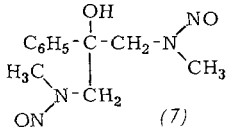
[*] Prof. Dr. D. Seebach and D. Enders
Institut für Organische Chemie der Universität
63 Giessen, Ludwigstrasse 21, (Germany)

[**] Most nitrosamines are organotropic carcinogens [1]. All manipulations must be carried out with due care. However, cancer research scientists are interested in testing new types of nitrosamines which might become available through organometallic derivatives. We thank Prof. Dr. *H. Druckrey*, Freiburg, and Dr. *R. Preussmann*, Heidelberg, for valuable discussions.—Financial support by the Fonds der Chemischen Industrie is appreciated.

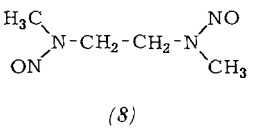
using methyl-, *tert*-butyl-, and phenyllithium for metalation and benzaldehyde as an electrophile was 75% (by NMR spectroscopy of the product mixture).

Quantitative lithiation to give *(6)* can be accomplished, however, with lithium diisopropylamide, as shown by the isolation in more than 95% yield of *(5b)* after successive addition (within 10 min) of the amide and the aldehyde to a solution of DMNA in THF. If the aldehyde is added after a longer period of time the yield of *(5b)* decreases, thus demonstrating the instability of *(6)* (halflife at −80 °C *ca.* 2 h, decomposition product not yet identified). The table contains data about the nitrosamines *(5)* obtained with various electrophiles.

With benzoyl chloride a product (70% yield, m.p. 110 °C) is formed to which we tentatively assign structure *(7)* on the basis of its elemental composition, molecular weight (exp. osmom. 270, calc. 250), and IR spectrum (strong absorption at 3.3 μm). Iodine converts *(6)* into the dimer *(8)* (95% yield, m.p. 57 °C, identical with authentic[7] sample). The



(7)



(8)

scope of the new reaction as applied to further electrophiles and other nitrosamines is currently under investigation[**].

Received: February 1, 1972 [Z 582 IE]
German version: Angew. Chem. *84*, 350 (1972)

[1] *H. Druckrey, R. Preussmann, S. Ivankovic,* and *D. Schmähl,* Zeitschr. Krebsforsch. *69*, 103 (1967).

[2] *L. K. Keefer* and *C. H. Fodor,* J. Amer. chem. Soc. *92*, 5747 (1970); see also *R. R. Fraser* and *Y. Y. Wigfield,* Tetrahedron Lett. *1971*, 2515.

[3] Literature compilation of preparations and reactions of nitrosamines: *A. L. Fridman, F. M. Mukhametshin,* and *S. S. Novikov,* Usp. Khim. *40*, 34 (1971).

[4] The grouping $H_2N—CH_2^{\ominus}$ for nucleophilic introduction of a primary aminomethyl group is available in several forms: $N\equiv C^{\ominus}$, $O_2N—CH_2^{\ominus}$, $:C=N—CH_2^{\ominus}$ [*U. Schöllkopf,* Angew. Chem. *82*, 795 (1970); Angew. Chem. internat. Edit. *9*, 763 (1970)], $(C_6H_5)_2C=N—CH_2^{\ominus}$ [*T. Kauffmann, E. Köppelmann,* and *H. Berg,* Angew. Chem. *82*, 138 (1970); Angew. Chem. internat. Edit. *9*, 163 (1970)].

[5] a) *P. Rademacher* and *W. Lüttke,* Spektrochim. Acta *27A*, 715 (1971), and literature cited therein; b) *G. J. Karabatsos* and *R. A. Taller,* J. Amer. Chem. Soc. *86*, 4373 (1964), and literature cited therein.

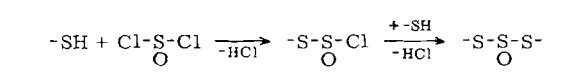
[6] *R. Preussmann,* Dissertation, Universität Freiburg 1966.

[7] *P. Schneider,* Ber. Dtsch. Chem. Ges. *28*, 3076 (1895).

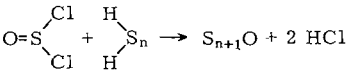
Preparation of *cyclo*-Octasulfur Oxide, S_8O[1]

By *Ralf Steudel* and *Michael Rebsch*[*]

Thionyl chloride reacts with thiols (RSH) and with hydrogen sulfide with elimination of HCl, as follows:

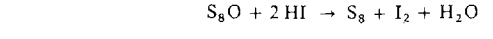


In this way disulfane oxide chlorides RS_2OCl[3] and trisulfane oxides R_2S_3O[4,5] are obtained from RSH, and polysulfane oxides[6] from H_2S. If now $SOCl_2$ is treated with polysulfanes (H_2S_n) in the molar ratio 1:1 by the dilution principle, a ring closure reaction affords cyclopolysulfur oxides:



In this way we have been able to prepare the new sulfur oxide S_8O as the first compound of that class which can be isolated in a pure state; this was effected by condensation of $SOCl_2$ with "crude sulfane" (H_2S_n; $n=3,4,5...$) at −40 °C in $CS_2/(CH_3)_2O$.

S_8O crystallizes from CS_2 as intensely yellow needles some millimeters in length. The solubility in CS_2, *ca.* 8 g/l (25 °C), is large enough to permit osmometric determination of the molecular weight at 0 and 25 °C. This gave values between 270 and 285 with a mean value of 278 (calc.: 272.5). Sulfur and oxygen were determined separately, S acidimetrically after combustion to H_2SO_4, and O iodometrically thus:



The analytical results confirm the molecular composition.

Crystalline S_8O is stable (metastable) for weeks at −20 °C in the dark. At room temperature the substance can be kept for several hours without decomposition, but on longer storage an odor of SO_2 develops. Warming causes spontaneous decomposition with evolution of SO_2 at 78 °C, and at higher temperatures the crystals liquefy. In this process polymeric sulfur (S_n) is formed, which is plastic on cooling:

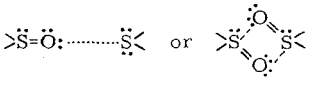
The same decomposition occurs in boiling CS_2, the intensely yellow solution decolorizing and S_n being precipitated.

In a vacuum thermal decomposition occurs at 80—120 °C, thus:



For this reason no molecular ion was found in the mass spectrum[7] even on variation of the probe and source temperatures and of ionization energy. S_2O^+ and S_8^+, their fragments SO^+ and S_n^+ ($n=1$ to 7), and occasionally S_3O^+ were detected.

IR spectrum[8] of crystalline S_8O (CsCl disc)[9]: 340w, 351w, 383s, 397s, 424w, 440vw, 515w, 1085vs, and 1094w cm^{-1}. In CS_2 solution the SO stretching vibration was found at 1134 cm^{-1}, which corresponds exactly to the value for other compounds containing the —S—SO—S— group[3,4,5]. In the solid state ν(SO) at 1085 cm^{-1} is shifted to somewhat smaller wave number, which can be explained by very weak coordinate bonding of the following type:



On use of known formulas[2] the stretching force constant $f(SO)=7.40$ mdyn/Å obtained from the two-mass model leads to the bond order $b(SO)=1.6$ in crystalline S_8O

[*] Prof. Dr. R. Steudel and Dipl.-Chem. M. Rebsch
Institut für Anorganische und Analytische Chemie der Technischen Universität
1 Berlin 12, Strasse des 17. Juni 135 (Germany)

and the bond length $d(SO) = 1.49$ Å. The structure of the S_8O molecule is probably that of a zigzag S_8 ring with an equatorial or axial O atom (symmetry C_s).

In light from an argon ion laser (488.0 and 514.5 nm) S_8O decomposes slowly into SO_2 and S_8, so that it was impossible to obtain an unambiguous Raman spectrum.

Experimental:

"Crude sulfane"[10] (104 g) of mean composition $H_2S_{6.2}$, dissolved in CS_2 (266 ml), and $SOCl_2$ (62 g), dissolved in CS_2 (290 ml), were added in equimolar amounts simultaneously to a mixture of CS_2 (800 ml) and $(CH_3)_2O$ (200 ml) at −40 °C during 8 h. After being stirred for a further hour the orange solution, from which a yellow precipitate had separated, was concentrated by 100 ml at −50 °C in a vacuum. The solution was then separated from the precipitate and was concentrated to half its volume in a vacuum at temperatures rising slowly from −50 to −20 °C. By then HCl and $(CH_3)_2O$ had been almost completely removed. The solution was next cooled slowly to −60 °C, whereupon a flocculent precipitate separated. This was filtered off, washed with a little ether at 20 °C, dried in a vacuum, and recrystallized three times from CS_2. Further S_8O was isolated from the solid formed in the main reaction. Yield: *ca.* 3 g. All operations were carried out under dry N_2 and with carefully dried solvents.

Received: November 10, 1971 [Z 585 IE]
German version: Angew. Chem. *84*, 344 (1972)

[1] Part 18 of Sulfur-Oxygen Compounds.—Part 17: [2].

[2] *R. Steudel*, Z. Naturforsch. *26b*, 750 (1971).

[3] *R. Steudel* and *G. Scheller*, Z. Naturforsch. *24b*, 351 (1969).

[4] *R. Steudel, P. W. Schenk*, and *J. Bilal*, Z. Anorg. Allg. Chem. *353*, 250 (1967).

[5] *L. Field* and *W. B. Lacefield*, J. Org. Chem. *31*, 3555 (1966).

[6] *P. W. Schenk, W. Kretschmer, R. Ludwig, R. Steudel*, and *M. Töpert*, Angew. Chem. *77*, 1089 (1965); Angew. Chem. internat. Edit. *4*, 1093 (1965).

[7] Varian CH 7

[8] Beckman IR-12.

[9] The IR spectrum will be published in the DMS catalog (Verlag Chemie, Weinheim/Bergstr., and Butterworths, London).

[10] *F. Fehér* in *G. Brauer*: Handbuch der präparativen anorganischen Chemie. F. Enke-Verlag, Stuttgart 1960, Vol. 1, p. 315.

A Stable Aromatic Diradical with Strong Dipolar Electronic Interaction[**]

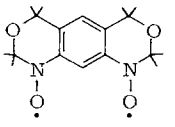
By *André Rassat* and *Hans Ulrich Sieveking*[*]

Bisnitroxides in which the radical centers are not widely separated have only recently become known[1–5]. Various types of information about the conformation, symmetry, and electronic state of the diradicals can be obtained from their ESR spectra. However, the shape of the ESR spectra is also sensitively influenced by the arrangement and mobility of the environment of such molecules.

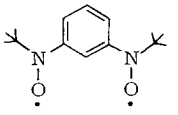
[*] Prof. Dr. A. Rassat and Dr. H. U. Sieveking
Laboratoire de Chimie Organique Physique
Centre d'Études Nucléaires de Grenoble CEDEX n° 85
F-38 Grenoble-Gare (France)

[**] Nitroxides, Part 50. This work was supported by a NATO Fellowship administered by the Deutscher Akademischer Austauschdienst (H.U.S); we thank *H. Lemaire* and *J. Ronzaud* for stimulating discussions.—Part 49: *R. Ramasseul* and *A. Rassat*, Tetrahedron Lett. *1971*, 4623.

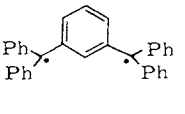
Thus increasing interest attaches to bisnitroxides as spin probes for investigations of isotropic and anisotropic liquids (liquid crystals) and for clarification of the structure and mode of action of biological systems (membranes, enzymes)[3a, 5, 6]. For such purposes stability and as rigid a conformation as possible are particularly important.



(1)



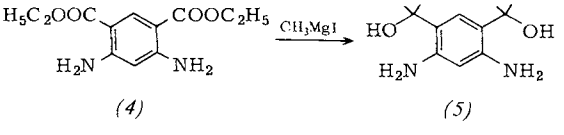
(2)



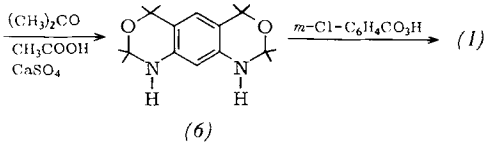
(3)

The bisnitroxide *(1)* described below contains two nitroxide groups in *meta*-position to one another and is expected to exist as a triplet in the ground state, as is the case in the related diradicals *(2)* and *(3)*[2, 7]. Like *(2)*, it cannot form a quinonoid diamagnetic bisnitrone, in contrast to analogous *ortho*- and *para*-compounds[2, 8]. In comparison with *(2)*, which is only moderately stable, *(1)* has the advantage that the reactive *para*-positions to the radical centers are shielded by tertiary alkyl groups[2, 9]. In contrast to compounds *(2)* and *(3)*, the conformational mobility of *(1)* is only slight since the nitroxide groups are kept in one plane by the condensed benzobisoxazine system.

The synthesis of *(1)* starts from diethyl 4,6-diaminoisophthalate *(4)* which, in analogy to work by *Bogert et al.*[10], is obtained in four steps from 4,6-dinitro-*m*-xylene.



(4) *(5)*



(6)

Reaction of *(4)* with methylmagnesium iodide gives a 40% yield of the diamino dialcohol *(5)* (m.p. 150—152 °C), which is only moderately stable because of its ready elimination of H_2O. *(5)* reacts with acetone as *o*-aminobenzyl alcohol does with ketones[11], yielding the diamine *(6)* by double ring closure. This product was purified (m.p. 144—145 °C, yield 40%) by chromatography. Spectroscopic data for *(5)* and *(6)* are in agreement with expectation.

On oxidation by an excess of *m*-chloroperbenzoic acid in ether, *(6)* affords a *ca.* 10% yield of 1,2,8,9-tetrahydro-2,2,4,4,6,6,8,8-octamethyl-4*H*,6*H*-benzo[1,2-*d*;5,4-*d'*]bis-(1,3-oxazine)-1,9-dioxyl *(1)*, which can be isolated by thin-layer chromatography and forms red needles, dec. 159.5—161 °C. *(1)* is stable for several months in the crystalline state but decomposes slowly in solution.

ESR spectra of *(1)* in dilute solution usually show a single broad band, which indicates the presence of a diradical with large zero-field splitting[2, 5]. In solutions of low

viscosity the ESR spectrum of *(1)* shows a poorly resolved hyperfine structure (six lines), which we ascribe to a diradical whose exchange energy J is large compared with the N coupling constant a_N[12] ($J \gg a_N$; $a_N/2 = 5.5 \pm 1$ G); in addition there is the interaction energy of the electrons with the *ortho*-proton ($a_{H^o} = 3.5 \pm 1$ G); cf. 1,2-dihydro-2,2-dimethyl-4*H*-benz[*d*]-[1,3]-oxazine[13]: $a_N = 10.8$, $a_{H^{o,p}} = 3.1$, $a_{H^m} = 0.95$ G.

In ethanol glass, *(1)* shows the characteristic spectrum of a non-cylindrically symmetrical triplet. The half-field resonance shows the ($\Delta m = 2$) transition. In the ($\Delta m = 1$) spectrum (Fig. 1) there are three pairs of bands from whose

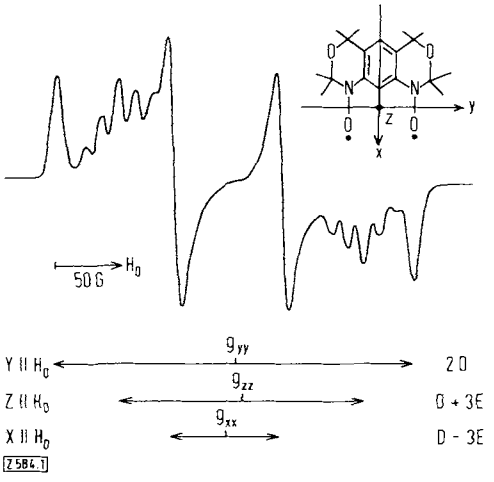


Fig. 1. ESR spectrum of *(1)* in ethanol glass at −130 °C (in definition of the axes the molecular skeleton is assumed to be planar to a first approximation).

separations the zero-field parameters of the dipolar electron-electron interaction can be obtained[1–5]: $D = 140$ G and $E = 18$ G. From the value of D it can be concluded that for the triplet *(1)* the distance between the radical centers in the point-dipole approximation amounts to about 5.8 Å; Dreiding models give the following N—N and O—O separations: double half-chair form, 4.9—5.1 Å; double half-boat form, 5.0—5.8 Å.

That the midpoints of the pairs of bands do not coincide arises from the anisotropic g factor; in agreement with results for mononitroxides[14, 15] we find for the diagonal elements: $g_{xx} > g_{yy} > g_{zz}$ (Fig. 1).

Hyperfine structure due to aniosotropic coupling with the N nuclei can be recognized only for the z components: five equidistant bands with intensity relations 1:2:3:2:1. This corresponds to the spectrum of a diradical with $J \gg D$[16] and $A_{zz}/2 = 12$ G. That the hyperfine structure of the other pairs of bands is not resolved agrees with the fact that the xx and yy diagonal elements of a coupling tensor (assumed to be cylindrically symmetrical) are expected to have appreciably lower values than those observed for the zz element[15, 16].

$$A_{xx} = A_{yy} = \frac{3a_N - A_{zz}}{2} = \frac{33 - 24}{2} = 4.5 \text{ G}$$

Studies of biological systems by means of *(1)* as spin label are in progress.

Received: November 8, 1971 [Z 584 IE]
German version: Angew. Chem. *84*, 353 (1972)

[1] *A. Rassat*, Int. Symp. Conformational Analysis, Brussels 1969; Pure Appl. Chem. *25*, 623 (1971).

[2] *A. Calder, A. R. Forrester, P. G. James*, and *G. R. Luckhurst*, J. Amer. Chem. Soc. *91*, 3724 (1969).

[3] a) *J. F. W. Keana* and *R. J. Dinerstein*, J. Amer. Chem. Soc. *93*, 2808 (1971); b) *J. Michon* and *A. Rassat*: French Pat. 7115999 (May 4, 1971).

[4] *A. R. Forrester* and *R. Ramasseul*, J. Chem. Soc. *B 1971*, 1645.

[5] *R. M. Dupeyre, G. Gagnaire, J. Michon, P. Michon, C. Morat, A. Rassat*, and *J. Ronzaud*, unpublished.

[6] *J. P. C. Smith* in *J. R. Bolton, D. Borg*, and *H. Schwarz*: Biological Applications of Electron Spin Resonance Spectroscopy. Interscience-Wiley, New York 1971 and literature cited therein.

[7] *G. Kothe, K. H. Denkel*, and *W. Sümmermann*, Angew. Chem. *82*, 935 (1970); Angew. Chem. internat. Edit. *9*, 906 (1970).

[8] *A. R. Forrester, R. H. Thomson*, and *G. R. Luckhurst*, J. Chem. Soc. *B 1968*, 1311.

[9] *A. Calder* and *A. R. Forrester*, J. Chem. Soc. *C 1969*, 1459.

[10] *M. T. Bogert* and *A. H. Kropff*, J. Amer. Chem. Soc. *31*, 841 (1909).

[11] *F. W. Holly* and *A. C. Cope*, J. Amer. Chem. Soc. *66*, 1875 (1944).

[12] *R. Brière, R. M. Dupeyre, H. Lemaire, C. Morat, A. Rassat*, and *P. Rey*, Bull. Soc. Chim. Fr. *1965*, 3290.

[13] *E. G. Rozantsev*: Free Nitroxyl Radicals. Plenum Press, New York—London 1970, p. 139.

[14] *O. H. Griffith, D. W. Cornell*, and *H. M. McConnell*, J. Chem. Phys. *43*, 2909 (1965).

[15] *H. Lemaire*. Thèse, Grenoble 1967; Rapport C.E.A. n° R 3119.

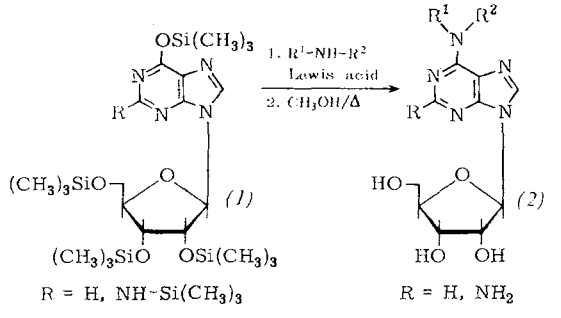
[16] *J. Ronzaud*, unpublished work; see also *K. Itoh, H. Hayashi*, and *S. Nagakura*, Mol. Phys. *17*, 561 (1969).

Simple New Synthesis of N^6-Substituted Adenosines and 2-Aminoadenosines[**]

By *Helmut Vorbrüggen*[*]

Since their isolation from tRNA[1] the N^6-substituted adenosines have become increasingly important as cytokinins[2] and experimental drugs[3].

Up to now, inosine and guanosine were converted in several steps into the free or protected 6-chloro, 6-bromo or 6-alkylthiopurine nucleosides[4], which gave with amines the N^6-substituted adenosines and 2-aminoadenosines respectively. To simplify this reaction sequence in analogy to our new cytidine synthesis[5], we converted the nucleosides into their persilylated derivatives *(1)* in order to protect the alcoholic hydroxy groups and activate the 6-position of the purine moiety. But even on heating with amines for days up to 180 °C the persilylated derivatives *(1)* gave only traces of the N^6-substituted adenosines or 2-amino-adenosines *(2)*.

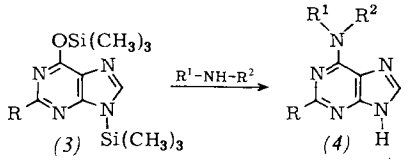


[*] Dr. H. Vorbrüggen
Forschungslaboratorien der Schering A.G.
1 Berlin 65, Müllerstrasse 170—172 (Germany)

[**] Synthesis of Nucleosides, Part 6.—Part 5: [5].

As a typical addition-elimination reaction to the imino-trimethylsilyl ether partial structure[6] of the purine moiety the reaction of *(1)* with amines should be accelerated by attack of a proton or a Lewis acid on the basic N^1-nitrogen. We therefore treated *(1)* with amines in the presence of 0.1—0.2 equivalents of amine salts or Lewis acids and obtained in this "one-step reaction" the N^6-substituted adenosines and 2-aminoadenosines *(2)*, often in very good yields. Most effective were stannic chloride, mercuric chloride and mercuric acetate, although the mercuric salts led to considerable oxidation of the amines, which were used in a threefold molar excess and served as solvents.

This reaction can be applied to the corresponding persilylated purines *(3)*[7], which on treatment with amines in the presence of $HgCl_2$ afford the corresponding N^6-substituted purines *(4)* in good yields.



(3) R = H, NH-Si(CH$_3$)$_3$ *(4)* R = H, NH$_2$

A similar activation by Lewis acids, especially by mercuric chloride, was recently described by *E. P. Gracheva et al.*[8] in the reaction of 6-methylthiopurines with amines.

Several examples of this reaction are listed in the following table.

Table. Synthesis of compounds *(2)* and *(4)*.

	(1), R	R^1—NH—R^2	Catalyst	*T* (°C)	*t* (h)	*(2)*, Yield (%)	*(2)*, M.p. (°C)
a	H	homoveratrylamine	$HgCl_2$	145	20	68	122
b	H	β-phenylethylamine	$SnCl_4$	145	22	70	166–167 [9]
c	H	β-phenylethylamine	$(NH_4)_2SO_4$	145	21	50	166–167 [9]
d	H	β-phenylethylamine	BF_3-ether	145	20	41	166–167 [9]
e	H	β-phenylethylamine	$Hg(OAc)_2$	145	22	90	166–167 [9]
f	H	pyrrolidine	$HgCl_2$	120	72	54	142–144
g	NH_2 [a]	pyrrolidine	$SnCl_4$	120	22	41	208–210
h	NH_2 [a]	*p*-anisidine	$HgCl_2$	145	96	35	225–232
	(3)						*(4)*
a	H	β-phenylethylamine	$HgCl_2$	140	60	62	241–244
b	H	pyrrolidine	$HgCl_2$	120	24	83	297–300
c	NH_2 [a]	pyrrolidine	$HgCl_2$	120	26	50	263–266

[a] Is present in *(1)* and *(3)* in the silylated form as $(CH_3)_3$ SiNH-group.

N^6-(β-Phenethyl)adenosine[9] *(Example (2e))*

Inosine (5.36 g, 20 mmol) was dissolved by 16 hours' refluxing at 155 °C (bath temperature) in 100 ml hexamethyldisilazane and 0.5 ml trimethylchlorosilane. The reagents were then removed under reduced pressure and with exclusion of moisture and the residue stirred with 7.6 ml (60 mmol) β-phenethylamine and 0.638 g (2 mmol) mercuric acetate for 22 h at 145 °C under nitrogen. The dark solution was evaporated in vacuum and the residue thus obtained was refluxed for 3 h in 250 ml methanol, decolorized with charcoal, and filtered. On cooling 6.67 g (90%) of N^6-(β-phenethyl)adenosine was obtained in two crops, m.p. 166—167 °C.

Received: December 27, 1971 [Z 581a IE]
German version: Angew. Chem. *84*, 347 (1972)

[1] *K. Biemann et al.*, Angew. Chem. *78*, 600 (1966); Angew. Chem. internat. Edit. *5*, 590 (1966); R. H. Hall, Progr. Nucl. Acid Mol. Biol. *10*, 57 (1970).

[2] *F. Skoog* and *D. J. Armstrong*, Annu. Rev. Plant Physiol. *21*, 359 (1970).

[3] *K. Dietmann, H. Birkenheier*, and *W. Schaumann*, Arzneim.-Forsch. *20*, 1749 (1970).

[4] *J. J. Fox, I. Wempen, A. Hampton*, and *I. L. Doerr*, J. Amer. Chem. Soc. *80*, 1669 (1958); *J. F. Gerster, J. W. Jones*, and *R. K. Robins*, J. Org. Chem. *28*, 945 (1963).

[5] *H. Vorbrüggen* and *U. Niedballa*, Angew. Chem. *83*, 729 (1971); Angew. Chem. internat. Edit. *10*, 657 (1971).

[6] *C. K. Banks*, J. Amer. Chem. Soc. *66*, 1127 (1944); *G. Illuminati*, Advan. Heterocycl. Chem. *3*, 285 (1964); *R. Roger* and *D. G. Nelson*, Chem. Rev. *61*, 193 (1961).

[7] *T. Nishimura* and *I. Iwai*, Chem. Pharm. Bull. *12*, 352 (1964).

[8] *E. P. Gracheva et al.*, Izvest. Akad. Nauk SSSR, Ser. Khim. *1970*, 420.

[9] *M. Thiel, K. Stach, K. Dietmann, W. Kampe*, and *W. Schaumann*, DOS 1670077 (1970), Boehringer Mannheim GmbH.

Simple Amination of Aromatic Hydroxy-Nitrogen Heterocycles

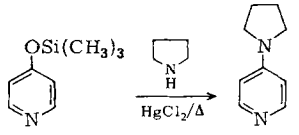
By *Helmut Vorbrüggen*[*]

Aromatic hydroxy-nitrogen heterocycles are usually aminated *via* their chloro derivatives[1], which are obtained by treatment with phosphorus oxychloride or phosphorus pentachloride. In some cases, *e.g.* with 4-hydroxyquinoline[2], an amination with higher boiling amines can be achieved directly by acid catalyzed dehydration. However, the reaction of hydroxy-nitrogen heterocycles with tetrakis-(dimethylamino)titanium[3] or with amines and equimolar amounts of titanium tetrachloride[4] gives only low yields of the aromatic amino derivatives.

We have found that our method for the amination[5] of purines and purine nucleosides can be applied to the mono- and poly(trimethylsilyl) ethers[6] of aromatic

[*] Dr. H. Vorbrüggen
Forschungslaboratorien der Schering A.G.
1 Berlin 65, Müllerstrasse 170—172 (Germany).

hydroxy-nitrogen heterocycles, which are easily accessible by reaction with hexamethyldisilazane/trimethylchlorosilane. The silyl derivatives can be reacted with ammonia or primary or secondary amines in the presence of 0.1—0.2 equivalents of Lewis acids at 145 °C to give (generally in good yields) the amino derivatives of the nitrogen heterocycles. The amine was used in threefold molar excess and served as solvent. Thus the trimethylsilyl derivative *(1)* of 4-pyridone afforded the 4-pyrrolidinopyridine *(2)*[7] in 67% yield.



(1) *(2)*

Several further examples are listed in the table.

Table. Amino derivatives of hydroxy-nitrogen heterocycles.

Starting heterocycle	Amine	Catalyst	T (°C)	t (h)	Product	Yield (%)	M.p. (°C)
2-hydroxy-quinoline	benzylamine	$HgCl_2$	145	24	2-benzylamino-quinoline [8]	74	98— 99
2-oxindole	pyrrolidine	$SnCl_4$	120	60	2-pyrrolidino-3*H*-indole	36	134—137
uracil	β-phen-ethylamine	$HgCl_2$	145	46	2,4-bis(β-phen-ethylamino)pyri-midine	57	—
2-thio-6-azauracil	homovera-trylamine	$SnCl_4$	145	48	3,5-bis(3′,4′-dimethoxy-β-phenethyl)-1,2,4-triazine	55	136—137
cyanuric acid	pyrrolidine	$HgCl_2$	120	48	2,4,6-tris-pyrrolidino-1,3,5-triazine [9] plus	10	184—186
					2,4-dipyrrolidino-6-hydroxy-1,3,5-triazine	52	313—315

4-Pyrrolidinopyridine[7]

4-Pyridone (9.51 g, 0.1 mol) (distilled in high-vacuum) was refluxed for 5 h in hexamethyldisilazane (125 ml) and trimethylchlorosilane (0.5 ml) at 155 °C (oil-bath temperature) and the excess of reagents subsequently removed at 150 °C. The residue was stirred in 25 ml (0.3 mol) pyrrolidine and 2.715 g (0.01 mol) mercuric chloride for 48 h at 120 °C (bath temperature) under nitrogen and subsequently refluxed for 3 h with 200 ml methanol. After removal of the solvents in vacuum, the dark residue was extracted four times with 150 ml boiling pentane. The yellowish extracts gave on evaporation 9.86 g (67%) crystalline 4-pyrrolidinopyridine, m.p. 57 °C after recrystallization from pentane.

Received: December 27, 1971 [Z 581b IE]
German version: Angew. Chem. 84, 348 (1972)

[1] Houben-Weyl: Methoden der organischen Chemie. Thieme Verlag, Stuttgart 1957, Vol. XI/1, p. 68.

[2] *W. S. Johnson* and *B. G. Buell*, J. Amer. Chem. Soc. *74*, 4517 (1952).

[3] *J. D. Wilson*, *J. S. Wager*, and *H. Weingarten*, J. Org. Chem. *36*, 1613 (1971).

[4] *R. I. Fryer*, *J. V. Earley*, *G. F. Field*, *W. Zally*, and *L. H. Sternbach*, J. Org. Chem. *34*, 1143 (1969).

[5] *H. Vorbrüggen*, Angew. Chem. *84*, 347 (1972); Angew. Chem. internat. Edit. *11*, 304 (1972).

[6] *A. E. Pierce*: Silylation of Organic Compounds. Pierce Chem. Co., Rockford, Ill. 1968.

[7] *W. Steglich* and *G. Höfle*, Tetrahedron Lett. *1970*, 4727.

[8] *H. H. Fox* and *W. Wenner*, J. Org. Chem. *16*, 225 (1951).

[9] *W. K. Detweiler* and *E. D. Amstutz*, J. Amer. Chem. Soc. *74*, 1483 (1952).

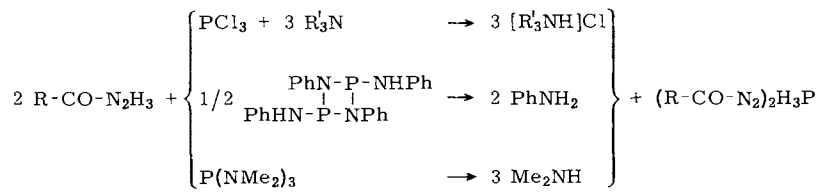
Spirophosphoranes from Acylhydrazines and Phosphorus(III) Compounds[1]

By *Alfred Schmidpeter* and *Jörg Luber*[*]

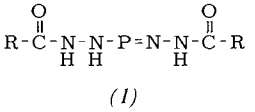
The reaction of carboxylic acid hydrazides with P^{III} compounds has been reported in two patents[2, 3]: from PCl_3 or PBr_3 and a hydrogen halide-acceptor, or from diaminodiazadiphosphetidines, products are formed in which one phosphorus atom replaces three hydrogen atoms of two acylhydrazine molecules. We have found that such compounds are obtained particularly simply by warming the hydrazide with tris(dimethylamino)-phosphane (under the same conditions, however, not by means of trimethyl phosphite).

The products were previously assigned structure *(1)* or *(2)*[2, 3]. The formulation *(1)* with two-fold coordinated phosphorus can be excluded straightaway: all phosphorus(III) imide amides have so far proved to be dimeric, with the phosphorus attaining its normal three-fold coordination by formation of a diazadiphosphetidine ring. However, the compounds now in question are monomeric. If the coordination deficiency of the phosphorus in *(1)* is filled by the oxygen of an acylhydrazine group and, to equalize charges, a proton is moved to the neighboring nitrogen, then the other formulation *(2)* is

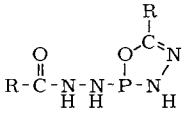
[*] Priv.-Doz. Dr. A. Schmidpeter and Dipl.-Chem. J. Luber
Institut für Anorganische Chemie der Universität
8 München 2, Meisterstrasse 1 (Germany)



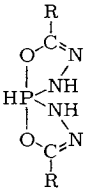
obtained. But this also cannot be correct since the two R groups are then in different environments, whereas the ^{1}H-NMR spectrum (for, *e.g.*, R = CH_3) shows them to be equivalent.



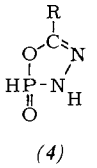
(1)



(2)



(3)



(4)

A symmetrical, spirocyclic structure *(3)* results if the oxygen of the second acylhydrazine group is also coordinated to the phosphorus and, to balance the charges resulting, a proton bonded to nitrogen is transferred to the phosphorus. This can be proved, not only by the equivalence of the R groups, but also by the equivalence of the NH-protons which is recognizable by a triplet splitting of the ^{31}P-NMR signal, by the PH stretching vibration, by the $^1J_{PH}$ coupling, and by the large corresponding coupling constant that is characteristic of pentacoordinated phosphorus[4] (reference-value for a phosphorus atom surrounded by O_2N_2: 765 Hz[5]) and the high ^{31}P shielding (cf. Table).

Table. Characteristic IR and NMR data for *(3)* (shifts to higher field from TMS or H_3PO_4 positive; signal multiplicity in parentheses).

R	νPH	νCN	$\delta^1H \times 10^6$			$\delta^{31}P \times 10^6$	J_{PH}	J_{PNH}
	(cm^{-1})		PH	NH	CH_3		(Hz)	
CH_3	2460	1650	−8.60 (2)	−7.40 (2)	−1.86	+51.9 (2 × 3)	810	35
C_6H_5	2460	1630	−8.61 (2)	−8.73 (2)		+55.5 (2 × 3)	828	36
4-C_5H_4N	2450	1625						

A tautomeric equilibrium between *(2)* and *(3)* does not appear impossible. However, a contribution from the phosphane form *(2)* cannot be detected spectroscopically or chemically; the reactions characteristic of other phosphanes, *e.g.* with boiling CCl_4 or with S_8 in boiling benzene, do not occur; compounds *(3)* are at least comparable in stability under such conditions with the PH-spirophosphoranes[6, 7] derived from unsubstituted α-amino alcohols. On treatment with water in dimethylformamide *(3)* is hydrolyzed to an isolable intermediate that is probably *(4)* (R = CH_3: $\delta^{31}P = +7.8 \cdot 10^{-6}$; J_{PH} = 653 Hz); complete hydrolysis takes place on treatment with boiling water.

2,2'-Spirobi(1,3,4,2-oxadiaza-P^V-phospholines):

A solution of $P(NMe_2)_3$ (0.1 mol) in benzene (50 ml) is heated at the b.p. for some hours with the acylhydrazine (0.05 mol). Compound *(3)* crystallizes in about 90% yield when the solution is cooled. When R = 4-C_5H_4N the product is barely soluble at the boiling point.

Received: November 5, 1971 [Z 583 IE]
German version: Angew. Chem. *84*, 349 (1972)

[1] Four- and five-membered phosphorus heterocycles, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft.—Parts 1, 2, and 3: *J. Ebeling* and *A. Schmidpeter*, Angew. Chem. *81*, 707 (1969); Angew. Chem. internat. Edit. *8*, 674 (1969); *A. Schmidpeter, H. Rossknecht*, and *K. Schumann*, Z. Naturforsch. *25b*, 1182 (1970); *A. Schmidpeter* and *W. Zeiss*, Angew. Chem. *83*, 397 (1971); Angew. Chem. internat. Edit. *10*, 396 (1971).

[2] *H. Schmidt, F. Meyer*, and *G. Domagk*, German Pat. 961346 (1957).

[3] *H. Weidinger* and *H. Eilingsfeld*, German Pat. 1144274 (1963).

[4] *M. Sanchez, L. Beslier, J. Roussel*, and *R. Wolf*, Bull. Soc. Chim. Fr. *1969*, 3053.

[5] *A. Schmidpeter* and *K. Schumann*, EUCHEM-Conf. "Organic Chemistry of Phosphorus", Elmau 1971.

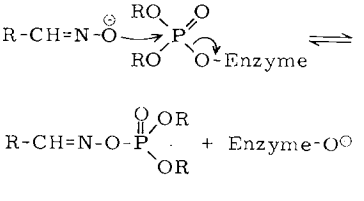
[6] *T. Reetz* and *J. F. Powers*, US-Pat. 3172903; Chem. Abstr. *63*, 2981 (1965).

[7] *M. Sanchez, I. F. Brazier, D. Houalla*, and *R. Wolf*, Bull. Soc. Chim. Fr. *1967*, 3920.

Reactivation of Phosphorylated Acetylcholinesterase—Dependence upon Activator Acidity

By *Ilse Hagedorn, Irmo Stark*, and *Hans Peter Lorenz*[*]

Acetylcholinesterase (AChE) inhibited by phosphorylation can be reactivated by 2- or 4-(hydroxyiminomethyl)-pyridinium halides such as *(13)*[1] or *(9)*[2].

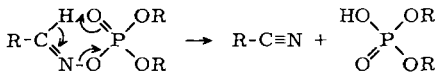


(A)

The first step in the enzyme reactivation is formulated as an equilibrium (A)[3].

The second step, in which the equilibrium (A) is shifted in favor of the intact enzyme, is a cyclic α, β-*cis*-elimination (B)[4].

[*] Prof. Dr. I. Hagedorn, Dr. I. Stark, and Dipl.-Chem. H. P. Lorenz
Chemisches Laboratorium der Universität
78 Freiburg, Albertstrasse 21 (Germany)

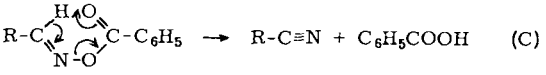


(B)

To determine the relations between oxime acidity[5] and enzyme reactivation[6] we have prepared 60 (hydroxyiminomethyl)pyridinium halides, a representative selection of which is shown in Table 1. The acidity of the compounds was determined by potentiometric titration[7].

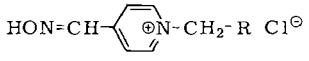
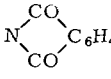
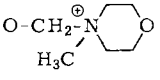
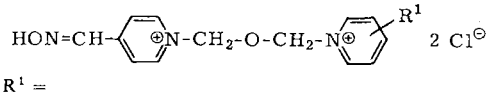
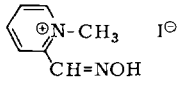
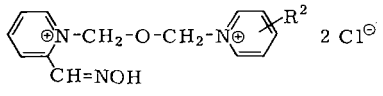
We found that the optimum of AChE reactivation was attained with oximes whose pK_a values lay at 7.8. Structurally similar substances with $pK_a < 7.5$ and > 8.0 cannot be used (Table 1).

The ineffectiveness of the more acidic oximes *(14)* to *(18)* rests on the fact that the nucleophilicity of their anions is too slight for the primary step (A), as shown by UV spectroscopy: they do not react at pH = 7.8 even during 90 min with triethyl phosphate which was chosen as model for the inhibited enzyme[8]. The reaction between oximate anion and phosphoric acid triesters is in general quite slow, from which it can be assumed that the phosphate group removeable by oximes is attached to the enzyme by an energy-richer, non-ester-like bonding.



(C)

Table 1. Relation between the acidity of (hydroxyiminomethyl)-pyridinium halides and their ability to reactivate phosphorylated acetylcholinesterase [6].

	Compound	pK_a ±0.03	Reactivation (%) at an oxime concentration of (mol/liter)			Ref.
			7.5×10^{-4}	7.5×10^{-5}	7.5×10^{-6}	
						
	R=					
(1)	$O-CH_2-C_6H_{11}$	8.13	0	0	0	[5]
(2)		8.11	0	0	0	[9]
(3)	$O-C_6H_{11}$	8.09	0	0	0	[5]
(4)		8.05	0	0	0	[9]
(5)	$O-CH_2-C_6H_5$	8.01	17	0	0	[5]
(6)		7.89	50	14	0	[8]
						
	R^1 =					
(7)	$3\text{-}CONH_2$	7.83	74	29	0	[10]
(8)	$4\text{-}CONH_2$	7.81	62	40	0	[10]
(9)	4-CH=NOH	7.80	56	49	17	[2, 11]
(10)	$3\text{-}CO-CH_3$	7.79	53	28	0	[10]
(11)	3-CH=NOH	7.78	50	27	0	[10]
(12)	H	7.78	60	50	8	[10]
(13)		7.68	49	14	1	[1]
						
	R^2 =					
(14)	$3\text{-}CONH_2$	7.30	0	0	0	[12]
(15)	$4\text{-}CONH_2$	7.28	0	0	0	[10]
(16)	3-CH=NOH	7.24	20	0	0	[12]
(17)	H	7.20	0	0	0	[12]
(18)	2-CH=NOH	7.09	0	0	0	[12]

The less acidic oximes *(1)* to *(5)* are ineffective because the acidity of their methine-protons is too low to permit reaction (B) to occur sufficiently fast. This effect, which had been observed previously[4], was measured by means of reaction (C).

Table 2. Decomposition constants for benzoylated oximes in aqueous solution at pH 8.1, determined by UV spectroscopy ($\lambda_{max} = 280$ nm).

Benzoate of	*(13)*	*(12)*	*(8)*	*(7)*	*(5)*	*(19)* [a]
$t_{1/2}$ (min)	3	570	700	860	1825	3600
$k \times 10^4$ (min^{-1}) [b]	2310	120	99.0	80	38	19
pK_a value of the oxime group	7.68	7.78	7.81	7.83	8.01	8.34
Reactivation (%) [c]	49	60	62	74	17	0

[a] *(19)* = 4-(Hydroxyiminomethyl)-1-methylpyridinium iodide.
[b] The reaction is pseudo-first order.
[c] At an oxime concentration of 7.5×10^{-4} mol/liter.

Since the rate of the decomposition (C) depends on the kinetic methine acidity the half-reaction time $t_{1/2}$ serves as a measure for this (Table 2).

Rapid enzyme activation occurs only if the nucleophilicity of the oximate anion and acidity of the methine proton have minimum values.

Received: January 31, 1972 [Z 595 IE]
German version: Angew. Chem. *84*, 354 (1972)

[1] *J. B. Wilson* and *S. Ginsburg*, Biochim. Biophys. Acta *18*, 1681 (1955).

[2] *A. Lüttringhaus* and *I. Hagedorn*, Arzneimittel-Forsch. *14*, 1 (1964); *W. D. Erdmann* and *H. Engelhard*, *ibid.* *14*, 5 (1964).

[3] *C. Fest* and *K.-J. Schmidt* in *R. Wegler*: Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel. Springer-Verlag, Heidelberg 1970, pp. 363 and 411.

[4] *I. Hagedorn*, *W. H. Gündel*, and *K. Schoene*, Arzneimittel-Forsch. *19*, 603 (1969).

[5] *H. P. Lorenz*, Diploma thesis, Universität Freiburg 1970.

[6] Prof. *W. D. Erdmann*, of the Toxicological Institute of the University of Göttingen determined this value as the maximal attainable enzyme activity (%) after addition of the reactivator to AChE completely blocked by diisopropyl fluorophosphate (DFP, 1×10^{-6} mol/liter).

[7] The method of *A. Albert* and *E. P. Serjeant* (Ionization Constants of Acids and Bases. Methuen, London 1962) was modified [8].

[8] *I. Stark*, Dissertation, Universität Freiburg 1971.

[9] *W. Hohler*, Diploma thesis, Universität Freiburg (1969).

[10] *I. Stark*, Diploma thesis, Universität Freiburg (1968).

[11] The pK_a value is derived from $pK_{a1} = 7.54$ and $pK_{a2} = 8.12$. The two oxime groups of the symmetrically structured compound are identical in chemical behavior and the nucleophilicity of their anions correspond to that of a monooxime with $pK_a = 7.80$.

[12] *K. Schoene*, Dissertation, Universität Freiburg 1967.

Cyclodimerization of Methylenecyclopropane on a Ni(0) Catalyst

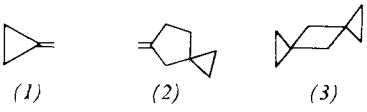
By *Paul Binger*[*]

Methylenecyclopropane *(1)*[1,2], which is now readily available in good yield, is thermally stable up to *ca.* 150 °C, but can be oligomerized by bis(1,5-cyclooctadiene)-nickel $[Ni(COD)_2]$[3] at as low a temperature as −15 °C. Irrespective of whether it is conducted without a solvent or in pentane, benzene, or diethyl ether, the exothermic reaction yields a mixture containing 45% of dimers [65% of *(2)* and 20% of *(3)*], *ca.* 10% of trimers (6 isomers), and about 45% of higher-molecular oligomers with a mean cryoscopic molecular weight of 1100. In these experiments *ca.* 1 mol of pure *(1)* was treated with 1 mg-atom of Ni.

[*] Dr. P. Binger
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

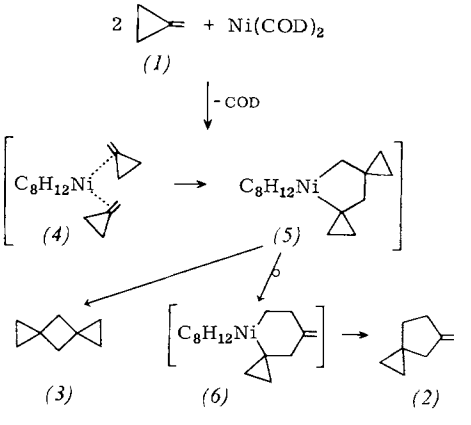
A nickel catalyst freshly prepared in 1,5-cyclooctadiene[4] or in methylenecyclopropane from 2,4-pentanedionato-nickel and ethoxydiethylalane affords an oligomer mixture of the same composition. However, in the presence of a titanium catalyst prepared from 1 mmol of titanium tetrachloride and 10 mmol of chlorodiethylalane[4] higher-molecular oligomers $(C_4H_6)_n$ are formed almost exclusively (>95%).

The dimers separated in pure form by preparative gas chromatography were previously unknown. They could be identified by their spectra as 5-methylenespiro[2.4]heptane *(2)* and dispiro[2.1.2.1]octane *(3)*. [*(2)*: mol. wt. (MS)



108. IR (neat): 1658 ($\nu_{C=C}$), 1010 cm^{-1} (δ_Δ). ^{1}H-NMR (100 MHz, neat): $\tau = 5.31$ (2 H/m), 7.68 (2 H/t), 7.89 (2 H/m), 8.55 (2 H/t), and 9.68 ppm (4 H/s). — *(3)*: Mol. wt. (MS) 108. IR (neat): 3090 ($\nu_{CH\Delta}$) 1000 cm^{-1} (δ_Δ). ^{1}H-NMR (100 MHz, neat): $\tau = 7.80$ (4 H/s) and 9.55 (8 H/s)].

Transition-metal catalyzed syntheses of four-membered rings resembling the formation of *(3)* from *(1)* are known for several dienes[5-7] but have hitherto been observed for monoalkenes in only one isolated case[8]. Presumably *(2)* and *(3)* are formed *via* the same unstable organonickel intermediates *(4)* with π-Ni(C=C) bonds



and *(5)* with σ-NiC bonds. The ring of *(1)* should not open immediately on complex formation with the nickel[9] but, as with the cyclopropylmethyl compounds of several main-group elements (Li[10], Mg[11], and B[1]), only during isomerization to the 3-butenyl group [*(5)* → *(6)*].

Methylenecyclopropane is known to form complexes with nickel(0) using its C=C bond without ring opening[12].

Experimental:

$Ni(COD)_2$ (0.25 g) is treated dropwise at −15 °C during 1 h with *(1)* (40 g, 0.74 mol). The dark red solution is stirred for a further 20 h and volatile constituents (23.2 g) are then removed in a vacuum (0.001 torr, max. bath temp. 120 °C). There remains a dark viscous oil (15.7 g).—Fractionation (spinning band column): 18.5 g (46%) of b.p. 58—62 °C/100 torr [GC: 19% of *(3)* and 67% of *(2)*, residue (14%) containing 15 unknown compounds]; 0.35 g of b.p. 70—90 °C/100 torr [GC: 5.9% of *(2)*, 57.3% of 1,5-cyclooctadiene and 17.1% of C_8H_{10} (mol. wt. (MS) 106), residue (19.8%) containing 16 unknown compounds]; and 3.8 g (9.5%) of b.p. 100—118 °C/20 torr [GC/MS: 96% of $C_{12}H_{18}$ (≧6 isomers; mol. wt. 162).—^{1}H-NMR spectrum of C_8H_{10} (60 MHz, benzene): τ = 3.46 (m), 4.00 (s), 4.8—5.18 (m) and 7.62 ppm (s) in the ratio 0.9:1.1:[4]:4; presumably 3-methylene-1-vinyl-1-cyclopentene, calc. 1:1:[2+2]:4.

Received: November 22, 1971 [Z 600 IE]
German version: Angew. Chem. *84*, 352 (1972).

[1] *R. Köster, S. Arora,* and *P. Binger,* Synthesis *1971*, 322.

[2] *R. Köster, S. Arora,* and *P. Binger,* Angew. Chem. *81*, 186 (1969); Angew. Chem. internat. Edit. *8*, 205 (1969).

[3] *B. Bogdanović, M. Kröner,* and *G. Wilke,* Liebigs Ann. Chem. *699*, 1 (1966).

[4] *H. Breil, P. Heimbach, H. Müller,* and *G. Wilke,* Makromol. Chem. *69*, 18 (1963).

[5] *P. Heimbach* and *W. Brenner,* Angew. Chem. *79*, 813 (1967); Angew. Chem. internat. Edit. *6*, 800 (1967).

[6] *G. N. Schrauzer,* Advan. Catal. *18*, 377 (1968).

[7] *F. V. Hoover* and *R. V. Lindsey jr.,* J. Org. Chem. *34*, 3051 (1969).

[8] *F. J. Weigert, R. L. Baird,* and *J. R. Shapley,* J. Amer. Chem. Soc. *92*, 6630 (1970).

[9] *R. Noyori, T. Odagi,* and *H. Takaya,* J. Amer. Chem. Soc. *92*, 5780 (1970).

[10] *P. T. Lansburg* and *V. A. Pattison,* J. Amer. Chem. Soc. *85*, 1886 (1963).

[11] *J. D. Roberts* and *R. H. Mazur,* J. Amer. Chem. Soc. *73*, 2509 (1951).

[12] *M. Englert, P. W. Jolly,* and *G. Wilke,* Angew. Chem. *83*, 84 (1971); Angew. Chem. internat. Edit. *10*, 77 (1971).

cis,trans-Tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane, "*trans*-Trishomobenzene"

By *Martin Engelhard* and *Wolfgang Lüttke*[*]

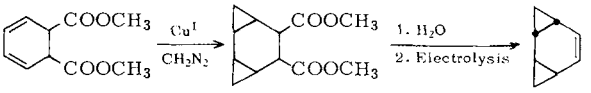
Our investigations of quasiconjugative interactions between three-membered rings have so far been devoted mainly to bicyclopropyl[1,2]. Such effects should be more clearly visible with compounds in which the cyclopropane rings are fixed by cyclic bonding. Particular interest appeared to attach to the system, called occasionally trishomobenzene, that can be constructed formally by adding three methylene groups to a benzene molecule. Two configurations are possible for this system: the completely *cis*-form (C_{3v} symmetry) ("crown") *(1)* and the mirror-plane symmetrical *trans*-form (C_s-symmetry) ("peaked cap") *(2)*.



(1) *(2)*

A bridged *cis*-trishomobenzene was recently obtained by *de Meijere, Kaufmann,* and *Schallner*[3]; heteroanalogous derivatives of *(1)* and *(2)* have been described by *Prinzbach* and *Stusche*[4].

We report here the preparation of the parent hydrocarbon *(2)*. Dimethyl tricyclo[5.1.0.0^{2,4}]octane-5,6-bicarboxylate *(4)* was obtained by cyclopropanation of dimethyl *trans*-1,2-dihydrophthalate *(3)*; hydrolysis of *(4)* and subsequent electrolytic decarboxylation afforded a hydrocarbon previously described by *Roth* and *Peltzer*[5] and identified as *trans*-tricyclo[5.1.0.0^{2,4}]oct-5-ene *(5)* by its IR and NMR spectra.

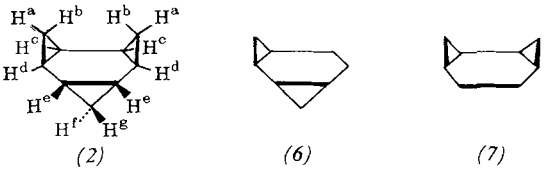


(3) *(4)* *(5)*

The Cu(I)-catalyzed reaction of *(5)* with diazomethane led to a product to which high-resolution mass spectroscopy assigned the molecular mass 120.093772; for *(1)* and *(2)* (*i.e.* for C_9H_{12}) calculation gives 120.093896. The structure and the "peaked cap" configuration with C_s symmetry *(2)* of the product are further proved by the ^{1}H-NMR spectrum: for the completely *cis*-form *(1)* only three types of proton are to be expected, but for *(2)* seven in the proportions $H^a:H^b:H^c:H^d:H^e:H^f:H^g = 2:2:2:2:2:1:1$.

The NMR spectrum (CCl_4, 100 MHz) confirms configuration *(2)*: τ = 10.1 ($2H^b$/q), 9.9 (H^f/q) (width of the quartets each *ca.* 15 Hz), 9.50 and 9.58 ($2H^a + H^g$/m) (width of the multiplets each *ca.* 20 Hz)[7], 8.9—9.4 ppm ($2H^c$, $2H^d + 2H^e$/m)[6].

The assignment of the secondary protons makes use of the known fact that the coupling constants between *trans*-protons on the cyclopropane ring are smaller than those between *cis*-protons[8]. All the assignments were further strengthened by results of analysis of the NMR spectra of *trans*- and *cis*-tricyclo[4.1.0.0^{2,4}]octane [*(6)* and *(7)*] by *Braun*[9].



(2) *(6)* *(7)*

Received: January 21, 1972 [Z 594 IE]
German version: Angew. Chem. *84*, 346 (1972)

[*] Dipl.-Chem. M. Engelhard and Prof. Dr. W. Lüttke
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

[1] *W. Lüttke, A. de Meijere, H. Wolff, H. Ludwig,* and *H. W. Schrötter,* Angew. Chem. *78*, 141 (1966); Angew. Chem. internat. Edit. *5*, 123 (1966).

[2] *O. Bastiansen* and *A. de Meijere,* Acta Chem. Scand. *20*, 516 (1966); cf. *J. Eraker* and *Chr. Rømming, ibid. 21*, 2721 (1967).

[3] *A. de Meijere, D. Kaufmann,* and *O. Schallner,* Angew. Chem. *83*, 404 (1971); Angew. Chem. internat. Edit. *10*, 417 (1971).

[4] *H. Prinzbach* and *D. Stusche,* Angew. Chem. *82*, 836 (1970); Angew. Chem. internat. Edit. *9*, 799 (1970).

[5] *W. R. Roth* and *B. Peltzer,* Liebigs Ann. Chem. *685*, 56 (1965).

[6] A singlet at τ = 8.7 ppm is ascribed to an impurity.

[7] *G. Schrumpf* and *W. Lüttke,* Liebigs Ann. Chem. *730*, 100 (1969).

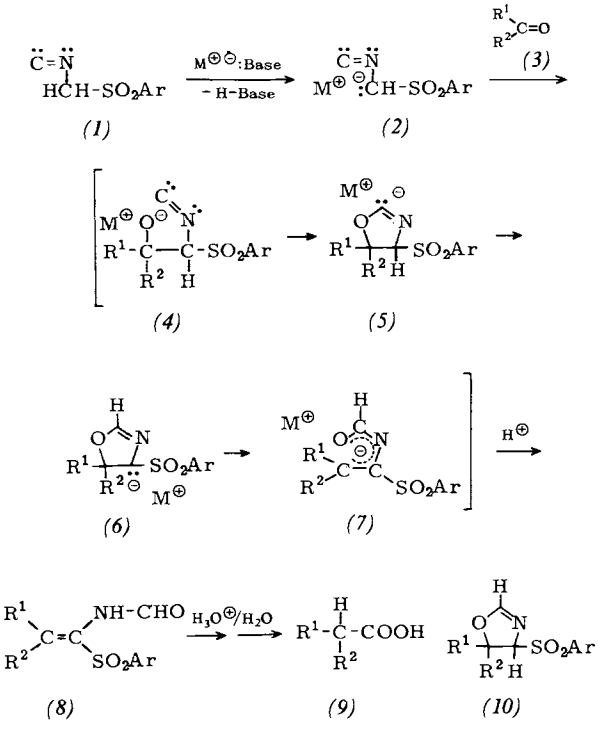
[8] *A. A. Bothner-By,* Advan. Magn. Resonance *1*, 195 (1965).

[9] *S. Braun,* Dissertation, Universität Göttingen 1970.

1-Formylamino-1-arylsulfonyl Alkenes from α-Metalated Isocyanomethyl Aryl Sulfones and Carbonyl Compounds; Conversion of a Carbonyl Compound into the Next Higher Carboxylic Acid[*]

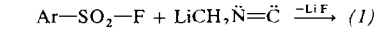
By *Ulrich Schöllkopf* and *Rolf Schröder*[*]

1-Formylamino-1-arylsulfonyl alkenes *(8)* are formed when α-metalated isocyanomethyl aryl sulfones *(2)*, prepared from isocyanomethyl aryl sulfones *(1)* and bases such as potassium *tert*-butoxide in tetrahydrofuran, are allowed to react with ketones and aldehydes *(3)*. The adducts *(4)*, as well as the oxazolines *(5)* and *(6)* metalated in the 2- and 4-positions and the open-chain anions *(7)*, can be looked upon as intermediates of this "formylaminomethylenation"[2] of the carbonyl compound.



If reaction of the isocyanomethyl aryl sulfone *(1)* with the carbonyl compound is carried out in ethanol in the presence of sodium cyanide as basic catalyst[4], the 4-arylsulfonyl-2-oxazolines *(10)*, which are formed by protonation of the intermediate *(5)*, can be isolated. On treatment with potassium *tert*-butoxide (in tetrahydrofuran at −10 °C) the azolines *(10)* are converted to the alkenes *(8)*. This route to *(8)* is sometimes superior to the direct route. For instance *(8e)* is obtained *via (10)* in 58% overall yield.

We obtained the isocyanomethyl aryl sulfone *(1)* from isocyanomethyllithium and arylsulfonyl fluoride.



Isocyanomethyl p-tolyl sulfone (1), Ar = p-tolyl

Butyllithium (0.08 mol; *ca.* 40 ml of a *ca.* 2.0 N solution in pentane) is added dropwise to a stirred solution of methyl isocyanide (3.28 g, 0.08 mol) in THF (100 ml) at −70 °C such that the temperature never rises above −60 °C. The solution of tosyl fluoride (6.96 g, 0.04 mol) in THF (30 ml) is added dropwise within *ca.* 3 min at −70 °C to the suspension of the isocyanomethyllithium while keeping the temperature below −65 °C. The resultant mixture is stirred for a further 10 min at −60 to −50 °C before addition of glacial acetic acid (2.4 g, 0.04 mol). The mixture is then allowed to warm and the solvent is evaporated off at 25 °C under vacuum. The residue is treated with 50 ml water and the resulting aqueous solution washed with two 75-ml portions of methylene chloride. The organic phase is dried over magnesium sulfate and worked up in the usual way.

Compound *(1)*, Ar = *p*-tolyl, [m. p. 110 °C after recrystallization from benzene/cyclohexane (1:3)] is obtained in 66% yield (based on tosyl fluoride), *i.e.* 5.26 g.

1-Formylamino-1-tosyl-2-methyl-1-propene (8f)

A solution of isocyanomethyl *p*-tolyl sulfone *(1)*, Ar = *p*-tolyl (1.95 g, 0.01 mol) in THF (10 ml) is added dropwise in *ca.* 3 min at 7—10 °C to a stirred suspension of potassium *tert*-butoxide (1.12 g, 0.01 mol) in THF (20 ml). After cooling to −10 °C the solution of acetone (0.58 g, 0.01 mol) in THF (10 ml) is added and the resultant mixture stirred for a further 5 min. Glacial acetic acid (0.6 g, 0.01 mol) is then added and the solvent removed by evaporation at 25 °C under vacuum. The residue is treated with water (25 ml) and the aqueous solution extracted with methylene chloride (50 ml). The organic phase is dried over magnesium sulfate and worked up in the usual way. The yield of *(8f)* (m. p. 100 °C after crystallization from ethanol) is 2.1 g (83%).

	R^1	R^2	Ar	*(8)* [a], Yield (%)	*(8)*, m. p. (°C)	*(9)* [c], Yield (%)
(a)	C_6H_5	H	C_6H_5	72	152 [b]	65
(b)	C_6H_5	CH_3	p-CH_3—C_6H_4	42	145 [b]	
(c)	α-Naphthyl	CH_3	p-CH_3—C_6H_4	50	186 [b]	
(d)	$C(CH_3)_3$	H	p-CH_3—C_6H_4	63	120 [b]	60
(e)	$CH(CH_3)_2$	H	p-CH_3—C_6H_4	10	83 [b]	
(f)	CH_3	CH_3	p-CH_3—C_6H_4	83	100	62
(g)	—$(CH_2)_5$—		p-CH_3—C_6H_4	61	132	55
(h)	C_6H_5—CH=CH	H	p-CH_3—C_6H_4	73	163 [b]	67

[a] Correct analysis for all products. Characteristic IR bands: 1630 cm^{-1} ($\nu_{C=C}$), 1680, 1670 cm^{-1} (ν_{CO}), 1310, 1140 cm^{-1} (ν_{SO_2}).
[b] Mixture of isomers; clear melt at this temperature.
[c] Based on *(1)*.

The synthesis deserves attention since the compounds *(8)* are converted into carboxylic acids *(9)* on heating with, *e.g.*, dilute hydrochloric acid for *ca.* one to three hours[3]; *i.e.* the reaction can be utilized for the preparation of the next higher carboxylic acid *(9)* from a ketone *(3)*, a conversion for which no simple method has previously been reported.

[*] Prof. Dr. U. Schöllkopf and Dipl.-Chem. R. Schröder
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

Cyclohexanecarboxylic acid (9g) from cyclohexanone

Cyclohexanone (0.98 g, 0.01 mol) is first treated in the manner described above. The crude *(8g)* thus obtained is heated gently under reflux with 2 N hydrochloric acid (20 ml) for 10 h. The mixture is then cooled, 2 N sodium hydroxide (30 ml) is added, and the whole washed with ether. (The ethereal phase contains *p*-tolyl *p*-toluenethiosulfonate—formed from *p*-toluenesulfinic acid[5].) The aqueous phase is adjusted to pH ≈ 1 by treatment with hydrochloric acid, extracted with ether, and the ether extract dried over magnesium sulfate. The yield of *(9g)* (b. p. 232 °C) obtained is 0.7 g (55%).—Ten hours' heating with dilute hydrochloric acid promotes conversion of *p*-toluenesulfinic acid into the thiosulfonate[5]. In the case of acid-sensitive carboxylic acids *e. g.* α-styrylacetic acid *(9h)*, hydrolysis is interrupted after formation of the acid (*ca.* 1 h) and the *p*-toluenesulfinic acid separated off by treatment with CCl_4 in which it is insoluble.

Received: November 18, 1971 [Z 570 IE]
German version: Angew. Chem. *84*, 289 (1972)

[1] Syntheses with α-metalated isocyanides, Part 11. – Part 10: *U. Schöllkopf* and *R. Schröder*, Angew. Chem. *83*, 358 (1971); Angew. Chem. internat. Edit. *10*, 333 (1971).

[2] By "formylaminomethylenation" is meant the conversion of type *(2)* → *(8)* of a carbonyl compound in formylamino-substituted alkenes. For the formylaminoalkoxycarbonylmethylenation of compounds. C.f. *U. Schöllkopf, F. Gerhart*, and *R. Schröder*, Angew. Chem. *81*, 701 (1969); Angew. Chem. internat. Edit. *8*, 672 (1969).

[3] Preliminary experiments have shown that hydrolysis can also be achieved by heating with 2 N caustic soda.

[4] As in the synthesis of 4-ethoxycarbonyl-2-oxazoline from isocyanoacetate and carbonyl compounds. Cf. *D. Hoppe* and *U. Schöllkopf*, Angew. Chem. *82*, 290 (1970); Angew. Chem. internat. Edit. *9*, 300 (1970).

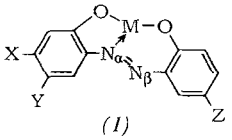
[5] Cf. *Houben-Weyl-Müller*: Methoden der Organischen Chemie, Vol. IX. Thieme, Stuttgart 1955, p. 331.

Structurally Isomeric Metal Chelates of Unsymmetrical *o,o'*-Dihydroxy Azo Compounds

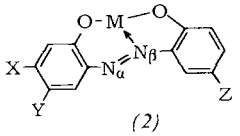
By *Helmut Pfitzner*[*]

Metal complexes from *o,o'*-dihydroxy azo dyes were first prepared sixty years ago[1]; since then this class of compounds has been intensively investigated and also tested for its industrial applicability[2].

There have been many discussions as to which of the two nitrogen atoms of the azo bridge should be regarded as ligand to the metal bound in the complex; for unsymmetrical *o,o'*-dihydroxy azo compounds two structurally isomeric metal chelates *(1)* and *(2)* are conceivable, which can be designated as N_α and N_β isomers.



(1)



(2)

(a), M = Cu
X = Cl, SO_2NH_2
Y = H, Cl, CH_3, OCH_3
Z = Cl, Br, CH_3, OCH_3, C_6H_5, cyclohexyl

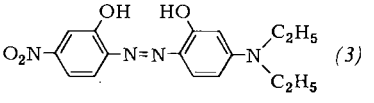
(b), M = Ni
X = H, Cl, OCH_3, NO_2, SO_2NH_2
Y = H, Cl, CH_3, OCH_3, NO_2
Z = Cl, Br, CH_3, OCH_3, $NHCOCH_3$, C_6H_5, cyclohexyl

[*] Dr. H. Pfitzner
Badische Anilin- und Soda-Fabrik, Farbenlaboratorium
67 Ludwigshafen (Germany)

We have studied this question for the 1:1 copper(II) and 1:1 nickel(II) complexes[3] of unsymmetrically substituted *o,o'*-dihydroxyazobenzene.

Chromatographic investigation showed that in many cases the presence of two compounds of the same composition could be proved, which are formed in about 1:1 proportions. The chromatographic separation succeeded with pyridine/benzene (*ca.* 1:9) on silica gel. The colors appeared visually the same; only for the nitro compounds were differences recognizable.

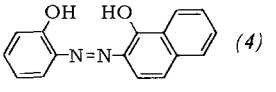
Particularly good separations were given by the metal complexes *(1a)* *(2a)* and *(1b)* *(2b)*. It was striking that the nickel chelates differed more than the corresponding copper complexes in R_F values.



(3)

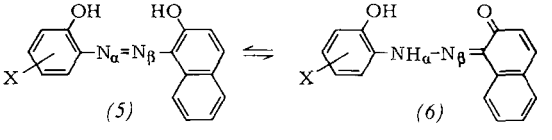
Strong polarization of the molecule, as in *(3)*, led to formation of only one complex.

As expected, no isomers were detected for the symmetrical chelates of *o,o'*-dihydroxyazobenzene (X = H and Y = Z); similarly none were found for the copper and nickel complexes of the symmetrical *o,o'*-dihydroxyazonaphthalenes. However, the complexes from the unsymmetrical parent compound *(4)* and its derivatives could be separated into



(4)

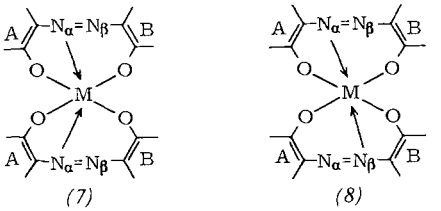
the N_α and the N_β isomer. *o,o'*-Dihydroxy azo dyes of types *(5)* and *(6)*, which contain β-naphthol as coupling component, yield always only one type of complex (N_α) which



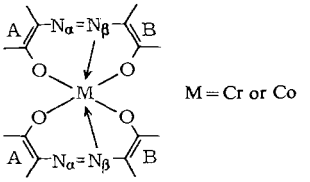
(5) *(6)*

is derived from the quinone hydrazone form of this class of compounds[4]; the same is the case for pyrazolone dyes that exist in the ketone hydrazone form[5].

From the homogeneous isomers isolated so far it could be established that the isomerization of N_α to N_β, and vice



(7) *(8)*



(9)

M = Cr or Co

versa, proceeds relatively easily; even gentle boiling in pyridine for a short while is sufficient to produce a mixture of both isomers.

Three isomers, *(7)* to *(9)*, are to be expected in the 1:2 chromium and 1:2 cobalt chelate series in those cases in which N_α and N_β isomers are found in the corresponding copper and nickel complexes. These also can be demonstrated by chromatography.

Received: January 17, 1972 [Z 597 IE]
German version: Angew. Chem. *84*, 351 (1972)

[1] DRP 282987, Badische Anilin- und Soda-Fabrik (1912); Friedländer *11*, 1201.

[2] Reviews: *H. Baumann* and *H. R. Hensel*, Fortschr. Chem. Forsch. *7*, Vol. 4 (1967). *R. Price* in *K. Venkataraman*: The Chemistry of Synthetic Dyes. Academic Press, New York 1970, Vol. III, Chapter VII.

[3] DRP 479373, I.G. Ludwigshafen (1926); Friedländer *16*, 975; DRP 474997, I.G. Ludwigshafen (1926); Friedländer *16*, 968; DRP 571859, I.G. Leverkusen (1931); Friedländer *19*, 1689; DOS 1901256, Badische Anilin- und Soda-Fabrik (Jan. 11, 1969).

[4] Numerous authors have concerned themselves with this theme. For reviews see: *H. Zollinger*, Chemie der Azofarbstoffe. Birkhäuser-Verlag, Basel 1958, pp. 214—216; *Y. Yagi*, Bull. Chem. Soc. Japan *37*, 1875 (1964); *E. Lippert et al.*, Ber. Bunsenges. Physik. Chem. *69*, 155 (1965); *V. Bekárek et al.*, Tetrahedron Lett. *1968*, 3711.

[5] *J. Yasuda* and *H. Midorikava*, J. Org. Chem. *31*, 1722 (1966); *F. A. Snavely* and *C. H. Yoder*, *ibid. 33*, 513 (1968).

Cyclovinylogous $[2\pi \rightarrow 2\sigma]$ Photoadditions[**]

By *Gerd Kaupp*[*]

In a recent communication[1] kinetic evidence was presented to show that the formally symmetry-allowed $[{}_\pi 2_s + {}_\pi 2_s]$ singlet photoaddition in intramolecular models actually proceeds in two steps. We now report on analogous mechanisms in some cyclovinylogous[2] $[2\pi \rightarrow 2\sigma]$ photoadditions.

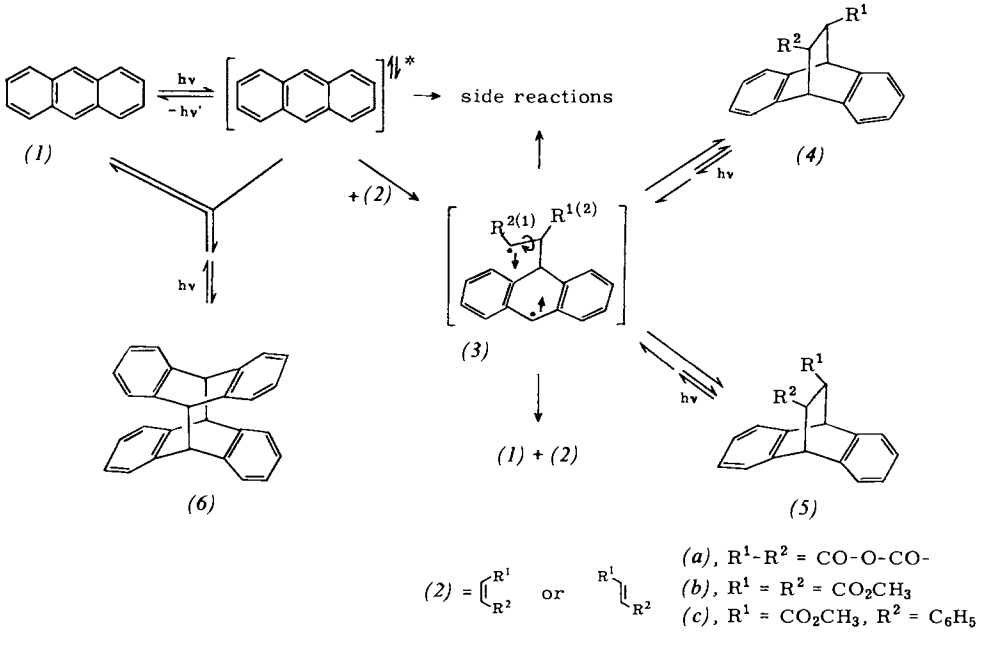
Electron-deficient alkenes *(2)* can undergo photochemical addition to anthracene *(1)* *via* a $[4\pi+2\pi]$-type reaction to give *(4)* or *(5)* (see Table). They thus compete with the $[4\pi+4\pi]$ dimerization of *(1)* to *(6)*. On selective excitation of *(1)* ($\lambda > 330$ nm) in presence of fumaric- and maleic dimethyl esters, [*trans-(2b)* and *cis-(2b)*, respectively], the more stable *trans* adduct *(4b)* is formed as principal product [*(4b)*/*(5b)* ≈ 98/2][2]; with cinnamic methyl ester [*trans-(2c)*] the same product *(4c)* is formed[3] as when the components are heated to 120 °C [*(1)*/*trans-(2c)* = 1/10, 3 days, 67%]. These results rule out symmetry allowed $[{}_\pi 4_s + {}_\pi 2_a]$ processes (cf. *e.g.* Ref. [4]) and lend support to the occurrence of intermediate products *(3)* with rotation about the original CC double bond.

Table. Yields [a] and quenching of fluorescence [b] in the reactions of anthracene *(1)* with alkenes *(2)* in benzene under N_2 at 25 °C.

Alkene	*(2)*, *cis*/*trans* [c]	Product (%) *(4)*	*(6)*	Fluorescence quenching (%)
(2a)	—	72 [d]	13	65
trans-(2b)	4/96	40	12	48
cis-(2b)	92/8	25	65	26
trans-(2c)	18/82	19	34	12

[a] $c_0 = 2.0 \times 10^{-3}$ mol *(1)*/l and 2.0×10^{-2} mol *(2)*/l; $\lambda > 330$ nm.
[b] $c = 2 \times 10^{-6}$ mol *(1)*/l and 2.0×10^{-2} mol *(2)*/l; $\lambda_{ex} = 378$ nm; self quenching of *(1)* can be neglected.
[c] At complete conversion of *(1)*.
[d] *(5a)*.

The data listed in the table show that the sterically less demanding, electron-deficient alkenes *(2)* can compete better with *(1)* for electronically excited singlet anthracene. (However, the amount of quenching of fluorescence cannot be used for the determination of photochemical rate constants because of reverse and side reactions.) In the case of more electron-rich olefins such as cyclopentene, cyclohexene or stilbene neither a quenching of the anthracene fluorescence nor formation of adducts of type *(4)* or *(5)* can be detected under standard conditions.



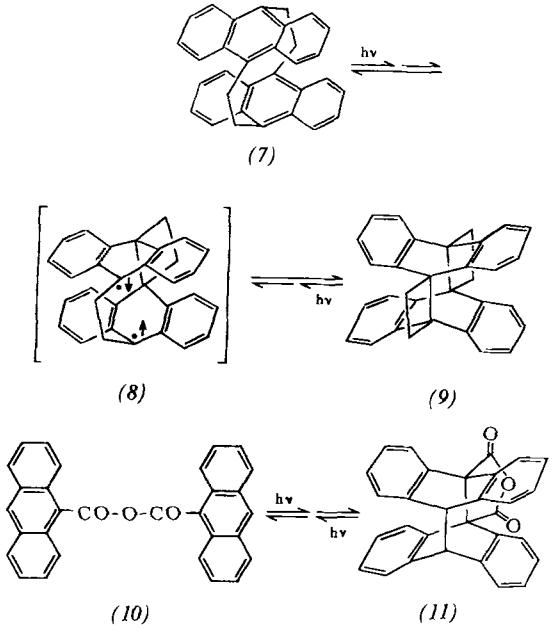
External heavy atom effects, which detectably favor the formation of triplet anthracene[5], serve as further confir-

[*] Dr. G. Kaupp
Chemisches Laboratorium der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

mation for the singlet mechanism of the $[4\pi+2\pi]$ photoaddition: In ethyl bromide under standard conditions the yields of *(6)* and *(4)* fall below 5% in all cases, and on terminating the irradiation at standard time the alkenes *(2b)* and *(2c)* are present in more than 99% in the *trans* form[6]. Also as expected, the addition of *(2a)* to *(5a)* is strongly retarded (yield under standard conditions: 26%).

The singlet $[4\pi+4\pi]$-dimerization of anthracene (derivatives)[7] can be interpreted formally as a symmetry allowed $[{}_{\pi}4_{s}+{}_{\pi}4_{s}]$ reaction in which both new σ bonds (bond length *ca.* 1.6 Å) are formed simultaneously from an excimer (typical inter-aromatic distance *ca.* 3.3 Å) with rehybridization at the four *meso* positions (cf. p. 320 in Ref. [5]). An experimental test for these concepts is feasible by measurement of the quantum yields of forward and reverse reactions for a model[1,2] already containing two anthracene nuclei in the molecule.



[2.2](9,10)Anthracenophane *(7)*[8] having a distance of about 3 Å between aromatic nuclei (molecular model; also comparable with [2.2]paracyclophane[9]) reacts uniformly and without detectable fluorescence (start of absorption at *ca.* 550 nm) with a quantum yield $\Phi=0.30$ (CH_2Cl_2 or C_2H_5Br; 450, 365, 334, or 282 nm; N_2 or O_2)[10] to give the polycyclic compound *(9)*[8], which is reconverted into *(7)* by 282 nm-excitation with $\Phi=0.6$; no fluorescence can be detected, although non-uniformly fluorescing by-products are formed on prolonged 282-nm irradiation. The sum of the quantum yields $\Phi_{forward}+\Phi_{rev.}$ remains below the limiting value of 1 and is thus in accord with a common singlet intermediate *(8)*, which is also indicated by the fact that neither oxygen nor ethyl bromide alter the quantum yields. These findings suggest that, contrary to theoretical concepts, a biradical intermediate [analogous to *(8)*] must be assumed in order to explain the kinetic data in the photodimerization of *(1)* and the photocleavage of *(6)*[2].

The almost quantitative formation of intermediate *(8)* from both directions (cf. Ref. [1]) shows that the primary photochemical process requires virtually no activation. Consequently, the photolysis of *(7)* or of *(9)* in a KBr pellet at −190 °C also proceeds without detectable luminescence[11]. By way of contrast, the anhydride *(10)*[12], whose longwave absorption appears up to about 470 nm, behaves mechanistically less clear-cut since several conformations of *(10)* are conceivable and since the photointermediates from *(10)* and *(11)*[12] do not have to be identical.

In absence of moisture, *(10)* reacts uniformly ($8\times10^{-5}-2\times10^{-4}$ mol/l, CH_2Cl_2, 25 °C, 365 or 334 nm, N_2 or O_2, $4\times10^{-7}-5\times10^{-7}$ einstein/min) with a quantum yield $\Phi=0.031$ to give *(11)*; there is competition from a relatively intense yellow-green fluorescence (in CH_2Cl_2, 365 nm, 25 °C: $\lambda_{max}^{corr.}=520$ nm, $\Phi_{Fl}=3.5\times10^{-3}$). At −190 °C ($CH_2Cl_2$) only a 17% conversion of *(10)* into *(11)* can be achieved. The photoreaction can also be carried out intermolecularly in a KBr pellet at 25 °C; however, crystalline *(10)* is *photostable* at −190 °C (IR detection).

As an explanation for the above findings it is assumed that only a small proportion of dissolved *(10)* is present in a conformation favorable for formation of the first σ bond and that further thermal supply of this conformer is frozen-in at −190 °C. The absence of a heavy-atom effect (observed in the dimerization of *(1)*) in ethyl bromide ($\Phi=0.0315$; 25 °C) also discounts the photochemical generation of the reactive conformation.

Received: October 26, 1971 [Z 569 IE]
German version: Angew. Chem. *84*, 259 (1972)

[1] *G. Kaupp*, Angew. Chem. *83*, 361 (1971); Angew. Chem. internat. Edit. *10*, 340 (1971).

[2] *G. Kaupp*, Chimia *25*, 230 (1971).

[3] M.p. 120 °C; NMR ($CDCl_3$): τ = 2.5—3.1 (11 H/m), 3.25—3.55 (2 H/m), 5.25 (1 H/d, $J=2.5$), 5.8 (1 H/d), 6.4 (1 H/dAB, $J=6.1$, 2.5), 6.45 (3 H/s), 7.0 ppm (1 H/dBA); UV/(CH_3CN): $\lambda_{max}(\varepsilon)=220$ (16000) (sh), 254 (770) (sh), 259 (960), 265.5 (1220), 272.5 (1270), 286 nm (40) (sh); fluorescence (cyclohexane 220—272 nm): $\lambda_{max}^{corr.}=286$ nm; $\Phi_{Fl}=0.38$.

[4] *D. R. Arnold, L. B. Gillis*, and *E. B. Whipple*, Chem. Commun. *1969*, 918; *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[5] *J. B. Birks*: Photophysics of Aromatic Molecules. Interscience, New York 1970, pp. 208 ff. and 439 ff.

[6] This clearly shows (see Table also) that both a singlet as well as triplet mechanism takes place in the *sensitized cis-trans* isomerization of electron-deficient alkenes.

[7] *E. J. Bowen*, Advan. Photochem. *1*, 23 (1963); *D. O. Cowan* and *W. W. Schmiegel*, Angew. Chem. *83*, 545 (1971); Angew. Chem. internat. Edit. *10*, 517 (1971) (the experimental data do *not* rule out other intermediates: *D. O. Cowan*, personal communication, June 25, 1971).

[8] *J. H. Golden*, J. Chem. Soc. *1961*, 3741.

[9] *D. K. Lonsdale, H. J. Milledge*, and *K. V. K. Rao*, Proc. Roy. Soc. *A 255*, 82 (1960).

[10] For the photokinetic determination of quantum yields cf. Ref. [2] and *G. Kaupp* and *H. Prinzbach*, Helv. Chim. Acta *52*, 956 (1969); Liebigs Ann. Chem. *725*, 52 (1969); Chem. Ber. *104*. 182 (1971).

[11] 1,2-Diphenyl- and 1-methoxycarbonyl-2-phenyl-norbornadiene (cf. [1]) also react reversibly at −190 °C in an ether/alcohol glass (2:1) without observable luminescence to give the quadricyclanes.

[12] *F. D. Greene, S. L. Misrock*, and *J. R. Wolfe*, J. Amer. Chem. Soc. *77*, 3852 (1955).

Solid-Phase Peptide Synthesis on an Inorganic Matrix having Organic Groups on the Surface[**]

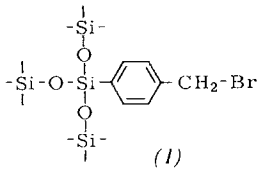
By *Wolfgang Parr* and *Karel Grohmann*[*]

We have recently shown[1] that an inorganic matrix *(1)* having organic groups located on the surface is suitable for the Merrifield solid-phase synthesis of peptides[2]. The

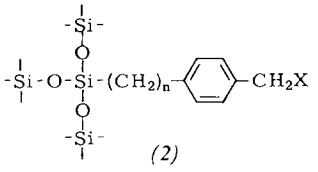
[*] Prof. Dr. W. Parr and Dipl.-Ing. K. Grohmann
Chemistry Department, University of Houston
Houston, Texas 77004 (USA)

[**] This work was supported by the Robert A. Welch Foundation, Houston, and the National Science Foundation.

synthesis of the model peptide Pro-Gly-Phe-Ala proceeded satisfactorily, but removal of the peptide from the silicate polymer presented difficulties.



(1)



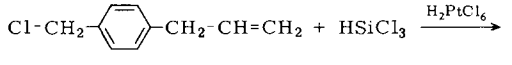
(2)

n = 1,2,3,...; X = Halogen

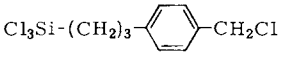
These difficulties can be overcome if, as in *(2)*, a short aliphatic chain is inserted between the three-dimensional silicate network and the active benzyl group.

We have now synthesized a matrix of structure *(2)* in which $n=3$ and X = Cl. For this synthesis we required the silicon trichloride derivative *(4)*, which was prepared for the first time using the following procedure:

1,4-Dibromobenzene is converted by a Wurtz synthesis with allyl bromide and magnesium into 1-allyl-4-bromobenzene[3], which can be transformed *via* the Grignard compound with formaldehyde into 1-allyl-4-hydroxymethylbenzene. Reaction of the latter with hydrogen chloride in the presence of anhydrous Na_2SO_4 (6 h, room temperature) yields 1-allyl-4-chloromethylbenzene *(3)* (NMR: $\delta=7.08$ (q), 5.85 (m), 5.06 (m), 4.83 (m), 4.42 (s), 3.28 ppm (d)). *(3)* reacts with trichlorosilane in the presence of chloroplatinic acid as catalyst[4] to give trichloro-[3-(4-chloromethylphenyl)propyl]silane *(4)* in 50% yield. According to NMR data only one isomer is formed (NMR: $\delta=7.15$ (q), 4.45 (s), 2.62 (t), 1.83 (m), 1.30 ppm (m)).



(3)



(4)

Compound *(4)* is allowed to react with the hydroxy groups of the glass surface and the remaining Si—Cl bonds are then hydrolyzed. The silicone layer is then polymerized at 100 °C in vacuum to *(2)*, $n=3$, X = Cl.

As a model peptide we synthesized the dodecapeptide H—(Phe-Ala)$_6$—OH[6], which was required for further investigation of the failure sequences that are formed as a result of incomplete coupling. For the synthesis, inorganic carrier *(2)* (8.9 g, 0.67 mmol Cl) was esterified with Boc-Ala in dioxane in the presence of triethylamine; all together 0.24 mmol Ala was attached to the carrier. The synthesis is then continued in the usual manner[6]. On treatment with HBr in trifluoroacetic acid, 240 mg (≈90%) peptide can be removed from 7 g of carrier. Ninhydrin tests and total hydrolysis of the carrier with 6 N HCl show that removal of the peptide was practically quantitative. According to amino-acid analysis the ratio of the Ala : Phe was 1.01 : 1.00. The hydrolyzate obtained by partial hydrolysis with 12 N HCl (37 °C, 72 h) is esterified with isopropanol and then trifluoracetylated. No dipeptide of the type Ala-Ala or Phe-Phe, *i.e.* no failure sequences, were observed by combined gas chromatography-mass spectrometry. Results of this type, however, are only semi-quantitative since partial hydrolysis yields not only dipeptides and free amino acids but also longer fragments which can not be detected by gas chromatography.

Experimental

A mixture of $HSiCl_3$ (37 g, 0.27 mol) and a 0.1 M solution of H_2PtCl_6 in isopropanol (0.3 ml) is treated with *(3)* (2 ml) and heated under reflux for 20 min. A further 38 ml of *(3)* is then added dropwise to the mixture such that it continues to boil without further heating. After heating under reflux for 3 h the excess of trichlorosilane is removed under vacuum. The oily residue thus obtained is then distilled; Yield: 36 g *(4)* (44%), b. p. 130 °C/0.1 torr.

(4) (2.5 g) is dissolved in anhydrous benzene (50 ml) and shaken together with porous glass beads (10 g, Porasil E, Waters Ass.) for 24 h in a 250 ml vessel. After filtration, the coated glass beads are washed free from unchanged *(4)* with benzene and the remaining Si—Cl bonds are hydrolyzed with water/ethanol (50:50). After further washing with ethanol and benzene the silicone layer is dried under vacuum at room temperature and finally polymerized by heating to 100 °C for 24 h in high vacuum. After washing with benzene and tetrahydrofuran the capacity of the silanized beads was determined by Volhard analysis for chlorine (0.07 mmol Cl/g glass)[5]. The chlorine content varied according to the conditions of preparation from 0.03 to 0.08 mmol/g.

Received: November 9, 1971 [Z 568 IE]
German version: Angew. Chem. *84*, 266 (1972)

[1] *W. Parr* and *K. Grohmann*, Tetrahedron Lett. *1971*, 2633.

[2] *R. B. Merrifield*, J. Amer. Chem. Soc. *85*, 2149 (1963); *86*, 221 (1969); Advan. Enzymol. *32*, 221 (1969).

[3] Belg. Pat. 660565 (1965), National Research & Development Corp.

[4] *A. D. Petrov, E. A. Chernysher, M. E. Dolgaya, Yu. P. Egorov*, and *L. A. Leites*, Zh. Obshch. Khim. *30*, 376 (1960).

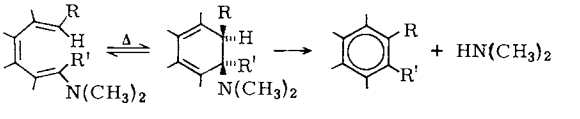
[5] Hydrolysis with pyridine/water (90:10) in an ampoule (100 °C, 2 h) followed by titration.

[6] *E. Bayer, H. Eckstein, K. Hägele, W. König, W. Brüning, H. Hagenmaier*, and *W. Parr*, J. Amer. Chem. Soc. *92*, 1735 (1970).

Synchronous Six-Electron Cyclization of Hexatriene Systems as a New Synthetic Principle for Preparation of Aromatic and Heteroaromatic Compounds[**]

By *Christian Jutz* and *Rudolph M. Wagner*[*]

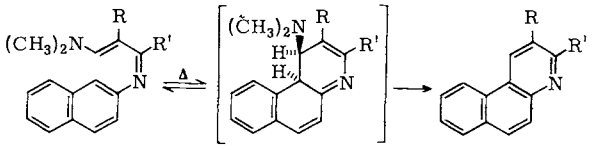
Thermal cyclization of hexatrienes to cyclohexadienes occurs as a disrotatory reversible process[1]. The irreversible conversion of the cyclohexadiene into a six-membered aromatic system can be effected in a subsequent elimination step if the starting hexatriene contains, *e.g.* a dimethylamino group, preferably *trans*, on C-1 and also a *cis*-proton on C-6.



[*] Prof. Dr. Ch. Jutz and Dipl.-Chem. R. M. Wagner
Organisch-Chemisches Laboratorium der Technischen Universität
8 München, Arcisstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Azalogous hexatriene systems occur in (dimethylamino-propenylidene)-*N*-arylamines *(1)* where one of the double bonds is part of an aromatic ring; when heated to *ca.* 150—200 °C these compounds are converted into quinolines *(2)* with loss of dimethylamine.

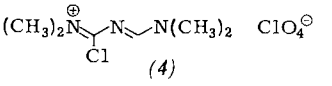


(1) *(2)*

+ $HN(CH_3)_2$

The thermolysis temperature is determined, *inter alia*, by the localization energy of two π-electrons in the aromatic systems of *(1)* with respect to a double bond of the hexatriene. This explains why with *(1)* from naphthylamines also be achieved in a single operation if equivalent amounts of arylamine and *(3c)* or *(3e)* are heated in pyridine or quinoline, respectively, with one equivalent of sodium ethoxide.

In *(3h)* the reactive chlorine may be replaced nucleophilically by an arylamino group. The 3-(dimethylamino)-acrylamidines isolated [in *(1)* R′ = $N(CH_3)_2$, and R = CN] cyclize particularly easily to quinoline derivatives (Table). Analogously, the azatrimethine *(4)* and arylamines afford finally dimethylaminoquinazolines. For example, 3-(dimethylamino)benzo[*f*]quinazoline,



(4)

m.p. 136—137 °C, is formed in 90% yield from *(4)* and 2-naphthylamine at 180—200 °C.

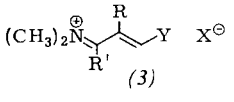
Table 1. Preparation of quinolines of type *(2)* from arylamines and trimethines *(3)*.

Arylamine	Trimethine	Cycln. temp. (°C)	Quinoline	M.p. (°C)	Yield (%)
Aniline	*(3d)*	180–200	3-Phenyl-	50– 51	68
p-Anisidine	*(3d)*	180–200	6-Methoxy-3-phenyl-	121–122	65
2-Naphthylamine	*(3b)*	200	Benzo[*f*]-	94	72
2-Naphthylamine	*(3c)* or *(3d)*	170	3-Phenylbenzo[*f*]-	115–116	95 [a]
2-Naphthylamine	*(3g)*	180–200	2-Methoxybenzo[*f*]-	88– 89	94
1-Naphthylamine	*(3b)*	210	Benzo[*h*]-	52	50
1-Naphthylamine	*(3c)* or *(3d)*	170	2-Phenylbenzo[*h*]-	113–114	91 [a]
1-Naphthylamine	*(3e)*	115	3-Nitrobenzo[*h*]-	166–167	71 [a]
Aniline	*(3h)*	160	3-Cyano-2-dimethylamino-	81– 82	99
p-Toluidine	*(3h)*	160	2-Dimethylamino-6-methyl-	111–112	99
p-Anisidine	*(3h)*	160	2-Dimethylamino-6-methoxy-	119–120	99
p-Chloroaniline	*(3h)*	160	2-Dimethylamino-6-chloro-	115–117	99
p-Nitroaniline	*(3h)*	180–200	2-Dimethylamino-6-nitro-	188–189	99
2-Naphthylamine	*(3h)*	160	2-Cyano-3-dimethylaminobenzo[*f*]-	148–149	99

[a] One-stage process.

the new hetero ring is angular and is formed at lower temperature than in the case of *(1)* from aniline. Further, substituents in the methine chain assist cyclization, but inductive and mesomeric effects of substituents in the benzene ring have little influence in this connection.

The bases *(1)* are conveniently accessible, by way of their crystalline perchlorates, from the dimethyl sulfate adducts of 3-(dimethylamino)acroleins *(3b)*, *(3d)*, and *(3g)* with arylamines[2]. Conversion into the quinolines *(2)* can

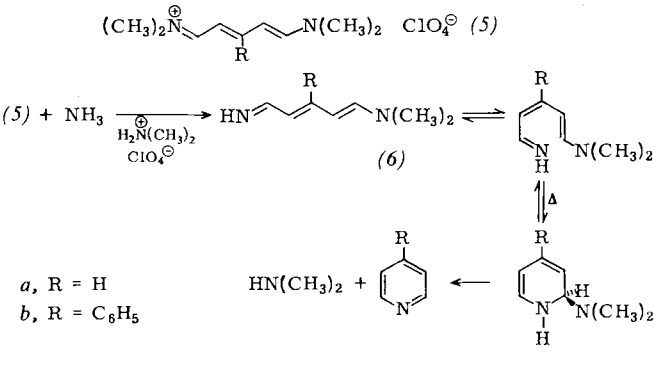


(3)

(3)	R′	R	Y	X⁻
a	H	H	$N(CH_3)_2$	ClO_4 [3]
b	H	H	OCH_3	CH_3OSO_3 [2]
c	H	C_6H_5	$N(CH_3)_2$	ClO_4 [4]
d	H	C_6H_5	OCH_3	CH_3OSO_3
e	H	NO_2	$N(CH_3)_2$	ClO_4 [6,7]
f	H	OCH_3	$N(CH_3)_2$	ClO_4 [5]
g	H	OCH_3	OCH_3	CH_3OSO_3
h	Cl	CN	$N(CH_3)_2$	ClO_4

The observation that 2-trifluoromethylbenz[*d*]-[1,3]-oxazin-4-one reacts with enamines (having one more free β position) by cleavage of secondary amine to give 2-trifluoromethylquinoline-8-carboxylic acid[8] even though the intermediate of type *(1)* postulated as being formed at the same time cannot be isolated and the reaction takes place at −40 °C, induced us to investigate the thermally stable *(1)*-bases.

The well-known Conradt-Limpach thermal synthesis of quinolones from β-arylamino acrylic esters[9] belongs



(5)

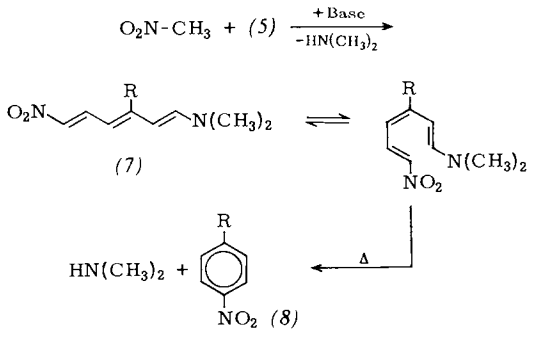
(6)

a, R = H
b, R = C_6H_5

to the class of "aza-hexatriene" cyclizations with elimination. The formation of pyridines by reaction of pentamethinium salts, such as *(5)*, with ammonia (ammonium acetate) is also a nucleophilic substitution only in the first step, which leads to a 1-aza-6-dimethylaminohexatriene *(6)*. Cyclization takes place very readily since no additional localization energy is necessary.

On the basis of previous findings it was expected that the unknown 1-dimethylaminohexatriene should also cyclize very readily with elimination of dimethylamine to give benzene. 6-Substituted 1-dimethylaminohexatrienes *(7)* are obtained by reaction of *(5)* with compounds containing an acidic methyl-group in the presence of a base (triethylamine or sodium methoxide).

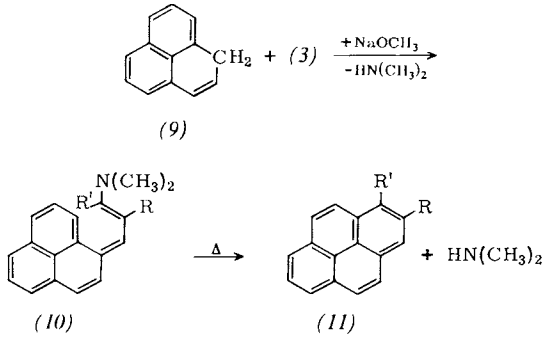
Ring-closure occurs even at 60—90 °C.



a, R = H
b, R = C_6H_5

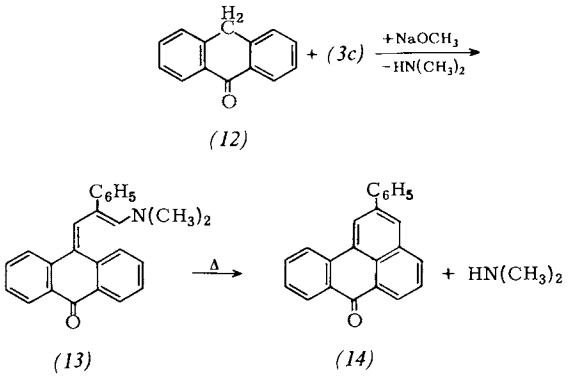
Nitrobenzene *(8a)* is obtained in 73% yield, and 4-nitrobiphenyl *(8b)*, m.p. 111—113 °C, in 66% yield. Acetophenone and 4-acetylpyridine react analogously with *(7b)* in pyridine on addition of one equivalent of sodium methoxide; dimethylaminoheptatrienone is formed as a deep red intermediate, but at 70—90 °C the color fades, dimethylamine is split off, and 4-benzoylbiphenyl, m.p. 100—101 °C (96%), and 4-pyridyl 4-biphenylyl ketone, m.p. 153—154 °C (95%), are obtained as products.

The synthesis of pyrenes *(11)* from the acid phenalene *(9)* and trimethine perchlorates *(3)* by way of the isolable, violet-red enamines *(10)*[7, 10] is an example of the cyclization of 1-(dimethylamino)hexatrienes in which the aromatic system participates. As expected, the thermolysis temperature is again higher in these cases (120—180 °C).

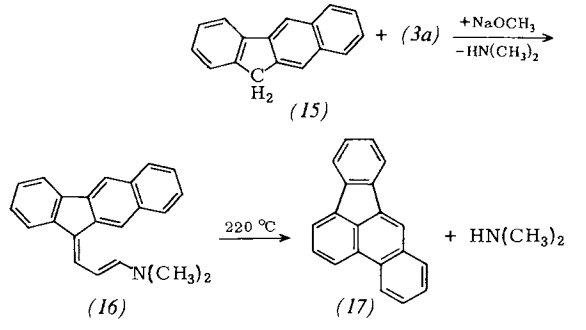


However, other, more easily accessible, starting materials with acidic methylene groups in the aromatic component permit also annelation of a further benzo ring in this way.

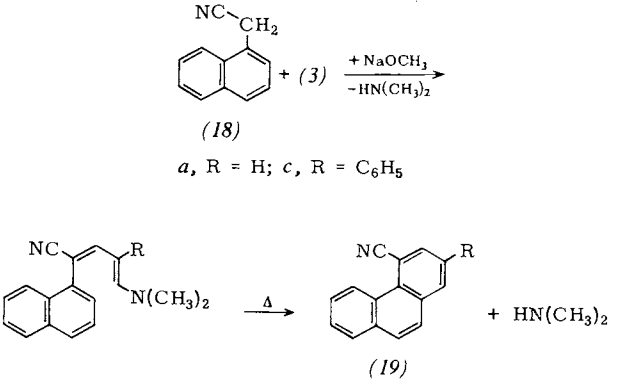
Anthrone *(12)* condenses with *(3c)* to give the orange-red enamine ketone *(13)*, which at 170—180 °C cyclizes to 2-phenylbenzanthrone *(14)*, m.p. 196—197 °C (87%).



With somewhat greater difficulty, fluorenes *(15)* can also be converted by way of aminofulvenes *(16)*[11] into fluoranthenes *(17)*, *e.g.* benzo[*b*]fluoranthene, m.p. 165—167 °C (34%).



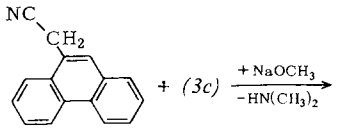
Phenanthrenes with substituents in specific positions can be conveniently built from naphthalene derivatives, *e.g.* 4-phenanthronitrile *(19a)*, m.p. 106—108 °C (91%), or 2-phenyl-4-phenanthronitrile *(19c)*, m.p. 169—177 °C (87%), from 1-naphthylacetonitrile and *(3a)* or *(3c)*, respectively.



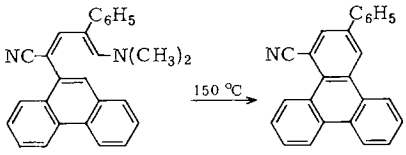
a, R = H; *c*, R = C_6H_5

One can proceed analogously from 9-phenanthrylacetonitrile into the triphenylene series *(21)*, *e.g.* from *(20)* and *(3c)* to 3-phenyl-1-triphenylenecarbonitrile, m.p. 161 to 163 °C (95%).

Indoles can be converted in carbazoles. We obtained 4-carbazolecarbonitrile *(23a)*, m.p. 156—158 °C (68%),

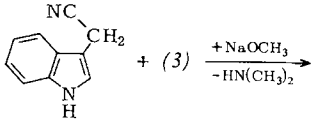


(20)

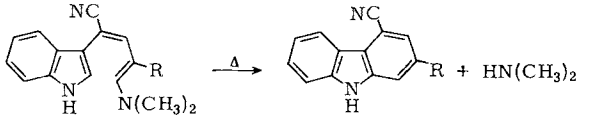


(21)

2-phenyl-4-carbazolecarbonitrile *(23c)*, m.p. 225—226 °C (91%), and 2-methoxy-4-carbazolecarbonitrile *(23f)*, m.p. 142—143 °C (72%), from 3-indolylacetonitrile *(22)* with *(3a)*, *(3c)*, or *(3f)*, respectively, by way of the orange-red enamine at 160—180 °C.



(22)



(23)

a, R = H; *c*, R = C_6H_5; *f*, R = OCH_3

These few examples suffice to show how the new synthetic principle is capable of generalization.

The known Ziegler-Hafner azulene synthesis and the formation of azuleno[5,6,7-*cd*]phenalene[7,10] constitute an extension of the electrocyclic reaction with elimination into ten-electron systems.

6-Methoxy-3-phenylquinoline

p-Anisidine (1.23 g) is added to a solution of the adduct *(3d)* from dimethyl sulfate (1.26 g) and 3-(dimethylamino)-2-phenylacrolein (1.75 g) in CH_2Cl_2 (25 ml), the solvent is evaporated, and the yellow syrup resulting is dissolved in a little water. On addition of sodium perchlorate the yellow perchlorate is precipitated; it forms yellow needles (3.61 g, 91%), m.p. 180—181 °C, from ethanol. 2N NaOH liberates the base of type *(1)* which is taken up in benzene. After removal of the benzene by distillation, the crude crystalline base (2.5 g) is heated slowly to 200—220 °C in a stream of N_2; dimethylamine is evolved above 180 °C and can be determined acidometrically. After 1 h thermolysis is complete. The dark residue is dissolved in hot benzene and filtered through a short column of Al_2O_3 (activity II, basic). From the eluate the sublimable compound of type *(2)* (1.30 g, 65%) is isolated and forms colorless needles, m.p. 122—123 °C, from *n*-hexane. ^{1}H-NMR ($CDCl_3$): τ = 1.03 (H-2/d), 1.90 (H-4/d), 2.0 (H-8/d), 2.25—2.53 (5 phenyl-H/m), 2.70 (H-7/dd), 2.94 (H-5/d), 6.10 (3 methoxy-H/s); J_{24} = 2.5 Hz; J_{57} = 2.7 Hz; J_{78} = 9.5 Hz.

6-Chloro-2-dimethylamino-3-quinolinecarbonitrile

The salt *(3h)* (2.15 g) is added to a solution of *p*-chloroaniline (1.9 g) in CH_2Cl_2 (20 ml) and the solvent is distilled off. The residue is digested with water containing sodium perchlorate and the solid perchlorate is filtered off; it forms colorless needles (2.25 g, 80%), from ethanol. The liberated base forms colorless needles, m.p. 115 °C, from benzene-hexane. ^{1}H-NMR ($CDCl_3$): τ = 2.7—3.6 (4 phenyl-H/m), 4.75 (1 methine-H/s), 6.9, 7.0, 7.06, 7.3 (12 N—CH_3—H/s). The thermolysis with loss of dimethylamine is already quantitative within 30 min at 180 °C. From 0.55 g of the above base is formed 0.46 g (99%) of the sublimable compound of type *(2)*, forming yellow needles of m.p. 116 °C from hexane. ^{1}H-NMR ($CDCl_3$): τ = 2.05 (H-4/s), 2.52—2.75 (3 H/m), 6.75 (6 N—CH_3—H/s); IR (KBr): ν_{CN} = 2225 cm^{-1}.

4-Biphenylyl 4-pyridyl ketone

A *ca.* 2N methanolic solution (5 mmol) of sodium methoxide is added dropwise to a stirred solution of 4-acetylpyridine (0.6 g) and *(5b)* (1.64 g) in pyridine (25 ml). The mixture at once assumes the intense reddish-violet color of the dimethylaminoheptatrienone. When the mixture is warmed to 90 °C the color fades. After 1 hour's heating, the pyridine is distilled off in a vacuum, the residue is digested with a little water, and the crystalline ketone is sucked off; it forms colorless leaflets (1.23 g, 95%), m.p. 153—154 °C, from ethanol. ^{1}H-NMR ($CDCl_3$): τ = 1.15 (2 H/d), 2.18 (2 H/d); J = 5 Hz (pyridine-H); 1.95—2.6 (9 phenyl-H/m).

2-Methoxy-4-carbazolecarbonitrile (23f)

A *ca.* 2N methanolic solution (10 mmol) of sodium methoxide is dropped into a solution of 3-indolylacetonitrile (1.56 g) and *(3f)* (2.57 g) in anhydrous quinoline (25 ml), and the whole is heated slowly with stirring under N_2 to 125 °C; after 1 h the bath temperature is raised to 160 °C, whereupon the stoichiometric amount of dimethylamine is evolved within 3 h. The quinoline is then largely distilled off in a water-pump vacuum, the residue is dissolved in CH_2Cl_2 with addition of water, and the organic phase is washed with dilute HCl and water. After removal of the solvent the crystalline residue is recrystallized from ethanol, yielding colorless needles of *(23f)* (1.52 g, 72%), m.p. 142—143 °C. ^{1}H-NMR ($CDCl_3$): τ = 1.87—2.06 (H-5/m), 2.5—2.88 (H-6, H-7, H-8/m), 2.95 (H-3/d), 3.13 (H-1/d); J_{13} = 2 Hz; 6.08 (OCH_3-H/s).

Received: December 29, 1971 [Z 580 IE]
German version: Angew. Chem. *84*, 299 (1972)

[1] *R. B. Woodward* and *R. Hoffmann*, J. Amer. Chem. Soc. *87*, 395 (1965); Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[2] *H. Bredereck, F. Effenberger*, and *G. Simchen*, Chem. Ber. *96*, 1350 (1963); *H. Bredereck, F. Effenberger*, and *D. Zeyfang*, Angew. Chem. *77*, 219 (1965); Angew. Chem. internat. Edit. *4*, 242 (1965); *H. Bredereck, F. Effenberger, D. Zeyfang*, and *K.-A. Hirsch*, Chem. Ber. *101*, 4036 (1968).

[3] *S. S. Malhotra* and *W. C. Whiting*, J. Chem. Soc. *1960*, 3812; *Z. Arnold* and *A. Holy*, Collect. Czechoslov. Chem. Commun. *30*, 2125 (1965).

[4] *Z. Arnold*, Collect. Czechoslov. Chem. Commun. *26*, 3051 (1961).

[5] *Z. Arnold* and *F. Šorm*, Collect. Czechoslov. Chem. Commun. *23*, 452 (1958).

[6] *J. Kučera* and *Z. Arnold*, Collect. Czechoslov. Chem. Commun. *32*, 1704 (1967).

[7] *Ch. Jutz, R. Kirchlechner*, and *H.-J. Seidel*, Chem. Ber. *102*, 2301 (1969).

[8] *W. Steglich*, private communication, unpublished.

[9] *H. Bredereck, F. Effenberger, H. Botsch*, and *H. Rehm*, Chem. Ber. *98*, 1081 (1965).

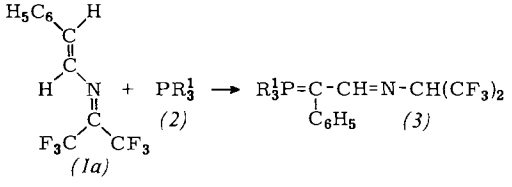
[10] *Ch. Jutz* and *R. Kirchlechner*, Angew. Chem. *78*, 493 (1966); Angew. Chem. internat. Edit. *5*, 516 (1966).

[11] *Ch. Jutz* and *H. Amschler*, Chem. Ber. *97*, 3331 (1964).

Addition of Phosphanes and Phosphites to Trifluoromethyl-Substituted 2-Aza-1,3-butadienes[**][1,2]

By *Klaus Burger, Josef Fehn, Josef Albanbauer*, and *Josef Friedl*[*]

4-Phenyl-1,1-bis(trifluoromethyl)-substituted 2-aza-1,3-butadiene (1,1,1-trifluoro-2-trifluoromethyl-5-phenyl-3-aza-2,4-pentadiene) *(1a)*[3] reacts with the phosphanes *(2a)* and *(2b)* to give the 1:1-adducts *(3a)* and *(3b)* respectively. The ^{31}P-NMR spectra of *(3a)* and *(3b)* show signals at -15.4 and -34.5 ppm, respectively (85% phosphoric acid as external standard), and thus rule out the product of a [4+1]-cycloaddition to a phosphorus heterocycle containing pentavalent phosphorus, as we have already found for the reaction of *N*-hexafluoroisopropylidenecarboxamides with phosphites[4]; the value is in the range of those found for phosphorus ylides[5]. In the IR spectra absorption occurs in the double-bond region at 1540—1570 cm^{-1}; similar values are observed for α-carbonyl ylides[6]. The coupling constants J_{PH} for the proton on C-2 are 28—35 Hz.



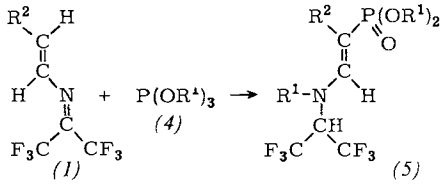
(1a) + PR^1_3 → $R^1_3P{=}C(C_6H_5)$-CH=N-CH$(CF_3)_2$ *(2)* *(3)*

(3)	R^1	Yield (%)	M.p. (°C)	IR (cm^{-1}) [a]
(a)	C_6H_5	62	138 (dec.)	1565 [7]
(b)	$CH(CH_3)_2$	84	84	1560

[a] In KBr with a Perkin-Elmer Infracord.

We assume that nucleophilic attack of the phosphane at position 4 takes place first to give a phosphonium betaine which is subsequently stabilized by 1,4-proton migration to the ylide *(3)*. The signal of the migrated proton appears in the NMR spectrum at $\delta = 3.62$ ppm (CCl_4, TMS); it is split into a septet ($J_{HF} = 7.0$ Hz) by the neighboring CF_3 groups. Similar 1,4- and 1,2-proton shifts are known. Hydrolysis of *(3a)* yields phenylacetaldehyde, which was characterized as dinitrophenylhydrazone.

Phosphites *(4)* also react with the compounds *(1)* to give 1:1-adducts, namely the phosphonates *(5)*. The ^{31}P-NMR spectrum[8] shows signals at -21 to -25 ppm and the ^{1}H-NMR spectrum [*(5a)*, *(5c)*] signals at $\delta = 3.6$ ppm (6 H/d, $J_{PH} = 11.0$ Hz), which are characteristic for a phosphonate grouping[9]. The signal of the migrated proton appears as a septet [$J_{HF} = 7.5$ Hz at $\delta = 6.0$ *(5a)*, 5.4 *(5b)*, and 5.8 ppm *(5c)* (CCl_4, TMS)]. The IR spectrum contains a signal in the double-bond region at 1610—1620 cm^{-1} as well as characteristic absorptions for the phosphonate group at 1250 (P=O), 1180 (P—OCH_3), 1060 and 1025 cm^{-1} (P—O-alkyl). The coupling constants J_{PH} of 18—19.2 Hz are indicative of a *cis*-configuration for the phosphonic group and proton[10]. This assumption is supported by the considerable difference in the chemical shift observed for the *N*-methyl group of *(5a)* ($\delta = 2.5$ ppm) and *(5c)* (3.12 ppm). The reaction *(1)* → *(5)* might proceed in the same way as *(1a)* → *(3)*; however the ylide is dealkylated by the nitrogen[11]. This step is analogous to the last step of the Arbusov reaction[12], for which a bimolecular process has been proved[13].



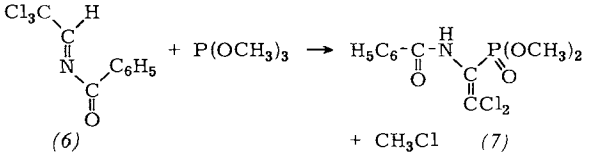
(1) + $P(OR^4)_3$ *(4)* → *(5)*

(5)	R^1	R^2	Yield (%)	M.p. (°C)	IR (cm^{-1}) [a]
(a)	CH_3	C_6H_5	51	179	1618
(b)	C_2H_5	C_6H_5	38	121	1615
(c)	CH_3	$CH(CH_3)_2$	40	97–98	1610

[a] In KBr with a Perkin-Elmer Infracord.

4,4-Disubstituted derivatives of *(1)* do not react under the conditions chosen; the trimethylphosphite merely rearranges to the phosphonate.

Unlike the analogous *N*-hexafluoroisopropylidenecarboxamides, but like the 2-azabutadiene *(1)*, *N*-(2,2,2-trichloroethylidene)benzamide *(6)*[14] reacts with trimethyl phosphite. The structure of the α-benzoylamino-β,β-dichloroethylenephosphonic acid dimethyl ester *(7)* formed by elimination of methyl chloride is confirmed unequivo-



(6) + $P(OCH_3)_3$ → *(7)* + CH_3Cl

[*] Dr. K. Burger, Dipl.-Chem. J. Fehn, J. Albanbauer and J. Friedl
Organisch-chemisches Institut der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

[1] Addition reactions to trifluoromethyl-substituted 2-aza-1,3-butadienes, Part 2; *K. Burger, G. George*, and *J. Fehn*, Liebigs Ann. Chem., in press, is to be regarded as Part 1.

[2] *K. Burger*, Lecture at 6th Internat. Symposium on Fluorine Chemistry, July 1971, Durham, England.

[3] *K. Burger, G. Dirnsteiner*, and *J. Fehn*, Liebigs Ann. Chem. *747*, 45 (1971).

[4] *K. Burger, J. Fehn*, and *E. Moll*, Chem. Ber. *104*, 1826 (1971).

[5] *S. O. Grim* and *J. H. Ambrus*, J. Org. Chem. *33*, 2993 (1968).

[6] *A. J. Speziale* and *K. W. Ratts*, J. Org. Chem. *28*, 465 (1968).

[7] *G. George*, Diplomarbeit, Technische Universität München 1971.

[8] We are indebted to Dr. *A. Schmidpeter*, Universität München, for recording the ^{31}P-NMR spectra.

[9] *F. Ramirez, O. P. Madan*, and *S. R. Heller*, J. Amer. Chem. Soc. *87*, 731 (1965).

[10] *A. M. Aguiar* and *D. Daigle*, J. Org. Chem. *30*, 3527 (1965); *W. A. Anderson, R. Freeman*, and *C. A. Reilly*, J. Chem. Phys. *39*, 1518 (1963); *S. Cawley* and *S. S. Danyluk*, J. Phys. Chem. *68*, 1240 (1964); *S. L. Manatt, G. L. Juvinall*, and *D. D. Ellemann*, J. Amer. Chem. Soc. *85*, 2664 (1963).

[11] *F. Ramirez* and *G. V. Loewengart*, J. Amer. Chem. Soc. *91*, 2293 (1969).

[12] *A. Michaelis* and *R. Kaehne*, Ber. dtsch. chem. Ges. *31*, 1048 (1898); *A. E. Arbusov*, J. Russ. Phys. Chem. Soc. *38*, 687 (1906).

[13] *W. Gerrard* and *W. J. Green*, J. Chem. Soc. *1951*, 2550.

[14] *F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Maierhofer*, and *W. Oettmeier*, Chem. Ber. *99*, 1944 (1966).

cally by spectral data [NMR ($CDCl_3$, TMS): $\delta = 3.85$ (2 CH_3/d, $J_{PH} = 11.8$ Hz), 7.35—7.6 (m) and 7.9—8.1 (m) (3 and 2 aromat. H resp.), 9.15 ppm (NH/d, $J = 2.5$ Hz). These structural elements are confirmed by the IR spectrum: 3160 (NH), 1660, 1570, 1280 (amide), 1240, 1180, 1050, and 1030 cm^{-1} (dimethyl phosphonate)].

5,5,5-Trifluoro-1-phenyl-4-trifluoromethyl-3-aza-2-pentenyl-idenetriisopropylphosphorane (3b)

A solution of triisopropylphosphane *(2b)* (1.6 g, 10 mmol) in *n*-hexane is slowly added dropwise to a cold (ice/salt), stirred solution of *(1a)*[3] (2.67 g, 10 mmol) in *n*-hexane (10 ml). The mixture is stored in a refrigerator for three days and the volatile components allowed to evaporate. The crystalline residue thus obtained is recrystallized from *n*-hexane plus activated charcoal (ice/bath); yield 3.6 g (84%) *(3b)*.

Dimethyl-5,5,5-trifluoro-3-methyl-1-phenyl-4-trifluoromethyl-3-aza-1-pentenephosphonate (5a)

A mixture of trimethyl phosphite *(4a)* (2.48 g, 20 mmol) and *(1a)*[3] (5.34 g, 20 mmol) is allowed to stand for 3 days at room temperature. The solids formed are then recrystallized from CCl_4; yield 4.0 g (51%) *(5a)*.

Received: November 2, 1971 [Z 571 IE]
German version: Angew. Chem. *84*, 258 (1972)

CONFERENCE REPORTS

International Symposium on the Chemistry of Small Rings

A symposium on the chemistry of small rings and activated multiple bonds was held at Louvain (Belgium), September 12—16, 1971.

From the lectures:

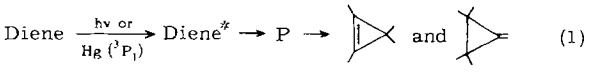
Some Properties of a Three-Membered Cyclic Diradical Intermediate

By *R. Srinivasan* and *S. Boué*[*]

The photoinduced electrocyclization of a conjugated diene to a cyclobutene is a well documented process[1] formally arising from the $\psi_1^2\psi_2\psi_3$ state. It has been shown[2], however, that the driving force is supplied by a significant contribution of the $\psi_1^2\psi_3^2$ state to the total wavefunction and accordingly the reaction obeys[1] the ψ_3 orbital symmetry, *i.e.* it is disrotatory for the ring closure and is specific for the singlet excited state.

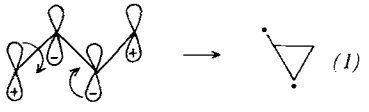
Three years ago we discovered[3] that electronic excitation of a linear conjugated diene also yields three-membered ring products, namely cyclopropene and methylene-cyclopropane derivatives. Thus the excited diene can relax through a 1,3-p_π bonding overlap of atomic orbitals and this process was found to be independent of the state multiplicity as it took place on $Hg(^3P_1)$ sensitization as well as on direct irradiation in the vapor phase or in solution[4]. Kinetic analyses[4-6] of quenching measurements have ruled out production of the cyclopropenes by ring closure concerted with a hydrogen migration and have called for a labile precursor P which would be the real primary photoproduct [eq. (1)].

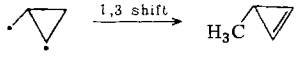
[*] Dr. R. Srinivasan
IBM Corporation, T. J. Watson Research Center
P. O. Box 218,
Yorktown Heights, N. Y. 10598 (USA)
Dr. S. Boué
Free University of Brussels, Department of Organic Chemistry
1050 Brussels (Belgium)



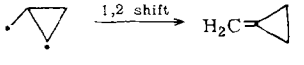
(1)

We then surmised that P would have the structure of the previously proposed[1] cyclic diradical *(1)* which can rearrange by hydrogen migrations, as shown in eq. (2) to (4).

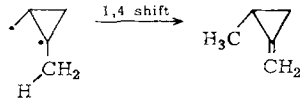




(2)



(3)



(4)

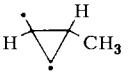
This is supported by several facts, the most important being:

1) P [≡ *(1)*] is quenchable by the ground state diene while $\Phi_{cyclobutene}$ is not dependent on the diene concentration.

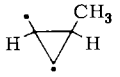
2) P leads to the final products by a hydrogen shift which is subject to a free activation energy $\Delta G^{\neq}$ obeying the se-

quence 1,3 < 1,2 ≈ 1,4; expectedly, the distribution of products was observed to be strongly influenced by the excess of vibrational energy possessed by P.

3) The S_1 state of *cis*- and *trans*-1,3-pentadienes yields distinctly different precursors interpreted as *(2)* from the *trans* and *(3)* from the *cis*.



(2)

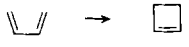


(3)

4) There is an energy barrier to the formation of P[7], since the cyclopropenes are observed as products on $Hg(^3P_1)$ sensitization ($E_T = 112$ kcal/mol) and on direct irradiation at 253.7 nm but not on sensitization with organic sensitizers ($E_T \leq 75$ kcal/mol) while *cis*⇌*trans* isomerization remains operative under these conditions.

It is proposed that the cyclic diradical species is of primary importance for explaining the $S_1 \rightarrow S_0$ internal conversion in the diene systems. Indeed, while in the T_1 diene the configuration relaxed by a 90° twist of one terminal p_π orbital is energetically degenerate with the correspondingly twisted ground state and thus offers a pathway for $T_1 \rightarrow S_0$ crossover, this is no longer true for the S_1 state[8].

Oosterhoff and *van der Lugt*[2] have shown that the energy profiles for the transformation

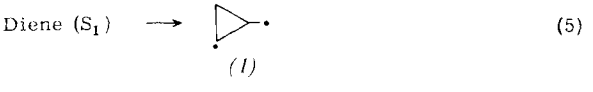


in S_1 and in S_0 are degenerate somewhere along the reaction coordinate; hence this would be a mechanism for energy dissipation in the S_1 diene but it can only account for the small proportion of molecules lying in the *s-cis* configuration when excited. A symmetry controlled 1,3-p_π bonding overlap would neither be subject to this restriction nor require a $\psi_1^2\psi_3^2$ contribution to provide the driving force for cyclization which is thus possible for a "hot" T_1^n state (ψ_2 and ψ_3 having the same symmetry with respect to a 1,3 closure), and would explain how internal conversion in S_1 preserves the geometrical configuration up to 90% ($\Phi_{cis \rightleftharpoons trans}$ on direct irradiation is of the order of 10% for the 1,3-pentadienes[4]).

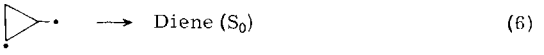
It is therefore assumed that the energy profiles in S_1 and S_0 for the conversion



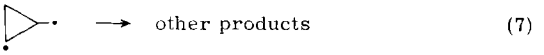
become degenerate as the reagent progresses along the reaction coordinate, this being the major pathway for energy dissipation in S_1 as well as for *cis*⇌*trans* isomerization about a double bond of the diene. The process



(1) (5)



(6)



(7)

appears to be most unusual since cyclization and ring-opening are both conrotatory. Expressed kinetically in terms of eq. (5) and (6) this is a "no reaction" reaction, involving a transient diradical similar to that invoked by *Turro*[9] to explain the dissipation of electronic energy.

Given the low barrier expected for reaction (6) while activation energies are reported for H migrations corresponding to reactions (7), the mechanism looks quite plausible and accounts for the low quantum yields ($\approx 10^{-2}$) in cyclopropene and methylenecyclopropane formation.

[1] *R. Srinivasan*, J. Amer. Chem. Soc. *90*, 4498 (1968), and references therein.

[2] *W. Th. A. M. van der Lugt* and *L. J. Oosterhoff*, J. Amer. Chem. Soc. *91*, 6042 (1969).

[3] *R. Srinivasan* and *S. Boué*, Tetrahedron Lett. *1970*, 203.

[4] *S. Boué* and *R. Srinivasan*, J. Amer. Chem. Soc. *92*, 3226 (1970).

[5] *R. Srinivasan* and *S. Boué*, J. Amer. Chem. Soc. *93*, 5606 (1971).

[6] *S. Boué* and *R. Srinivasan*, Mol. Photochem. *4*, 93 (1972).

[7] An energy barrier to ring closure has been found for the 2,4-dimethyl-1,3-pentadiene → 1,3,3-trimethylcyclobutene conversion; see *R. Srinivasan* and *S. Boué*, J. Amer. Chem. Soc. *93*, 550 (1971).

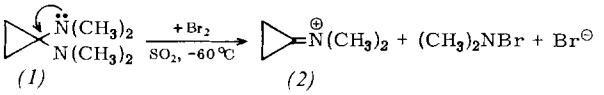
[8] *N. C. Baird*, Mol. Photochem. *2*, 53 (1970); *N. C. Baird* and *R. M. West*, J. Amer. Chem. Soc. *93*, 4427 (1971); *E. M. Evleth*, Chem. Phys. Lett. *3*, 122 (1969); *J. Saltiel*, J. Amer. Chem. Soc. *90*, 6393 (1968), and references therein.

[9] See *N. J. Turro*, Angew. Chem. *84*, 312 (1972); Angew. Chem. internat. Edit. *11*, 331 (1972).

Cations and Radicals from Cyclopropanone Adducts

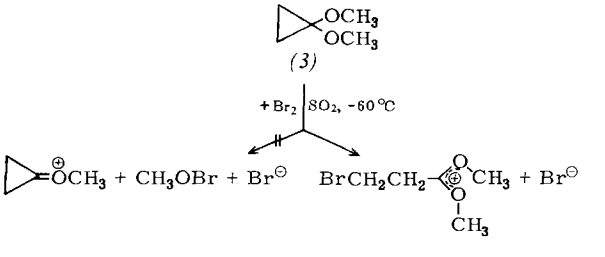
By *Th. J. de Boer*[*]

Cations: Cyclopropyl cations are highly unstable species, existing only when substituted by a *powerful* electron donor such as the dimethylamino group. Such cations are accessible by reaction of cyclopropanone adducts like *(1)* with Lewis acids (*e.g.* Br_2).



(1) *(2)*

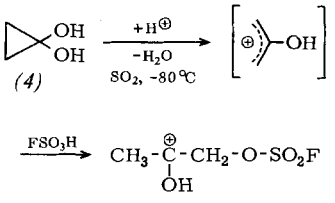
The cyclopropyldimethylimmonium ion *(2)* can be observed clearly in the NMR spectrum. Treatment of the dimethylacetal *(3)* of cyclopropanone with bromine leads exclusively to ring opening. No trace of the closed-ring oxonium ion can be detected, although such ions are easily formed from larger-ring acetals.



(3)

[*] Prof. Dr. Th. J. de Boer
Universiteit van Amsterdam
Laboratorium voor Organische Scheikunde
Nieuwe Achtergracht 129
Amsterdam (The Netherlands)

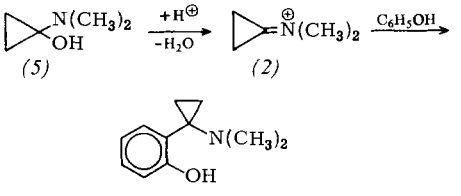
In the cyclopropyl series the tendency to form double bond exocyclic to the positively charged oxygen is apparently extremely low. This is also reflected in the behavior of cyclopropanone [or its hydrate *(4)*] towards strong Brønstedt acids, *e.g.* FSO_3H, at low temperatures. *O*-Protonated cyclopropanone cannot be detected in the



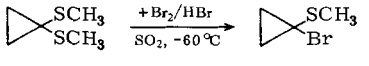
NMR spectrum but ring cleavage again prevails, albeit with rupture of a different C—C bond than in the bromination of the acetal *(3)*.

Disrotatory ring opening of *(4)* leads to the 2-hydroxyallyl cation, not observed in the NMR spectrum because of rapid subsequent reaction with fluorosulfuric acid to give the protonated fluorosulfate of hydroxyacetone[1].

The (mono)-dimethylamine adduct *(5)* of cyclopropanone undergoes Mannich reaction with ketones and (ph)enols, presumably *via* the immonium ion *(2)*.

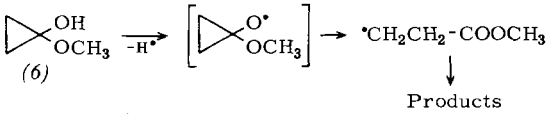


A (non-planar?) cyclopropyl cation stabilized by neighboring sulfur seems to be an intermediate in the reaction of cyclopropanone dithioacetal with bromine.

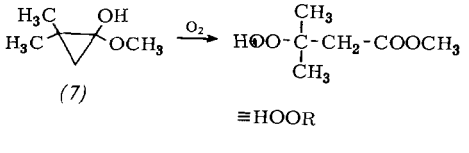


This substitution process is in striking contrast with the ring opening of the acetal *(3)*.

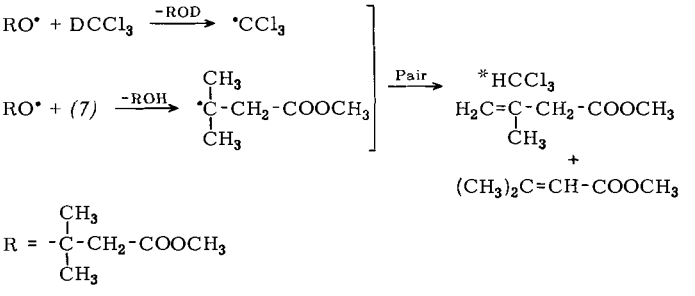
Radicals: Cyclopropanone hemiacetal *(6)* is easily oxidized by metal ions at room temperature, possibly *via* the (never detected) cyclopropyloxy radical.



Reaction of *(6)* with molecular oxygen is slow, but a phenyl group or two methyl groups in the ring [as in *(7)*] have a strong accelerating effect.



When the hemiacetal *(7)* is freshly dissolved in $CDCl_3$ the NMR spectrum shows strong emission signals for $CHCl_3$ after a brief induction period. During this period atmospheric oxygen spontaneously forms a hydroperoxide (ROOH), and this acts as an initiator, generating RO· for various radical processes.



Singlet-triplet mixing within the radical pair explains the emission signal for $CHCl_3$. Under suitable conditions, especially in benzene with added peroxide, absorption/emission multiplets are found for unsaturated products, the nature of which is in full agreement with recent CIDNP theories.

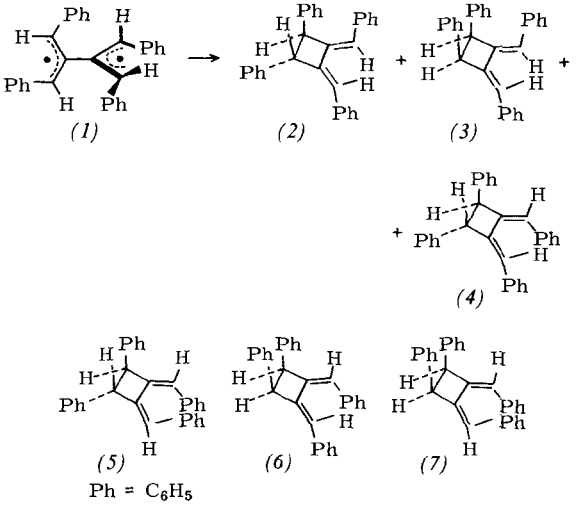
[1] This explanation differs from the one given previously by *G. A. Olah* and *M. Calin*, J. Amer. Chem. Soc. *90*, 938 (1968).

Dimerization of Optically Active 1,3-Diphenylallene

By *E. V. Dehmlow*[*]

Dimerization of allenes to substituted 1,2-bis(methylene)-cyclobutanes is usually formulated as a two-stage process occurring by way of a 2,2'-bis(allyl) radical *(1)* in which the two halves of the molecule are mutually perpendicular[1]. 1,2-Cyclononadiene is the only optically active allene with a high rotation that has been investigated; the results obtained in that case are in line with interpretation as a concerted $[{}_{\pi}2_s + {}_{\pi}2_a]$ reaction[2]. It therefore appeared desirable to study another optically active allene.

The rotation of 1,3-diphenylallene ($[\alpha]_D^{31} = 360°$) in aprotic solvents decreases according to a second-order rate law. The



Ph = C_6H_5

[*] Prof. Dr. E. V. Dehmlow
Organisch-Chemisches Institut der Technischen Universität
1 Berlin 12, Strasse des 17. Juni, No. 135 (Germany)

products are optically inactive; after two half-lives the starting material recovered has unchanged activity. Detailed investigation of the product mixture showed the presence of two new isomers [*(2)* and *(4)*] and clearly higher oligomers as well as the readily crystalline dimer *(3)* previously studied[3,4]. Accordingly, the reaction proceeds through an intermediate of type *(1)*.

A total of six structures *(2)* to *(7)* is possible. Irradiation of the long-known[3] dimer *(3)* in ethereal solution (mercury-vapor high-pressure lamp, Jena glass filter) afforded the three isomers *(5)*—*(7)* still missing. All the structures could be allocated by means of the degradation carried out previously and the NMR spectra. These showed that *(2)*, *(3)*, and *(4)* are formed in approximately equal amounts in the thermal reaction. It is striking that these are the thermodynamically favored isomers, whereas in other cases[1] compounds are obtained with the substituents in sterically unfavorable positions of the exocyclic double bonds. Our results clearly depend on the considerable stabilization of the two halves of the radical in the intermediate *(1)*.

[1] For a review see *J. E. Baldwin* and *R. H. Fleming*, Fortschr. Chem. Forsch. *15*, 281 (1970).

[2] *W. R. Moore*, *R. D. Bach*, and *T. M. Ozretich*, J. Amer. Chem. Soc. *91*, 5918 (1969).

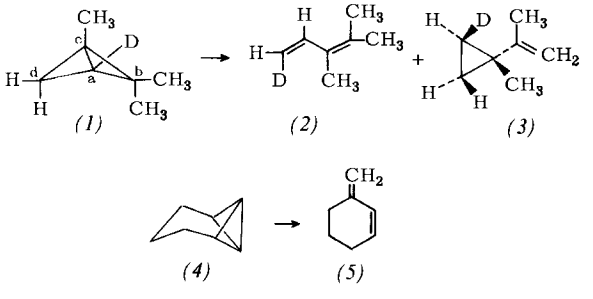
[3] *E. V. Dehmlow*, Chem. Ber. *100*, 3260 (1967).

[4] *H. A. Staab* and *H.-A. Kurmeier*, Chem. Ber. *101*, 2697 (1968).

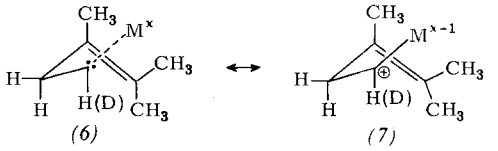
Reactions of Highly Strained Polycyclic Molecules Promoted by Transition Metal Complexes

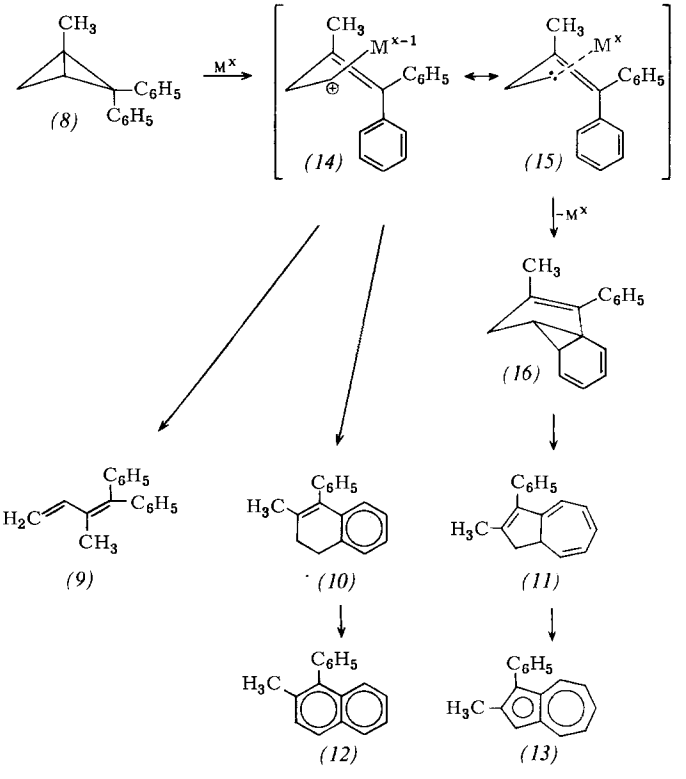
By *Paul G. Gassman*[*]

The catalytic isomerization of highly strained ring systems such as bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, or tricyclo[4.1.0.0^{2,7}]heptane has been shown to proceed at low temperatures in the presence of a variety of transition metal complexes. Examples of these metal-catalyzed rearrangements are the conversion of *(1)* into a mixture of *(2)* and *(3)*, and the isomerization of *(4)* into *(5)*. Both of these isomerizations occur readily at 25 °C in the presence of trace amounts of dicarbonylchlororhodium.



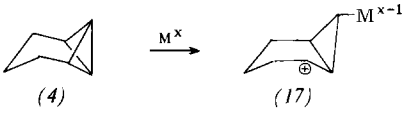
The formation of *(2)* from *(1)* demonstrated that the isomerization involved cleavage of the center (a—c) bond and a side (a—b) bond, accompanied by a hydrogen shift from C_d to C_a. Formally, this transformation can be pictured as occurring *via* the hybrid intermediate represented by the resonance structures *(6)* and *(7)*. Substantial evidence for the carbenoid character of this hybrid intermediate was obtained when 1-methyl-2,2-diphenylbicyclo[1.1.0]butane *(8)* was isomerized by dicarbonylchlororhodium. This rearrangement led to a





mixture of *(9)*, *(10)*, and *(11)*. Addition of chloranil to the crude mixture of rearrangement products converted *(10)* and *(11)* into *(12)* and *(13)*, respectively. Mechanistically, it is assumed that *(8)* is converted into an intermediate represented by the resonance hybrids *(14)* and *(15)*. Carbene type addition to the aromatic ring would then produce *(16)* which on valence tautomerization would furnish *(11)*.

The rearrangement of *(4)* and of its 1-methyl derivative was investigated in detail. It was observed that different metal complexes led to different products. Evidence was obtained which supported the contention that the



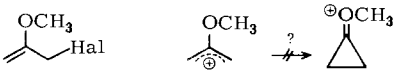
initial step in the isomerization of *(4)* was cleavage of a side bond to yield *(17)*. The fate of *(17)* was a function of M^x. Use of a nucleophilic solvent led to the trapping of *(17)* prior to further rearrangement.

[*] Prof. Dr. P. G. Gassman
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210 (USA)

Cycloadditions and Rearrangements of 2-Oxyallyl Systems

By *H. M. R. Hoffmann*[*]

The hitherto unknown 2-methoxyallyl halides *(1a)*—*(1c)* have been synthesized by two independent routes, *viz.* (i) reaction of 2-methoxypropene with *N*-halosuccinimides



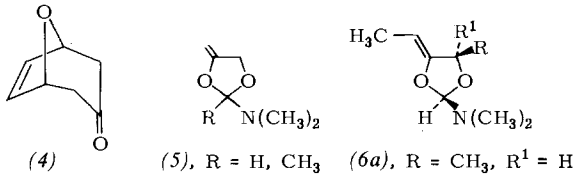
(1a), Hal = Cl
(1b), Hal = Br
(1c), Hal = I

(2)

(3)

and (ii) pyrolysis of 1-halo-2,2-dimethoxypropanes in the presence of a mildly acidic catalyst[1].

Attempts to generate a long-lived 2-methoxyallyl cation *(2)* from *(1b)* under a variety of conditions were unsuccessful owing to the sensitivity of the starting material[2]. However, treatment of 2-methoxyallyl bromide *(1b)* with silver trifluoroacetate in the presence of conjugated dienes and sodium carbonate afforded seven-membered cycloadducts[3]. For example, 8-oxabicyclo-[3.2.1]oct-6-en-3-one *(4)* was obtained in the presence of furan[4]. Reaction of 2-methoxyallyl bromide with



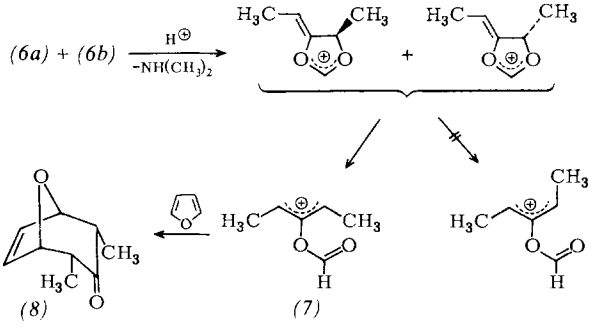
(4)

(5), R = H, CH_3

(6a), R = CH_3, R^1 = H
(6b), R = H, R^1 = CH_3

silver trifluoroacetate in the absence of conjugated diene provided no evidence for an electrocyclic closure to 1-methoxycyclopropyl cation *(3)*.

The debromination of α,α'-dibromoketones with a zinc-copper couple in dimethylformamide and dimethylacetamide yields 2-dimethylamino-4-methylene-1,3-dioxolanes *(5)* in a new and general reaction[5]. The heterocyclics formed, which can be formally regarded as 1,3-dipolar adducts of oxyallyl systems and dimethylformamide, are highly reactive and undergo numerous reactions. For example, on standing at room temperature furan and *(6a)* + *(6b)* furnish exclusively the *cis*-diequatorial adduct *(8)*.



(8)

(7)

[*] Dr. H. M. R. Hoffmann
Department of Chemistry,
University College
London WC1H OAJ (England)

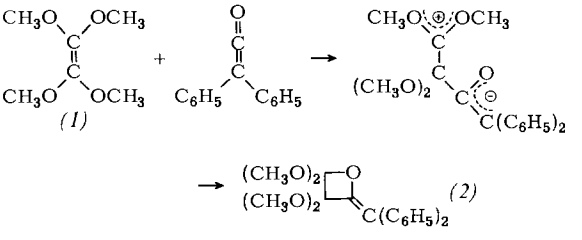
Hence, the intermediate 1,3-dimethyl-2-formoxyallyl cation is generated stereospecifically in the W configuration *(7)* and then combines with furan in a boat-like seven-membered transition state. 2-Oxyallyl cations have also been generated by an organometallic route in the presence of furan and cyclopentadiene, and a bevy of 8-oxabicyclo-[3.2.1]oct-6-en-3-ones and bicyclo[3.2.1]oct-6-en-3-ones has been prepared[6].

[1] *G. Greenwood* and *H. M. R. Hoffmann*, J. Org. Chem. *37*, 611 (1972).
[2] *G. A. Olah et al.*, unpublished work personally communicated.
[3] Cf. *H. M. R. Hoffmann, G. F. P. Kernaghan*, and *G. Greenwood*, J. Chem. Soc. *B 1971*, 2257, and references therein.
[4] *G. Greenwood, A. E. Hill*, and *H. M. R. Hoffmann*, to be published.
[5] *H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt*, and *R. H. Smithers*, J. Amer. Chem. Soc. *94*, (1972), in press.
[6] *H. M. R. Hoffmann, K. E. Clemens*, and *R. H. Smithers*, J. Amer. Chem. Soc., in press.

Reactions of Double Bonds Activated by Methoxy Groups

By *Reinhard W. Hoffmann*[*]

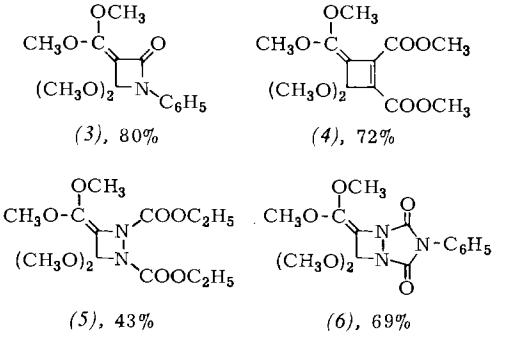
Methoxy-substitution at a π-electron system causes an increase in the π-electron density at the carbon atoms involved. These substances react much more readily with electrophiles than their unsubstituted counterparts. Permethoxy-substitution maximizes this effect, as is demonstrated by the ease with which the electron-rich olefin tetramethoxyethylene *(1)* undergoes cycloadditions to electrophilic double bonds and to heterocumulenes[1]. These [2+2]-cycloadditions appear to be polar two-step processes, as is hinted by the formation of an oxetane *(2)* rather than a cyclobutanone on addition of *(1)* to diphenylketene.



(1)

(2)

These [2+2]-cycloadditions have now been extended to an electron-rich allene, tetramethoxyallene, which had been prepared starting from *(1)*[1]. The following adducts have thus been generated:



(3), 80%

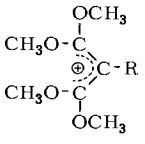
(4), 72%

(5), 43%

(6), 69%

[*] Prof. Dr. R. W. Hoffmann
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

These products most probably also arise in a two-step cycloaddition involving an intermediate tetramethoxyallyl cation *(7)*. Thus the adduct of tetramethoxyallene to tetracyanoethylene equilibrates rapidly at room temperature with the 1,4-dipole *(7a)*[2]. More insight into the behavior of such 1,4-dipoles is provided by a study of the tetramethoxyallyl cation *(7b)* itself, which is generated by protonation of tetramethoxyallene by fluorosulfuric acid. Only one methoxy signal is observed in the NMR spectrum of *(7b)* at 20 °C. Equilibration of the methoxy groups in *(7b)* at −20 °C requires $\Delta G^{+} = 12.7$ kcal. This is probably the barrier to allyl rotation in the cation, rather than that to methoxy rotation.



(7a), R = $C(CN)_2$-$\overset{\ominus}{C}(CN)_2$
(7b), R = H

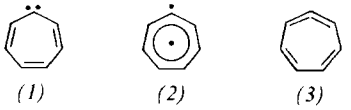
[1] *R. W. Hoffmann*, Angew. Chem. *80*, 823 (1968); Angew. Chem. internat. Edit. *7*, 754 (1968).

[2] *R. W. Hoffmann* and *W. Schäfer*, Angew. Chem. *82*, 700 (1970); Angew. Chem. internat. Edit. *9*, 733 (1970).

Cycloheptatrienylidene: Structure and Role in Carbene-Carbene Rearrangements

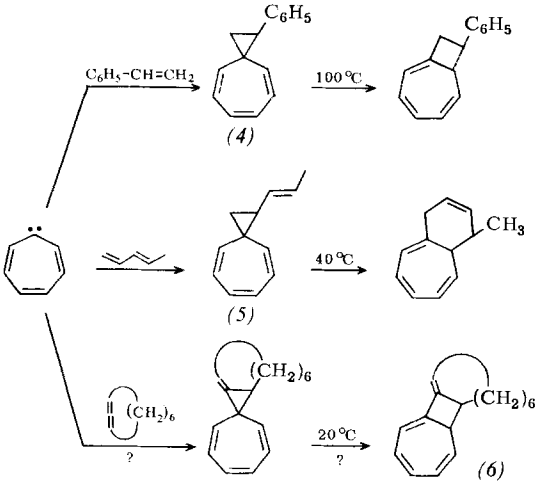
By *W. M. Jones*[*]

Three structures may be envisaged for the intermediate resulting from the photolytic or thermal decomposition of the sodium salt of tropone tosylhydrazone: the singlet carbene *(1)*, the diradical (triplet) *(2)*, and the allene *(3)*.

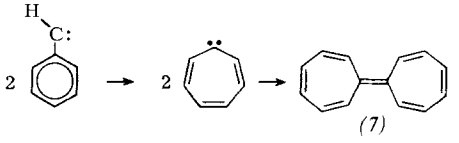


(1) *(2)* *(3)*

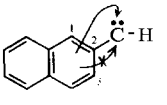
Although earlier results[1] had pointed to the singlet carbene structure, the recent discovery[2] that the low temperature addition of the intermediate to cyclononadiene gives a cyclobutane product *(6)* re-opened the question. However, it has now been found[3] that the cyclopropane ring of the styrene adduct *(4)* expands to a cyclobutane at 100 °C and that of the 1,3-pentadiene adduct expands at 40 °C (half life, *ca.* 30 min). By extrapolation, the cyclononadiene adduct would be expected to expand to the observed product *(6)* under the reaction conditions, thus vitiating the need for the cycloheptatetraene structure *(3)*.



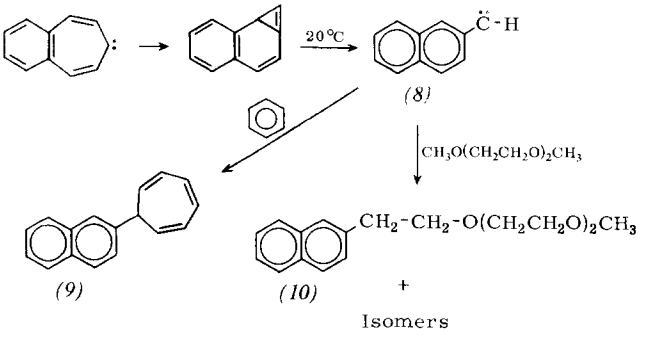
Singlet cycloheptatrienylidenes are also believed to result from carbene-carbene rearrangements of arylcarbenes. For example, in the gas phase, phenylcarbene gives heptafulvalene *(7)*[4], the formal dimer of cycloheptatrienylidene.



Evidence has how been obtained for the assumed[4] cyclopropene mechanism (in contrast to a Wolff zwitterion mechanism) for this rearrangement. Thus, in the gas phase, 3-methyl-2-naphthylcarbene gives over 70% 2-vinylnaphthalene, the product resulting from a two-step rearrangement with initial migration of C-1 of the naphthalene nucleus to the carbene center and net cleavage of the bond between C-1 and C-2. In contrast, 1-methyl-2-naphthylcarbene gives no vinylnaphthalene, the product that would result from migration of C-3 to the carbene center on C-2 with cleavage of the C-2—C-3 bond.



An additional result that is consistent with the cyclopropene mechanism is the facile rearrangement of benzocycloheptatrienylidene to *beta*-naphthylcarbene *(8)*. This rearrangement is extraordinary in that it takes place at low temperatures (as low as room temperature) in solution. The rearranged naphthylcarbene has been identified by its



[*] Prof. Dr. W. M. Jones
University of Florida, Department of Chemistry
Gainesville, Florida 32601 (USA)

[1] *W. M. Jones* and *C. L. Ennis*, J. Amer. Chem. Soc. *91*, 6391 (1969).

[2] *K. G. Untch*, personal communication.

[3] *K. G. Untch*, Syntex; *E. Waali* and *W. M. Jones*, University of Florida.

[4] *R. C. Joines*, *A. B. Turner*, and *W. M. Jones*, J. Amer. Chem. Soc. *91*, 7754 (1969); *P. O. Schissel*, *M. E. Kent*, *M. J. McAdoo*, and *E. Hedaya*, *ibid. 92*, 2147 (1970); *C. Wentrup* and *K. Wilczek*, Helv. Chim. Acta. *53*, 1459 (1970).

reaction products with solvent. For example, both thermal (80 °C) and photolytic (20 °C) decomposition of the salt of benzotropone tosylhydrazone in benzene gives *beta*-naphthylcycloheptatriene *(9)* in good yield. In diglyme, the rearranged carbene gives the expected insertion products such as *(10)*. Possible rearrangement of a carbene precursor has been excluded. These results point to a reaction proceeding through a cyclopropene that is thermally so unstable that, even at room temperature, it undergoes facile ring opening, sacrificing a *sigma* bond to give what is normally considered to be a high energy intermediate, an arylcarbene.

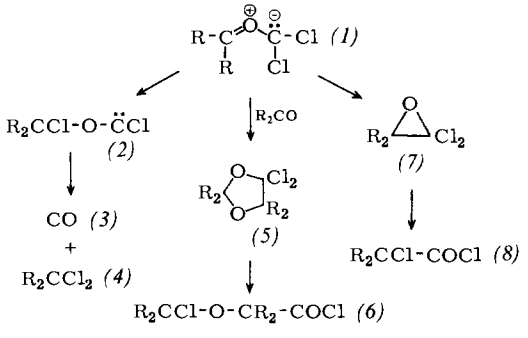
Carbonyl Ylides and Dichlorooxiranes in Carbene Reactions

By *John A. Landgrebe, Charles W. Martin,* and *Erich Rapp*[*]

The treatment of phenyl(bromodichloromethyl)mercury with an excess of either benzaldehyde or benzophenone results in the formation of several products which are most easily rationalized by Scheme 1.

Once formed, carbonyl ylide *(1)* can follow three distinctly different paths. The ylide *(1a)* from benzophenone[1] undergoes ring closure followed by a known type of rearrangement of dichlorooxirane *(7)* to produce chloroacetyl chloride *(8)*, the major product. None of product *(6)* and only a few percent yield of products *(3)* and *(4)* were noted.

In stark contrast, the ylide *(1b)* from benzaldehyde[2] gave substantial yields only of products *(3)*, *(4)*, and *(6)*. The ease with which alkoxyhalocarbenes such as *(2)* lose carbon monoxide is well known[3]. The conversion of *(1)* into *(2)* requires a 90° twist of the CCl_2 group followed by 1,3-migration of halogen. Production of acid chloride *(6)* apparently involves initial 1,3-dipolar addition of benzaldehyde to carbonyl ylide *(1b)* followed by rearrangement of the anticipated dichlorodioxolane *(5)* (not isolated). Attempted independent synthesis of *(5)* resulted only in the formation of *(6)*.



Scheme 1. *(1a)*, R_2CO = benzophenone; *(1b)*, R_2CO = benzaldehyde.

The different behavior of benzaldehyde and benzophenone may be due to the unavoidable steric interactions between the *ortho*-hydrogen and halogen in the carbonyl ylide *(1a)* from benzophenone which promotes rapid conrotatory closure to the oxirane followed by rearrangement to *(8)*.

[*] Prof. Dr. J. A. Landgrebe, C. W. Martin, and E. Rapp
Department of Chemistry, University of Kansas
Lawrence, Kansas 66044 (USA)

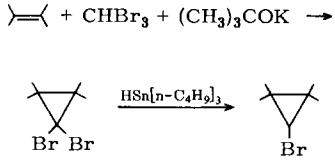
The use of benzaldehyde substituted with strong electron withdrawing and donating substituents supported the rationale of Scheme 1.

[1] *C. W. Martin* and *J. A. Landgrebe*, Chem. Commun. *1971*, 15.
[2] *C. W. Martin, J. A. Landgrebe,* and *E. Rapp*, Chem. Commun. *1971*, 1438.
[3] *J. A. Landgrebe*, Tetrahedron Lett. *1965*, 105, and references cited.

A New Direct Synthesis of Monobromocyclopropanes

By *Bernard Martel* and *Jean Michel Hiriart*[*]

Up until now, the synthesis of monobromocyclopropanes has usually been carried out *via* the reduction of dibromocyclopropanes with tributyltin hydride [eq. (1)][1]; no direct method has been available.



We have now developed a direct method [eq. (2)] using sodium bis(trimethylsilyl)amide which has been shown to be useful in α-elimination reactions[2, 3]. Our results are shown in Table 1.

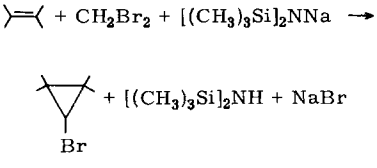
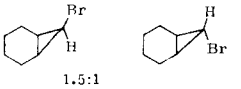
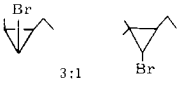
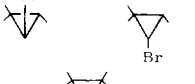
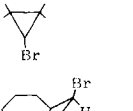
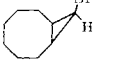
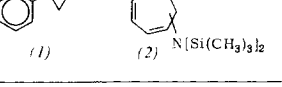
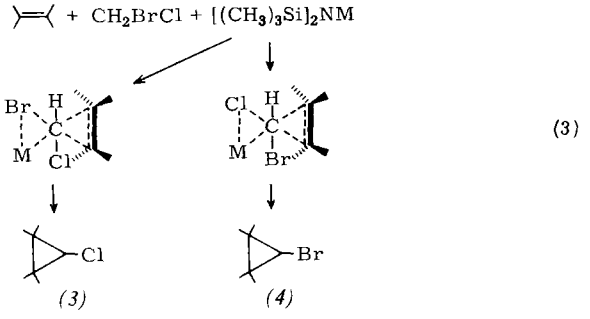


Table 1. Yields of bromocyclopropanes obtained *via* eq. (2).

Alkene	Products	Yield (%)
	 1.5:1	40
	 3:1	30
		50
		45
		40
	 (1) (2) N[Si(CH3)3]2	(1) 25 (2) 6

[*] Dr. B. Martel and J. M. Hiriart
Laboratoire de Chimie Organique associé au C.N.R.S.
Université de Bordeaux I
351, cours de la Libération
F-33 Talence (France)

The use of potassium and lithum bis(trimethylsilyl)amide has also allowed us to study the effects of alkali metals on the behavior of the dihalomethyl-metal intermediates towards the alkenes. Table 2 shows the results obtained when bromochloromethane is used as in eq. (3).



(3)

(3) *(4)*

Table 2. Yields of chloro- *(3)* and bromocyclopropane *(4)* obtained *via* eq. (3).

M	Relative yield (%)	
	(3)	*(4)*
Li	87	13
Na	95	5
K	98	2

The relative rates of addition of intermediate $LiCHBr_2$ and $NaCHBr_2$ to various alkenes are shown in Table 3.

Table 3. Reactivity of dibromomethylsodium and dibromomethyllithium with various alkenes.

Alkene	Reactivity ($k_{alkene}/k_{cyclohexene}$)	
	$NaCHBr_2$	$LiCHBr_2$
	0.68	0.45
	1.20	1.1
	1	1
	1.65	—
	2.3	3.0

We are presently continuing these studies and extending them to various other polyhaloalkanes.

[1] *D. Seyferth, H. Yamazaki* and *D. L. Alleston*, J. Org. Chem. *28*, 703 (1963).

[2] *B. Martel* and *E. Aly*, J. Organometal. Chem. *29*, 61 (1971).

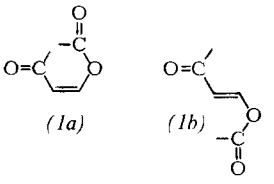
[3] *B. Martel* and *J. M. Hiriart*, Tetrahedron Lett. *1971*, 2737.

Synthesis and Photochemical Behavior of Enone Lactones

By *P. Margaretha*[*]

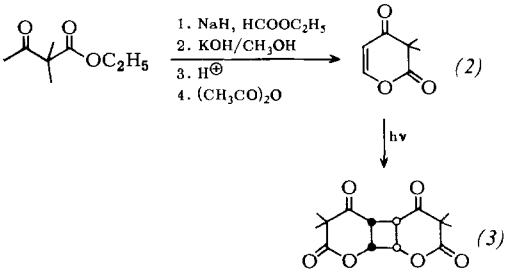
Some results pertaining to the synthesis and photochemical behavior of cyclic alkenes substituted as in *(1a)* and *(1b)* will be discussed.

[*] Dr. P. Margaretha
Max-Planck-Institut für Kohlenforschung, Abt. Strahlenchemie
433 Mülheim/Ruhr, Stiftstrasse 34/36 (Germany)



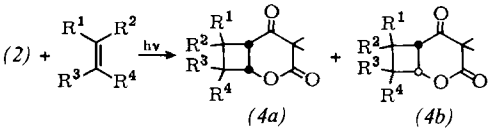
(1a) *(1b)*

As the simplest non-enolizing compound of the type *(1a)*, compound *(2)* was synthesized as follows:



(2) *(3)*

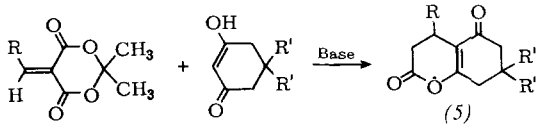
Irradiation of *(2)* in various solvents leads to only one product, which proves to be the HH *cis-anti-cis* dimer *(3)*. Irradiation of *(2)* in the presence of alkenes leads to *cis-* and *trans*-fused oxabicyclooctanes *(4)*. An evident specificity is observed in the orientation of addition.



(4a) *(4b)*

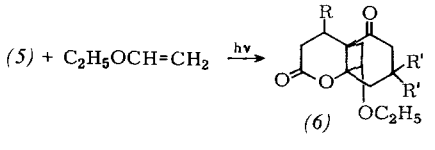
R^1	R^2	R^3	R^4
H	H	OCH_3	OCH_3
H	H	CH_3	CH_3
H	H	H	OC_2H_5
CH_3	CH_3	CH_3	CH_3

Compound *(5)* [as an example of type *(1b)*] is synthesized as follows:



(5)

In contrast to *(2)*, no dimerization was observed on irradiating *(5)* in solution. Cycloaddition leading to substituted propellanes *(6)* took place only with ethyl vinyl ether. The resulting isomers of *(6)* were separated by chromatography on silica gel; however, no precise assignment of configuration could be deduced from their NMR and IR spectra.

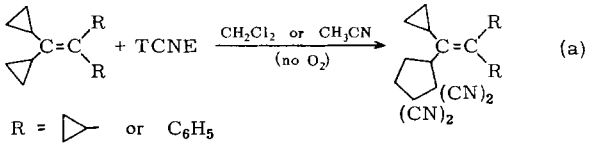


(6)

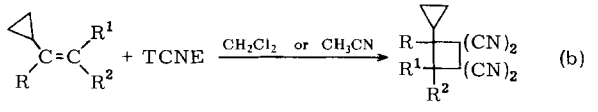
Cycloaddition of Cyclopropylethylenes with Tetracyanoethylene

By *Shinya Nishida*[*]

Cyclopropylethylenes are found to undergo facile cycloadditions with TCNE in two different manners, called type a and type b[1,2]. Type a cycloaddition, observed in the reaction of tetracyclopropylethylene[3] and 1,1-dicyclopropyl-2,2-diphenylethylene, gives a 1:1 cycloadduct formed by cleavage of one of the cyclopropane rings and subsequent incorporation of TCNE. This cycloaddition proceeds smoothly in the absence of oxygen; no charge-transfer color develops in the reaction. Most other cyclopropylethylenes produce charge-transfer color with TCNE and give [2+2]-cycloadducts in high yields (type b cycloaddition).



(a)



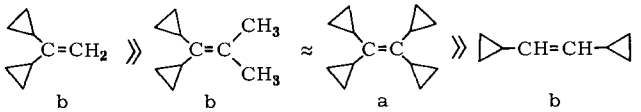
(b)

Type a cycloaddition most probably involves an electron transfer process to give TCNE anion radical (characterized both by electronic absorption spectrum and by ESR) and cyclopropylethylene cation radical. Cyclopropane cleavage could take place at this stage to give a five-membered cycloadduct.

On the other hand, type b cycloaddition could involve a charge-transfer complex as an intermediate, from which the [2+2]-cycloadduct is derived. The addition of excess mesitylene to the solution effectively slows down the reaction rate. In the transition state, there must be considerable charge separation because the rates of type b cycloadditions are influenced by the polarity of the solvent (the same adduct is formed as a single isolable product in all solvents studied, however), and 1,1-dicyclopropylethylene is the alkene of highest reactivity while *cis*- and *trans*-1,2-dicyclopropylethylene are those of lowest reactivity. However, the addition is found to be >90% stereospecific for the latter two compounds.

Steric effects cannot be a single major factor controlling the course of these two types of cycloaddition. Although the two olefins which underwent type a are both tetrasubstituted, 1,1-dicyclopropyl-2-methylpropene, which is also a tetrasubstituted ethylene, produces a blue solution with TCNE and yields a [2+2]-cycloadduct as the sole product.

The relative reactivity sequence of representative alkenes



b b a b

shown also supports this conclusion. Tetracyclopropylethylene is moderately reactive in cycloaddition with TCNE, and 1,2-dicyclopropylethylene reacts slowly. The fact that no charge-transfer color can be seen in type a cycloaddition suggests that these particular olefins have substantially low ionization potentials which makes the species formed by electron transfer more stable than a charge-transfer complex. In fact, cyclopropylethylenes are found to be alkenes of notably low ionization potential. For example, 1,1-dicyclopropylethylene has an *IP* of 8.08 eV[4] which is even lower than that of 1,3,5-hexatriene (8.26 eV)[5].

[*] Prof. S. Nishida
Hokkaido University, Department of Chemistry
Sapporo, Hokkaido (Japan)

[1] *S. Nishida, I. Moritani,* and *T. Teraji,* Chem. Commun. *1970,* 501.

[2] *S. Nishida, I. Moritani,* and *T. Teraji,* Chem. Commun. *1971,* 36.

[3] *S. Nishida, I. Moritani, E. Tsuda,* and *T. Teraji,* Chem. Commun. *1969,* 781.

[4] *S. Nishida,* to be published.

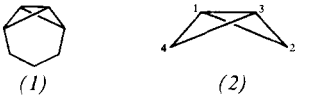
[5] *W. C. Price* and *A. D. Walsh,* Proc. Roy. Soc. (London) *A 174,* 220 (1940).

Catalysis of Strained σ-Bond Rearrangements by Silver(I) Ion

By Leo A. Paquette[*]

First recognized in 1969[1], the ability of Ag^+ ion to induce skeletal bond reorganizations of highly strained molecules lacking sites of unsaturation has quickly become established as a viable and fruitful area of research. Appealing because of their mechanistic import and synthetic potential, such transition metal-promoted rearrangements have given evidence of a strong undercurrent of interest.

In the specific case of bicyclo[1.1.0]butane isomerizations, kinetic studies[2] have revealed that bicyclobutane-Ag^+ complexes are definitive intermediates. Several equilibrium constants have now been measured and the experimentally derived values ($K = 0.29$—1.0 *vs.* benzene) reveal that the extent of complex formation is substantial. The activation parameters associated with a typical rearrangement (*e.g.*, of tricyclo[4.1.0.0^{2,7}]heptane *(1)* to 1,3-cycloheptadiene), $\Delta H^{\neq} = 18.5$ kcal mol^{-1}, $\Delta S^{\neq} = -11.5$ kcal mol^{-1}, accord well with subsequent rate-determining isomerization of the complex. Various degrees of alkyl substitution of the bicyclobutane nucleus *(2)* and the specific location of such groups are recognized to promote substantial alterations in which bond cleavages are kinetically dominant[3]. Generally speaking, positioning of substituents at C-2 and C-4 is seen to reinforce the propensity of the parent system for C-1—C-2 and C-3—C-4



(1) *(2)*

("double edge") bond cleavage. Contrariwise, substitution of the bridgehead positions promotes rupture of the central bond and one edge bond. In acuatl fact, the situation is considerably more complex. Structural[4] and deuterium isotope effect considerations[5] give evidence of the fact that "double edge" rupture is reconcilable with a model

[*] Prof. Dr. L. A. Paquette
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210 (USA)

in which Ag^+ inserts oxidatively into one of these bonds, followed by ring opening of the coordinated cyclopropylmethyl cation so produced and loss of Ag^+.

However, when a substituent resides at C-1, the first-formed intermediate now undergoes preferential central bond cleavage to generate a stabilized (tertiary) argento carbonium ion[3–5]. Such entities most frequently suffer subsequent 1,2-hydride shift (where structurally possible) and ejection of Ag^+. In an overall sense, this latter pathway bears many similarities to a reverse carbenoid addition to a double bond. Interestingly, it apparently gains prominence only when the formation of a tertiary argento carbonium ion can be realized.

With certain substitution patterns, cyclobutene derivatives are also produced. This rearrangement mode has been found to be subject to a primary deuterium isotope effect[5]. The magnitude of this effect suggests that such deep-seated chemical changes are triggered by migration of hydrogen (or deuterium) from C-3 to C-1 in the rate-determining transition state. Clearly, additional work is required before all of the mechanistic ramifications of Ag^+ catalysis are thoroughly understood. On the basis of the foregoing, however, there is little doubt that such phenomena will comprise an exciting new area of physical organic chemistry.

[1] *L. A. Paquette* and *J. C. Stowell*, J. Amer. Chem. Soc. *92*, 2584 (1970).

[2] *L. A. Paquette, S. E. Wilson*, and *R. P. Henzel*, J. Amer. Chem. Soc. *93*, 1288 (1971).

[3] *L. A. Paquette*, Accounts Chem. Res. *4*, 280 (1971).

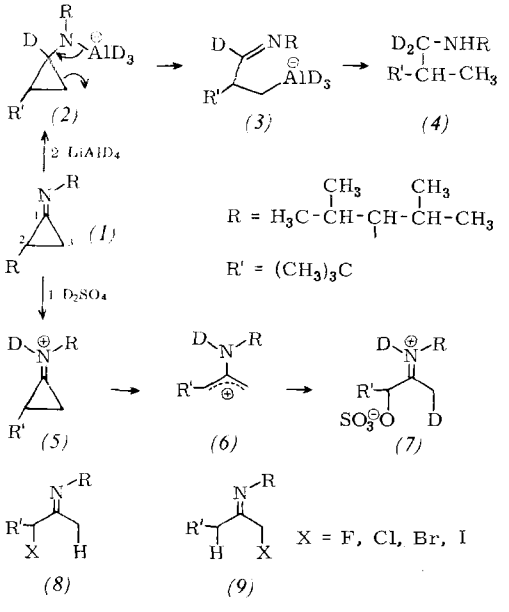
[4] *L. A. Paquette, R. P. Henzel*, and *S. E. Wilson*, J. Amer. Chem. Soc. *93*, 2335 (1971).

[5] *L. A. Paquette* and *S. E. Wilson*, J. Amer. Chem. Soc. *93*, 5934 (1971).

Cyclopropanimines

By *Helmut Quast, Rolf Frank*, and *Edeltraud Schmitt*[*]

A high yield synthesis of the cyclopropanimine *(1)* *via* a 1,3-elimination of HBr from *(8)* (X = Br) and several ring-opening reactions of this novel heteroanalog of methylenecyclopropane was reported[1].



Attack on C-1 by nucleophiles (KOH, $LiAlD_4$) is followed by a regiospecific 1,3-bond cleavage: After two days' refluxing two moles of $LiAlD_4$ in ether gave 80—90% of *(4)*. The isomerization *(2)* → *(3)* has a precedent in the cyclopropylmethyl carbanion rearrangement and in the base catalyzed ring opening of cyclopropanones in the Favorskii reaction.

In contrast, reaction with strong acids under mild conditions yields products of 2,3-bond cleavage. One mole of D_2SO_4 in methylene chloride smoothly converted *(1)* into the zwitterion *(7)* in 87—95% yield. Hydrogen halides in CH_2Cl_2 afford (only after addition of HSO_3F in the case of HF) 66—85% yields of the α-halo imines *(8)* and *(9)*, the ratio of isomers [*(8)*:*(9)* = 94:6 (F), 94:6 (Cl), 91:9 (Br), 93:7 (I)] proving to be independent of the nucleophilicity of the anion. This reaction is best rationalized in terms of disrotatory ring opening of *(5)*. Apparently, cyclopropanimines behave as convenient, leaving-group-free precursors of 2-aminoallyl cations [*e.g. (6)*].

[1] Cf. *H. Quast, E. Schmitt*, and *R. Frank*, Angew. Chem. *83*, 728 (1971); Angew. Chem. internat. Edit. *10*, 651 (1971).

[*] Doz. Dr. H. Quast, Dipl.-Chem. R. Frank, and Edeltraud Schmitt
Institut für Organische Chemie der Universität
87 Würzburg, Landwehr (Germany)

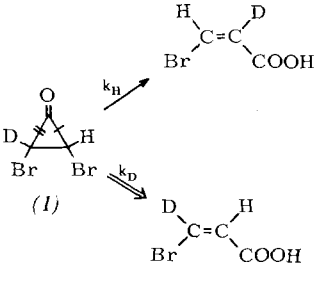
Cyclopropanones and the Favorskii Rearrangement. An Unexpectedly Large Secondary Isotope Effect

By *Christoffer Rappe* and *Leif Knutsson*[*]

Some years ago one of us found that treatment of 1,1,3-trihaloacetones with aqueous bases yielded *cis*-3-haloacrylic acids in 60—75% yield[1]. Further details of the reaction and its mechanism were revealed by experiments in a deuterating solvent (D_2O)[2]. We found that both the product and the starting bromo ketone were considerably deuterated. Furthermore, ^{1}H-NMR analyses of the product showed that the amount of deuterium incorporated in the α- and β-positions was unequal. The mean value from eight determinations of recrystallized acid gave α−H/β−H = 0.86. This can be rationalized in two ways:

1) an unsymmetric mechanism in the rearrangement;

2) an α-secondary isotope effect ($k_H/k_D = 1.6$—1.7) in the fission of the monodeuteriodibromocyclopropanone *(1)*.



We have now studied the rearrangement mechanism using ^{13}C-labeled starting compound. [3-^{13}C]-1,1,3-Tribromoacetone was prepared according to known methods

[*] Prof. Dr. C. Rappe and Dr. L. Knutsson
Institute of Chemistry, University of Umeå
S-901 87 Umeå (Sweden)

from sodium [2-^{13}C]-acetate[3]. If we neglect the small $^{12}C/^{13}C$-isotope effect and assume that the symmetric cyclopropanone mechanism is the only mechanism operating, we can predict an equal labeling in the 2- and 3-positions.

^{13}C-NMR spectroscopy provides a reliable method for the determination of the [2-^{13}C]-acid/[3-^{13}C]-acid ratio. The shifts were found to be 62.0 ppm (2-C) and 66.2 ppm (3-C) ($CS_2 = 0$). The ratio [2-^{13}C]/[3-^{13}C] was estimated to be 1.0 ± 0.1. Therefore only a symmetric cyclopropanone mechanism is operating in the rearrangement and the unexpected deuterium labeling can only be rationalized as due to an α-secondary isotope effect in the opening of the cyclopropanone ring. This value, $k_H/k_D = 1.6$—1.7, is an unusually large value for an α-secondary isotope effect with only one deuterium in the molecule[4-6]. One explanation for this could be the special conditions encountered in the cyclopropanone ring system.

We have also investigated the rearrangement using synthetically prepared 3,3-dideuterio-1,1,3-tribromoacetone. In this experiment we obtained the same value for the isotope effect.

[1] *C. Rappe*, Acta Chem. Scand. *19*, 31 (1965).

[2] *C. Rappe* and *L. Knutsson*, Acta Chem. Scand. *22*, 2910 (1968).

[3] *F. Weygand* and *O. P. Swoboda*, Chem. Ber. *89*, 18 (1956).

[4] *L. Melander*: Isotope Effects on Reaction Rates. Ronald, New York 1960, p. 87.

[5] *E. A. Halevi*, Progr. Phys. Org. Chem. *1*, 109 (1963).

[6] *J. March*: Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. McGraw-Hill, New York 1968, p. 215.

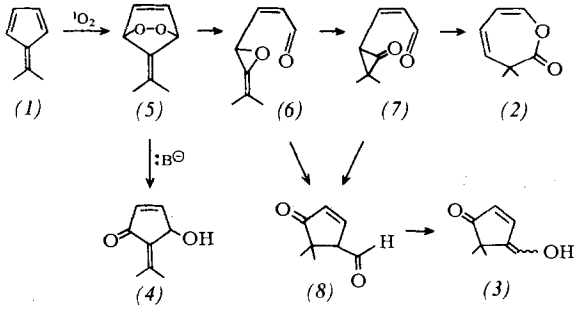
Dye-Sensitized Photooxygenation of 6,6-Dimethylfulvene: a New 1,2-Dioxolane Rearrangement

By *W. Skorianetz*, *K. H. Schulte-Elte*, and *G. Ohloff*[*]

The dye-sensitized photooxygenation of 6,6-dimethylfulvene *(1)* in solution at 15—20°C affords mainly (total yield 70%) the products *(2)*, *(3)*, and *(4)*[1].

The proportions in which they are produced depends greatly on the polarity and/or basicity of the solvent. In methylene chloride the enol lactone *(2)* but in pyridine the ketol *(4)* is formed as the main product. The structures of compounds *(2)*, *(3)*, and *(4)* were proved by chemical and physical methods.

A peroxide could be detected (KI/glacial acetic acid) after a photooxygenation carried out at −30°C. Thus *(2)*, *(3)*, and *(4)* are probably obtained by rearrangement of the 6,6-dimethylfulvene *endo*-peroxide *(5)*, which can be considered also as a 1,2-dioxolane. The annexed reaction course is suggested to explain the formation of *(2)*, *(3)*, and *(4)*.



(1) *(5)* *(6)* *(7)* *(2)* *(4)* *(8)* *(3)*

In a basic medium isomerization of *(5)* yields mainly the ketol *(4)* (Kornblum-de la Mare reaction). In an apolar medium (*e.g.* in CH_2Cl_2) *(5)* rearranges, in analogy to other 1,2-dioxolanes[2], with ring opening to afford the allene peroxide *(6)*, which in turn isomerizes to the cyclopropane derivative *(7)*. In a subsequent, new, probably electrocyclic reaction, *(2)* is then produced. *(3)* can arise by cyclization from *(6)* or *(7)* without participation of the aldehyde group. The keto aldehyde *(8)* first formed can be isolated in crystalline form as the enol *(3)*.

[*] Dr. W. Skorianetz, Dr. K. H. Schulte-Elte, and Dr. G. Ohloff
Firmenich & Cie, Forschungslaboratorium
CH-1211 Genève 8 (Switzerland)

[1] *W. Skorianetz*, *K. H. Schulte-Elte*, and *G. Ohloff*, Helv. Chim. Acta *54*, 1913 (1971).

[2] *K. H. Schulte-Elte*, *B. Willhalm*, and *G. Ohloff*, Angew. Chem. *81*, 1045 (1969); Angew. Chem. internat. Edit. *8*, 985 (1969).

Insights into Small Ring Carbocations Provided by MO Calculations

By *P. v. R. Schleyer*[*]

Very little is known experimentally about the detailed structure of carbocations. Molecular orbital calculations provide a means of obtaining such information[1-8] and inspire experimental tests of the conclusions reached[9-13]. A collaborative program of such calculations has been undertaken with Prof. *L. C. Allen*, Princeton[1-4], and especially with Prof. *J. A. Pople* and Dr. *Leo Radom*, Carnegie Mellon University[3,5-8].

Early experience revealed that semi-empirical (valence electron) treatments (CNDO, MINDO, NDDO) artificially favored small ring structures[2]; therefore, such methods were rejected for general use. *Pople*'s *ab initio* (all electron) procedure employs a complete geometry search with a minimal basis set (STO-3G); improved energies are obtained by use of a more extended basis set (4-31G). Results of this procedure, while not perfect, are in good agreement with the available experimental data. Some of the more important of the conclusions reached are the following:

1. Distortion of the methyl species, $(H_a)_2CH_b$, produces a different effect in the cation than in the anion and free radical[1,4]. Going from a 120° to a 90° H_aCH_a angle increases the inversion barrier in the methyl anion, and favors a non-planar structure for the methyl radical. However, such 90° distortion *raises* the out-of-plane $C\text{-}H_b$ bending force constant of the methyl cation.

2. "Classical", rather than proton bridged structures, are preferred for the ethyl and more strongly for the vinyl cations[2,3]. The latter are more stable in linear than bent arrangements[9]. However, the most stable structure for the ethyl cation is distorted, and has a slightly non-planar arrangement at the carbocation center[3]. Despite the strong tendency of carbonium ions toward planarity, this is possible only when symmetry permits.

3. Contrary to the usual literature assumptions, C—C hyperconjugation is appreciably more important than C—H hyperconjugation[5,6,8,10]. Hyperconjugation is

[*] Prof. Dr. P. v. R. Schleyer
Department of Chemistry
Princeton University, Princeton, New Jersey 08540 (USA)

enhanced when the C—C bonds are strained, as in the bisected conformations of the cyclopropylmethyl and cyclobutylmethyl cations. The perpendicular conformation of only the latter is stabilized also[11], and a relatively low rotational barrier results.

4. The isopropyl cation is the most stable $C_3H_7^+$ species[7, 8]. The *n*-propyl cation, corner protonated cyclopropane, and a strange, highly distorted structure with an 83° C—C—C bond angle, all have comparable energies, but only the last is a minimum on the energy surface[7, 8]. These results emphasize the arbitrary nature of "classical" and "nonclassical" designations of carbonium ions. Edge protonated cyclopropane is less stable than any of these structures, and face protonation is very unfavorable[12].

5. Bridged and non-bridged carbonium ions have quite different 1s orbital energies[8], confirming conclusions reached recently by *Olah* from ESCA spectroscopy[13]. This provides the most direct experimental way of distinguishing between these structural types[13].

[1] *J. E. Williams, Jr., R. Sustmann, L. C. Allen,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *91*, 1037 (1969).

[2] *R. Sustmann, J. E. Williams, M. J. S. Dewar, L. C. Allen,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *91*, 5350 (1969).

[3] *J. E. Williams, Jr., V. Buss, L. C. Allen, P. v. R. Schleyer, W. A. Lathan, W. J. Hehre,* and *J. A. Pople,* J. Amer. Chem. Soc. *92*, 2141 (1970).

[4] *V. Buss, P. v. R. Schleyer,* and *L. C. Allen,* J. Amer. Chem. Soc. *94*, in press (1972).

[5] *L. Radom, J. A. Pople, V. Buss,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *92*, 6380 (1970).

[6] *L. Radom, J. A. Pople, V. Buss,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *92*, 6987 (1970).

[7] *L. Radom, J. A. Pople, V. Buss,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *93*, 1813 (1971); *94*, 311 (1972).

[8] *L. Radom, J. A. Pople,* and *P. v. R. Schleyer,* unpublished observations.

[9] *W. D. Pfeifer, C. A. Bahn, P. v. R. Schleyer, S. Boche, C. E. Harding, K. Hummel, M. Hanack,* and *P. J. Stang,* J. Amer. Chem. Soc. *93*, 1513 (1971).

[10] *R. C. Bingham* and *P. v. R. Schleyer,* Tetrahedron Lett. *1971*, 23; J. Amer. Chem. Soc. *93*, 3189 (1971).

[11] *P. v. R. Schleyer* and *V. Buss,* J. Amer. Chem. Soc. *91*, 5880 (1969); *V. Buss, R. Gleiter,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *91*, 5880 (1969); *V. Buss, R. Gleiter,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *93*, 3927 (1971); cf. *B. Ree* and *J. C. Martin,* J. Amer. Chem. Soc. *92*, 1660 (1970).

[12] *R. C. Bingham, W. F. Sliwinski,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc. *92*, 3471 (1970); *S. A. Sherrod, R. G. Bergman, G. J. Gleicher,* and *D. Morris,* J. Amer. Chem. Soc. *92*, 3469 (1970).

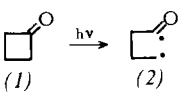
[13] *G. A. Olah, G. D. Mateescu, L. A. Wilson,* and *M. H. Gross,* J. Amer. Chem. Soc. *92*, 7231 (1970) and private communication.

Photoreactions of Cyclobutanones in Solution

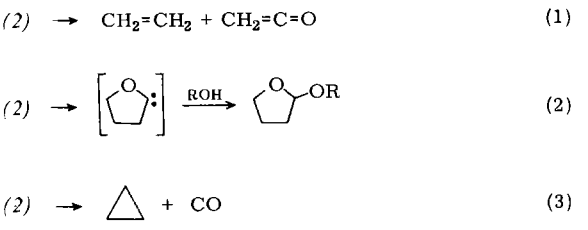
By *Nicholas J. Turro*[*]

The photochemistry of cyclobutanone and its derivatives possesses some unique opportunities for mechanistic and synthetic study. To date, essentially all of the photoreactions of cyclobutanones in solution are understandable on the basis of one primary photochemical process (homolytic cleavage of the bond α to the excited carbonyl) from the singlet state. Thus, for cyclobutanone the biradical *(2)* is produced and the products derived from it are listed

[*] Prof. Dr. N. J. Turro
Department of Chemistry
Columbia University
New York, New York 10027 (USA)



(1) *(2)*



(1)

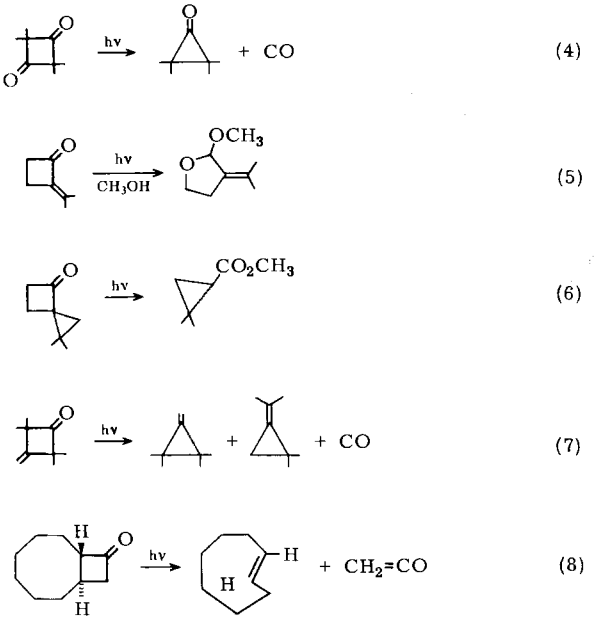
(2)

(3)

in eq. (1), (2), and (3), namely cycloelimination [eq. (1)], ring expansion [eq. (2)], and decarbonylation [eq. (3)].

Structural-reactivity studies reveal that (a) in asymmetrically substituted cyclobutanones, the most highly substituted α-C—CO bond breaks preferentially; (b) ring expansion is favored by substitution of electron releasing groups on the α-carbon and by the occurrence of an sp^2 carbon on the α-carbon; (c) cycloelimination and decarbonylation, while general reactions, do not display a clear cut structural dependence; (d) each of the processes. cycloelimination, ring expansion, and decarbonylation are stereospecific and stereoselective.

Some examples of special synthetic interest are listed in eq. (4)—(8).



(4)

(5)

(6)

(7)

(8)

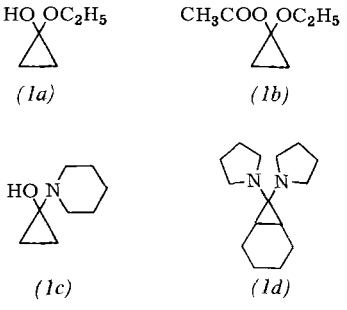
With respect to the mechanism of these reactions, it is important to note that some of the absorbed photons do not lead to observable reactions. This observation, when coupled with the high stereospecificity of these reactions, leads us to suggest that the biradical *(2)* is indeed formed, but that it closes to regenerate the starting material in competition with cycloelimination, ring expansion, and decarbonylation. All of these processes, however, must be assumed to be faster than bond rotations. The use of the technique of energy balance (*i.e.*, photons in *versus* product molecules out) may thus be employed to detect otherwise "chemically invisible" intermediates, such as *(2)*.

Recent Aspects of Cyclopropanone Chemistry

By *Harry H. Wasserman*[*]

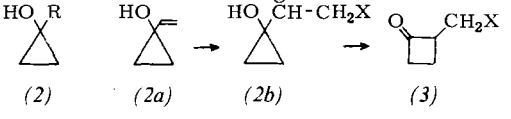
Cyclopropanones, incorporating the carbonyl group in a small, strained ring, are reactive compounds of considerable potential use in synthesis. Thus far, exploration of their chemistry has been limited by the inaccessibility of these ketones since they tend to undergo decomposition or polymerization during attempts to obtain them in the pure state.

It is possible, however, to observe reactions of cyclopropanes by generating them *in situ* from pure, isolable, labile intermediates such as hemiacetals, hemiacetal acetates, 1-amino alcohols, or 1,1-diamino derivatives [examples of which are given *(1a)*—*(1d)*].



(1a) *(1b)* *(1c)* *(1d)*

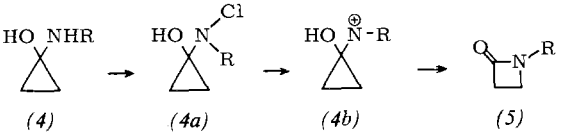
Thus, reaction of *(1a)* or *(1b)* with two moles of $LiAlH_4$ yields cyclopropanol, while, with a wide variety of Grignard reagents, 1-substituted cyclopropanols *(2)* can be obtained.



(2) *(2a)* *(2b)* *(3)*

1-Vinylcyclopropanol, prepared in this way, is a particularly useful cyclopropanol derivative since it may react with electrophilic reagents (X^+) including H^+, OH^+, Cl^+, or $CH_2^+—N(C_2H_5)_2$ to form cyclobutanones *(3)*.

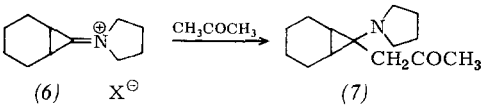
By reaction with azide ion at pH 5.5, cyclopropanone precursors such as *(1a)* and *(1d)* yield β-lactams. This ring enlargement reaction has recently been made generally useful for the preparation of *N*-substituted β-lactams by the following modification: Secondary amines are added to the solution containing the cyclopropane (diazomethane and ketene in methylene chloride at −78 °C) to form an intermediate unstable 1-amino alcohol *(4)*, which is then converted into the *N*-chloro derivative *(4a)* by addition of *tert*-butyl hypochlorite. Treatment of *(4a)* with silver ion in acetonitrile yields the lactam *(5)* presumably through the nitrenium ion *(4b)*.



(4) *(4a)* *(4b)* *(5)*

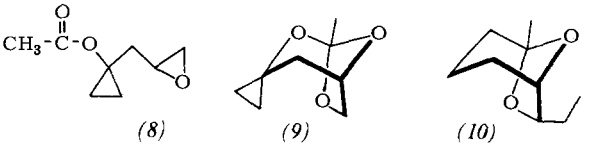
[*] Prof. Dr. H. H. Wasserman
Department of Chemistry
Yale University
New Haven, Connecticut 06520 (USA)

Other reactions of 1-aminocyclopropanes appear to take place *via* highly reactive cyclopropyliminium salts. Thus the fused-ring cyclopropyl derivative *(6)* reacts readily with acetone (or nitromethane) to form condensation products of type *(7)*.



(6) *(7)*

During studies on 1-allylcyclopropanol it was observed that the epoxy acetate *(8)* undergoes ready thermal conversion to the bicyclo[3.2.1]octane derivative *(9)*. This thermal isomerization has been shown to be a general method for the rearrangement of δ,ε-epoxy ketones to dioxabicyclo[3.2.1]octane systems and other hetero analogs, and has been employed in the synthesis of insect pheromones such as brevicomin *(10)*.



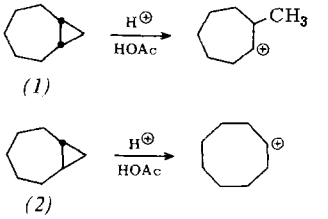
(8) *(9)* *(10)*

Bicyclic and Tricyclic Small Ring Compounds

By *Kenneth B. Wiberg*[*]

The past ten years have provided a number of remarkable examples of angular deformation of bonds to carbon. Two recently studied cases have been the *trans*-fused bicyclo[*n*.1.0]alkanes and the small ring propellanes. In both types of compounds the strain is especially localized at one carbon-carbon bond, and would be expected to lead to unusual reactivity.

We may first compare *cis*- and *trans*-bicyclo[6.1.0]-nonane with *cis*- and *trans*-cyclooctene. The former have been found to have the same heats of formation[1], whereas the latter differ in energy by 9 kcal/mole[2]. Thus cyclopropane rings are considerably better in tolerating *trans*-fusion than are double bonds. *trans*-Bicyclo[5.1.0]octane *(2)* is considerably more reactive toward electrophiles than *cis*- or *trans*-bicyclo[6.1.0]nonane[3]. Of more significance, whereas *cis*-bicyclo[5.1.0]octane *(1)* undergoes acetolysis with cleavage of one of the external cyclopropane bonds, *(2)* reacts predominantly by cleavage of the central bond.

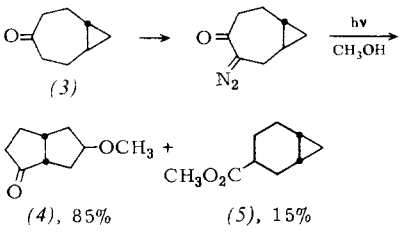


(1) *(2)*

An attempt was made to prepare a *trans*-bicyclo[4.1.0]-heptane *via* ring contraction of a ketone *(3)* related to *(2)*[4]. However, the products were partially rearranged to a

[*] Prof. Dr. K. B. Wiberg
Department of Chemistry, Yale University
New Haven, Connecticut 06520 (USA)

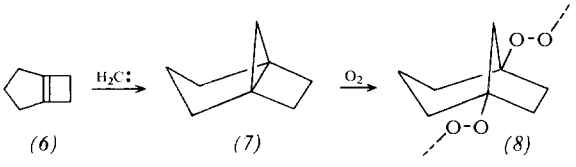
bicyclo[3.3.0]octane derivative *(4)*, and the resulting bicyclo[4.1.0]heptane *(5)* had a *cis*-ring junction. It is possible that the *trans* derivative is first formed, and rearranges to the *cis* compound *(5)* by a process similar to the interconversion of *cis*- and *trans*-[1,2-D_2]-cyclopropane[5]. Strain energy calculations suggest that the strain



(3) *(4)*, 85% *(5)*, 15%

in *trans*-bicyclo[4.1.0]heptane may be sufficient to permit the *trans-cis* isomerization to occur readily.

The smallest propellane prepared to date is tricyclo-[3.2.1.$0^{1,5}$]octane *(7)*[6]. It was prepared by the addition of a carbene to bicyclo[3.2.0]hept-1(5)-ene *(6)*. The structure of *(7)* is unique in that the bridgehead carbons have an "inverted" tetrahedral geometry[7]. Thus, a plane through the three methylene carbons attached to a bridgehead will intersect the central carbon-carbon bond. It is not surprising that this is one of the most reactive of known C—C single bonds. Thus, *(7)* reacts with oxygen spontaneously at room temperature to form a 1:1 copolymer *(8)*.



(6) *(7)* *(8)*

The hydrocarbon *(7)* also reacts with a variety of electrophiles at high rates even at low temperatures. It is, however, remarkably stable thermally ($t_{1/2}$ = 20 h at 200 °C). This results from a combination of orbital symmetry restrictions and the difficulty of forming double bonds to the bridgehead in a bicyclo[3.2.1]octane.

The propellane *(7)* may be prepared by the reduction of 1,4-dibromobicyclo[3.2.1]octane under dissolving metal conditions. However, attempts at preparing smaller propellanes *via* this procedure failed. It is hoped that the recently prepared bicyclo[2.2.0]hex-1(4)-ene[8] will serve as a satisfactory reactant for the preparation of some of these compounds.

[1] *E. C. Lupton, Jr.*, unpublished results, this laboratory.

[2] *R. B. Turner* and *W. R. Meador*, J. Amer. Chem. Soc. *79*, 4133 (1957).

[3] *K. B. Wiberg* and *A. de Meijere*, Tetrahedron Lett. *1969*, 519.

[4] *A. de Meijere*, unpublished results, this laboratory.

[5] *B. S. Rabinovitch, E. W. Schlag*, and *K. B. Wiberg*, J. Chem. Phys. *28*, 504 (1958).

[6] *K. B. Wiberg, J. E. Hiatt*, and *G. J. Burgmaier*, Tetrahedron Lett. *1968*, 5855; *K. B. Wiberg* and *G. J. Burgmaier*, Tetrahedron Lett. *1969*, 317; *P. A. Gassman, A. Topp*, and *J. W. Keller*, Tetrahedron Lett. *1969*, 1093.

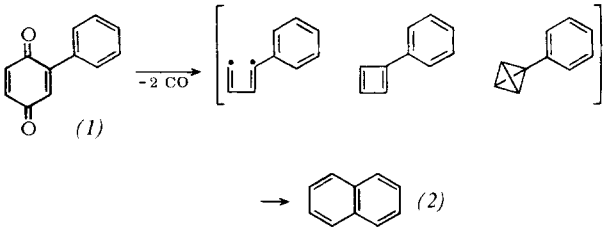
[7] *K. B. Wiberg, G. J. Burgmaier, K. Shen, S. J. La Placa, W. C. Hamilton*, and *M. D. Newton*, J. Amer. Chem. Soc. *94* (1972), in press.

[8] *K. B. Wiberg, G. J. Burgmaier*, and *P. Warner*, J. Amer. Chem. Soc. *93*, 246 (1971).

Flash-Vacuum Thermolysis of *p*-Benzoquinones

H. J. Hageman and *U. E. Wiersum*[*]

It was recently found[1] that flash-vacuum thermolysis of phenyl-*p*-benzoquinone *(1)* occurs with loss of two CO molecules. Naphthalene *(2)* was obtained as the major product (54% of converted starting material). The formation of *(2)* was visualized, in analogy with mass spectral data[2], to take place *via* intramolecular trapping of either a butadiene diradical, a cyclobutadiene, or a tetrahedrane by the phenyl group.



(1) *(2)*

The present contribution deals with the flash-vacuum thermolysis of *p*-benzoquinone *(3)* itself[3]. Loss of two CO molecules from *(3)* implies formation of a C_4H_4 species. The structure of such a species is of interest because cyclobutadiene and tetrahedrane are possible candidates, although there is evidence that vinylacetylene is a more stable isomer[4, 5].

If CO molecules are expelled stepwise, cyclopentadienone must also be considered as a transient intermediate. It has been reported[6] that the flash-vacuum thermolysis of *o*-benzoquinone gives a fair yield of 4,7-methano-3a,4,7,-7a-tetrahydroindene-1,8-dione, indicating that in this type of thermolysis the transient cyclopentadienone dimerizes rather than losing a further CO molecule.

The thermolysis of *p*-benzoquinone was carried out by subliming it *in vacuo* (pressure up to 1 torr) through an unpacked quartz tube externally heated to 850 °C. Analysis of the liquid product mixture trapped on a low temperature surface (liq. N_2) showed it to consist of vinylacetylene (70%), benzene (15.6%), styrene (8.8%), phenylacetylene (1.8%), indene (2.0%), and a number of other minor products, of which toluene and naphthalene were identified. No cyclopentadienone dimer was found in any of our experiments with *p*-benzoquinone. This indicates that cyclopentadienone is not an intermediate in the thermolytic degradation of *p*-benzoquinone. The main product vinylacetylene was shown not to arise from dimerization of acetylene that could be formed by direct fragmentation of *p*-benzoquinone.

[*] Dr. H. J. Hageman and Dr. U. E. Wiersum
Akzo Research Laboratories Arnhem,
Corporate Research Department
Velperweg 76, Arnhem (The Netherlands)

[1] *H. J. Hageman* and *U. E. Wiersum*, Chem. Commun. *1971*, 497.

[2] *T. A. Elwood* and *M. M. Bursey*, Org. Mass Spektrometry *1*, 537 (1968).

[3] *H. J. Hageman* and *U. E. Wiersum*, Tetrahedron Lett. *1971*, 4329.

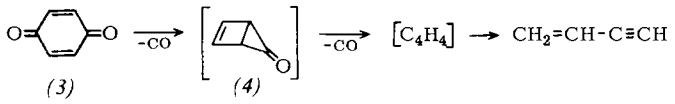
[4] *E. Hedaga, I. S. Krull, R. D. Miller, M. E. Kent, P. F. D'Angelo*, and *P. Schissel*, J. Amer. Chem. Soc. *91*, 6880 (1969).

[5] *P. B. Shevlin* and *A. P. Wolf*, J. Amer. Chem. Soc. *92*, 406 (1970).

[6] *D. C. De Jongh* and *D. A. Brent*, J. Org. Chem. *35*, 4204 (1970).

[7] *R. Breslow* and *C. Ryan*, J. Amer. Chem. Soc. *89*, 3073 (1967).

[8] *H. J. Hageman* and *U. E. Wiersum*, to be published.



(3) (4)

Excluding cyclopentadienone as an intermediate in the thermolysis of *(3)* we feel that the difference in thermolytic fragmentation of *o*- and *p*-benzoquinone can be explained by assuming that primarily a cyclopropanone-type intermediate is formed in the case of *p*-benzoquinone. Bicyclo-[2.1.0]pent-4-en-2-one *(4)* is likely to give a C_4H_4 species (butadiene diradical, cyclobutadiene or tetrahedrane) ultimately leading to vinylacetylene, since it is known[7] that cyclopropanones lose CO under relatively mild conditions. 1,2- and 1,4-Naphthoquinone show a similar difference in their thermal fragmentation patterns[8].

German version: Angew. Chem. *84*, 303 (1972) [VB 334 IE]

Macromolecular Colloquium

The Macromolecular Colloquium was held at Freiburg/Br. (Germany), March 2—4, 1972.

From the lectures:

Phase Transitions in Polymers

By *S. Blasenbrey, A. Baumgärtner* (lecturer), *W. Dollhopf*, and *W. Pechhold*[*]

Starting with a defect-free bundle of macromolecules (ideal crystal), the real crystal is obtained by the introduction of stable defects (kinks, torsion defects, jogs, and folds) that are compatible with the intramolecular and intermolecular potentials. The cooperative-statistical treatment of this bundle under certain conditions shows a first order phase transition, which is characterized by a sudden change in the defect concentrations. In the case of polyethylene, the transition data (T_m, ΔH_m, ΔV_m), the coefficient of expansion, and the compressibility of the melt, together with their pressure dependences, can be quantitatively explained. The calculated short-range order in the bundle model is in agreement with the X-ray and electron diffraction results for the polyethylene melt. Transition data for polyethylene terephthalate are reported and discussed in the light of the bundle model.

[*] Dr. S. Blasenbrey (deceased), A. Baumgärtner, W. Dollhopf, and Prof. Dr. W. Pechhold
Universität Ulm, Abteilung für Experimentelle Physik II
79 Ulm, Oberer Eselsberg (Germany)

Errors in the Determination of Narrow and Broad Molecular Weight Distributions by Gel Permeation Chromatography and Their Possible Elimination

By *K. C. Berger*[*]

Accurately determined molecular weight distributions are extremely useful sources of information on the formation of a polymer, and are therefore an important aid in kinetic studies. To obtain reliable information, however, it is necessary to recognize and to eliminate possible errors in the method. This was the aim of the experiments described below.

The gel-chromatographic elution curve results from the superposition of flow dispersion and separation on the basis of polymolecularity. By collection of eluate fractions and reintroduction into the gel chromatograph, therefore, it is possible to distinguish two limiting cases. In one case, all fractions now have the same elution volume; the original elution curve was then entirely due to flow dispersion. In the other case, all fractions have the elution volume at which they were collected; in this case, the original elution curve was entirely due to separation on the basis of polymolecularity. The results obtained in practice lie between these limiting cases. The situation becomes particularly clear with trimodal distributions such as may occur in the anionic polymerization of styrene.

The case of pure flow dispersion is important. In the experimental procedure described above, it relates to the system solvent-polymer solution-solvent. On the other hand, the flow dispersion in the system polymer solution-polymer solution-polymer solution, which influences the middle part of the elution curve in the case of broad molecular weight distributions, can be conveniently measured with radioactively labeled polymers, as was shown in the experiments.

On the basis of these measurements, the mathematical concept for the determination of molecular weight distribution from gel-chromatographic elution curves is clearly outlined.

[*] Dr. K. C. Berger
Institut für physikalische Chemie der Universität
65 Mainz, Jakob-Welder-Weg 15 (Germany)

Formation, Structure, and Function of the Flagella of Bacteria

By *W. Bode*[*]

For their active motion most bacteria use thin, often very long, helical filaments. These flagella appear in electron micrographs as sinusoidal waves having a constant and characteristic "wavelength". In addition to mobile bacteria with "normal" flagella, immobile mutants with tightly-coiled or even perfectly straight flagella have also been observed. The helical main filament is built up by non-covalent bonds from identical subunits, the protein flagellin, which has a molecular weight of about 40000. Isolated, dissolved flagellin behaves hydrodynamically and in its X-ray small angle scattering as a very highly elongated particle.

Under suitable conditions, flagellin can aggregate *in vitro* in a cooperative self-assembly process to form filaments that cannot be distinguished from intact flagella in the electron microscope or by X-ray studies. Conflicting results have been found for the growth of the flagella *in vivo*.

Several flagella models have been developed, in which flagellin forms the morphological subunit. The flagellin molecules in these models are arranged in several longitudinal strands, which in turn form a more or less hollow cylinder. As is shown by simple symmetry considerations,

[*] Dr. W. Bode
Max-Planck-Institut
für Eiweiss- und Lederforschung
8 München 2, Schillerstrasse 46 (Germany)

the individual flagellin protomers cannot occupy equivalent positions in the flagellum, owing to the superhelical structure of the flagella of bacteria. According to *Klug*, two different slightly incompatible sets of bonds could be made between the protomers. As a result the tube of the flagellum, which would be linear if only one set of bonds were used, would be deformed to a strained helix. According to *Asakura*, the protomers could be present in a flagellum in two conformations having different lengths, forcing the flagellum into a helical shape whose pitch differs according to the ratio in which the conformations are present. This could also explain the transitions between helices with different pitches that are observed *in vivo* and *in vitro*.

With sufficiently high cooperativity between the protomers within the longitudinal series, a cyclic exchange of the bonding and conformation pattern could be induced from the basal membrane, with a consequent rotational or even springing motion.

Mixtures of Polymers Having Different Tacticities with a Melting Point Maximum

By *W. Borchard* (lecturer), *G. Rehage*, and *E.-P. Uerpmann*[*]

On the basis of earlier investigations in which the association of polymethyl methacrylate mixtures with various tacticities in solutions was interpreted as crystallization, it was possible to measure the isobaric melting diagram of isotactic and syndiotactic polymethyl methacrylate (PMMA), whose mixtures were obtained from solutions. The liquidus curve found from calorimetric and microscopic measurements shows a melting point maximum situated about 30°C above the melting point of the syndiotactic component. The position of the "solidus" curve is strongly dependent on the crystallization conditions.

The characteristics of the melting diagram for high-molecular weight components are discussed in comparison with that of a binary low-molecular weight system with solid solution formation.

The density of pseudoternary solutions of isotactic and syndiotactic PMMA in toluene, determined at a constant solvent concentration, shows a maximum that agrees with mixed crystal formation at temperatures below the liquidus surface.

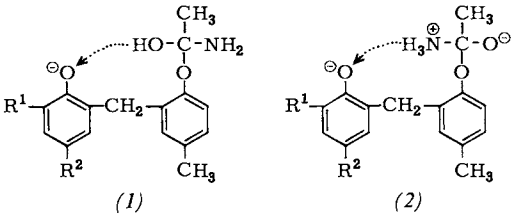
[*] Dr. W. Borchard, Prof. Dr. G. Rehage, and E.-P. Uerpmann
Physikalisch-Chemisches Institut der Technischen Universität Clausthal
3392 Clausthal-Zellerfeld, Adolf-Römer-Strasse 2A (Germany)

Neighboring Group Effects in the Ammonolysis of Acetic Esters of Polynuclear Phenolic Compounds

By *V. Böhmer* (lecturer), *K. Wörsdörfer*, and *H. Kämmerer*[*]

In dinuclear phenolic compounds esterified with acetic acid and containing a nitrophenol unit, the ester linkage in this unit has a reactivity similar to that of a mononuclear nitrophenyl ester. The ester linkage is readily broken *e.g.* by ammonia. In 2,2'-dihydroxydiphenylmethane derivatives, however, ammonia also cleaves the ester linkage in that unit which contains no nitro group, though ester linkages in dinuclear compounds containing no nitro group are not attacked under the same conditions.

On the other hand, the second acetyl group suffers practically no attack in 2,4'- and 4,4'-dihydroxydiphenylmethane derivatives, and is removed only extremely slowly in 4,2'-dihydroxydiphenylmethane derivatives. The nitro group is always in the first nucleus, *i.e.* that denoted by unprimed numbers. These results can be explained if it is assumed that the rate-determining step in the ammonolysis of the second acetyl group in the part of the molecule having no nitro group is the removal of a proton from the intermediate compound *(1)* or *(2)*.



(1) *(2)*

R^1 or R^2 or both equal NO_2

This removal takes place intramolecularly under the action of the phenoxide group of the neighboring part of the molecule, which has already been ammonolyzed. A steric arrangement that favors this step is possible only in 2,2'-dihydroxydiphenylmethane derivatives. However, the influence of the first phenoxide group also extends to a third phenol unit, presumably *via* intramolecular hydrogen bonds, if this third unit is also linked by a methylene bridge *ortho* to the phenolic OH group.

[*] Dr. V. Böhmer, K. Wörsdörfer, and Prof. Dr. H. Kämmerer
Organisch-chemisches Institut der Universität
65 Mainz, Johann-Joachim-Becher-Weg 18—20 (Germany)

The Influence of *N*-Acylation on the Three Dimensional Structure and the Properties of Insulin

By *D. Brandenburg* (lecturer), *H.-G. Gattner*, and *A. Wollmer*[*]

Homogeneous monosubstituted, disubstituted, and trisubstituted derivatives of bovine insulin have been obtained by attachment of aliphatic acyl groups to the amino groups, *e.g.* with *p*-nitrophenyl acetate in dimethyl sulfoxide/triethylamine or acetic anhydride and succinic anhydride in aqueous solution, followed by ion exchange chromatography.

Circular dichroism measurements at pH 8 show that the steric structure of insulin is only slightly modified by acetylation of phenylalanine^{B1} or lysine^{B29}, but undergoes a pronounced change on substitution of glycine^{A1}. In agreement with the CD data, the biological activity *in vitro* (fat cell test, *J. Gliemann*, Copenhagen) was found to be decreased to 30—50% for all derivatives in which the glycine amino group was acetylated; the immunological reactivity (*H. A. Ooms*, Brussels) is also reduced. Full insulin activity is found *in vivo* (hypoglycemia in rats, *W. Puls*, Wuppertal-Elberfeld) see also Ref.[11].

[*] Dr. D. Brandenburg and Dr. H.-G. Gattner
Deutsches Wollforschungsinstitut an der Technischen Hochschule
51 Aachen, Veltmanplatz 8 (Germany)
Dr. A. Wollmer
Abteilung Physiologische Chemie der Technischen Hochschule
51 Aachen, Alter Maastrichter Weg 1 (Germany)

Crystallization and gel filtration experiments in the presence of zinc ions show that the aggregation with binding of zinc becomes particularly difficult in the case of triacetylinsulin.

The experimental results were discussed with reference to the model of the insulin structure[2].

[1] *D. G. Lindsay* and *S. Shall*, Biochem. J. *121*, 731 (1971).

[2] *M. J. Adams, T. L. Blundell, E. N. Baker, E. J. Dodson, G. G. Dodson, M. M. Harding, D. C. Hodgkin, B. Rimmer, S. Sheat*, and *M. Vijayan*, Nature *224*, 491 (1969).

The Turbidimetric Titration of Polymers

By *H.-J. Cantow* (lecturer), *M. Kowalski*, and *S. Krozer*[*]

In conventional turbidimetric titration, the result always depends on the rate of addition of the precipitant, since the relatively slow nucleation process distorts the titration curve in relation to the equilibrium curve obtainable on stepwise addition. One of us achieved a much better separation according to molecular weight by a dissolution titration following the precipitation titration[1], since the dissolution of particles precipitated under suitable conditions proceeds much more rapidly than the phase formation in precipitation.

Advances in the dissolution titration of homopolymers (anionic polystyrenes) are reported first. The turbidity photometer[2] was supplemented for this purpose by a device for automatic correction for the dilution effect. With this arrangement, *e.g.* for a mixture of three preparations having average molecular weights of 0.982×10^5, 4.11×10^5, and 18.0×10^5, all three maxima were satisfactorily obtained. The change in the solubility of the components was detected by comparison with the dissolution curves of the individual preparations.

Initial attempts to determine the molecular weight distribution and the chemical distribution of copolymers by turbidimetric titration are also reported. This is not directly possible either in precipitation titration or in dissolution titration, since the scattering intensity per unit mass of precipitating polymer depends on the particle sizes and the refraction increment (which is generally also influenced by preferential solvation) of the gel droplets in the mixture. For chemically nonuniform copolymers whose structural units have different refractive indices, the analysis for molecular weight distribution and chemical distribution is unsuccessful, since the product of the refraction increment and the mass of the precipitating fraction determines the scattering effect.

We have tried to carry out this analysis of copolymers by making use of the fact that the precipitated gel droplets carry (usually negative) charges. They therefore migrate in a strong electric field and are deposited on the anode[3]. We modified the turbidity titration apparatus by fitting suitably shaped electrodes in the measuring cell.

The titration was carried out by successive addition of small portions of precipitant to this solution and application of a high-tension field after each addition of precipitant to deposit the precipitated gel droplets on the anode. The deposition process takes only a few minutes. The polymer is then removed from the cathode and its chemical composition is investigated spectrophotometrically. The first experiments (initially on mixtures of polystyrene and polymethyl methacrylates) showed that the method is feasible.

Another modification to the photometer will allow analysis for chemical heterogeneity without the need to remove the precipitate from the electrode after each titration stage. A photomultiplier is placed in the primary beam behind the cell, and is used to record the increase in transparency in a suitable spectral range as a result of the deposition of a component (absorbing) of the copolymer. Simultaneous evaluation of scattered light and consumptive absorption then allow deductions concerning the molecular and chemical heterogeneity.

[*] Prof. Dr. H.-J. Cantow, Dipl.-Chem. M. Kowalski, and Prof. Dr. S. Krozer[**]
Institut für makromolekulare Chemie der Universität
78 Freiburg, Stefan-Meier-Strasse 31 (Germany)

[**] Permanent address: Haifa (Israel).

[1] *H.-J. Cantow*, Makromolekulares Kolloquium Freiburg 1964; Angew. Chem. *76*, 350 (1964); *H.-J. Cantow* in *M. J. R. Cantow*: Polymer Fractionation. Academic Press, New York 1967, p. 233.

[2] We thank Chemische Werk Hüls A.G., Marl for allowing us to use one of their photometers for the turbidometric titrations.

[3] *S. Krozer* and *A. Pastusiak*, Kolloidnyi Zh. *18*, 239 (1966).

Characterization of the Intermittently Polymerization-Active Species of Soluble Ziegler-Natta Catalysts

By *G. Fink* (lecturer), *D. Schnell, B. Brenner*, and *R. Rottler*[*]

The kinetics of the polymerization of ethylene with soluble Ziegler-Natta catalysts of the type $(C_5H_5)_2TiX_2/AlX_3$ (with X = Cl, C_2H_5, or higher alkyl) both in a flow tube and in a stirred reactor with toluene and cyclohexane as solvents are discussed. Investigations on the complicated behavior of the polymerization rate on transition from the homogeneous to the heterogeneous phase due to precipitating polymer are also discussed. The catalyst concentration in the polymer is correlated with the polymerization rate, taking into account the fact that the active species is an equilibrium product.

The findings in solution are compared with the results of the ethylene polymerization in the gas phase, a "soluble" Ziegler-Natta catalyst system being used without solvents in the latter case, corresponding to its aggregation state at room temperature. The results are used in an effort to explain the relations between the formation, concentration, and lifetime of the active inserting species and peculiarities of the partition function of the oligomers formed.

[*] Dr. G. Fink, Dipl.-Chem. D. Schnell, Dipl.-Chem. B. Brenner, and Dipl.-Chem. R. Rottler
Institut für Technische Chemie der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

Possibilities and Limits of the Enzymatic Synthesis of Polynucleotides

By *G. Feix*[*]

Many enzymes that synthesize DNA or RNA have been isolated during the past few years from microorganisms and from cells of higher organisms. Some of these enzymes have been purified to such a degree that

[*] Doz. Dr. G. Feix
Institut für Biologie III
(Genetik und Molekularbiologie) der Universität
78 Freiburg, Schänzlestrasse 9—11 (Germany)

the cell-free synthesis of many polynucleotides that were not obtainable by chemical synthesis became possible with their aid.

The enzymes catalyze the linear linkage of nucleotides, the 3'-hydroxyl group of the ribose or deoxyribose of the growing polynucleotide chain being joined to the 5'-hydroxyl group of the entering nucleotide by a phosphoric acid diester bridge.

The nucleotides are incorporated into the nucleic acid either randomly according to the composition of the substrate nucleotides or in a specific sequence in a template-dependent reaction according to the Watson-Crick principle of base complementarity.

The high specificity of the enzymes on the one hand allows the synthesis of complicated nucleic acids, which are biologically active, but on the other hand constitutes a barrier to the synthesis of nucleic acids from substrates that are not accepted by the enzymes.

The synthesis of new nucleic acids has recently become possible by modification of the enzymes and by suitable adjustment of the incubation conditions of the enzymatic reaction. The preparative use of the enzymatic synthesis of polynucleotides will become increasingly important.

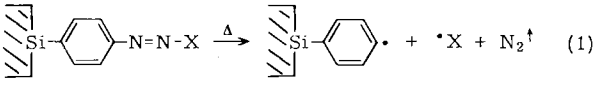
Graft Reactions on SiO_2 Surfaces

By *N. Fery*, *R. Hoene*, and *K. Hamann*[*]

1. *N. Fery* (lecturer): A stable linkage of organic macromolecules to the surface of amorphous SiO_2 is possible *via* the Si—C bond. By reaction with thionyl chloride, the siloxane and silanol groups on the surface of the particle were converted into Si—Cl groups after *Boehm*[1].

Polyfunctional initiators with inorganic skeletons are formed as follows. The Si—Cl groups on the surface are converted with phenyllithium into Si-phenyl groups; diazonium salt groupings are formed by nitration, reduction, and diazotization[2].

By coupling with H-active compounds, *e.g.* thiols, sulfinic acids, and amines, we have now obtained labile diazonium compounds covalently bonded to the SiO_2 surface that initiate the free-radical polymerization of vinyl monomers.



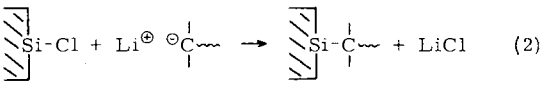
(1)

X = *e. g.* -S-Ar, $-SO_2$-Ar, -NH-Ar

Monomers used for the polymerization were: styrene, acrylamide, acrylic acid, methyl methacrylate, and vinylpyridine. The quantity of polymer grafted, based on silicon dioxide, is 10—60%.

2. *R. Hoene* (lecturer): Linear macromolecules with definite chain lengths can be grafted by reaction of the Si—Cl groups on the particle surface with polymeric carbanions.

The molecular weight of the grafted chains is varied by the ratio of styrene to initiator (butyllithium). An essentially



(2)

linear relation is found between the quantity of grafted polymer and the degree of polymerization of the chains.

Moreover, the number of Si—C bonds formed is smaller than in the reaction with phenyllithium, evidently because of steric effects of the polymer residue.

The properties of the SiO_2 particles are considerably changed by the grafting reaction. Amorphous SiO_2 (specific surface area 200 m^2/g) with about 50% of grafted linear polystyrene, for example, gives practically stable suspensions in aromatic solvents.

[*] Dr. N. Fery, Dr. R. Hoene, and Prof. Dr. K. Hamann
2. Institut für Technische Chemie der Universität
7 Stuttgart 1, Wiederholdstrasse 10/1 (Germany)

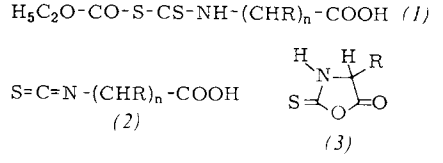
[1] *H. P. Boehm*, Angew. Chem. *78*, 617 (1966); Angew. Chem. internat. Edit. *5*, 533 (1966).

[2] *M. Schneider*, Dissertation, Universität Heidelberg 1962.

Rearrangement and Polymerization Mechanisms of DTE-Amino Acids and 2-Thioxo-5-oxazolidones

By *H. R. Kricheldorf*[*]

α-DTE-Amino acids[1] *(1)*, $n=1$, can be polymerized to polypeptides without racemization of optically active amino acids. *Kato*, *Higashimura*, *Suzuoki*, and *Okamura*[2], who were the first to study these reactions, considered the active monomer to be the α-isothiocyanatocarboxylic acid *(2)*, $n=1$, liberated on decomposition of *(1)*.



(1)

(2)

(3)

The present investigations show, however, that polycondensation is possible for β- and higher ω-isothiocyanatocarboxylic acids, but not for α-isothiocyanatocarboxylic acids. The active monomers in the polymerization of *(1)*, $n=1$, are in fact the 2-thioxo-5-oxazolidones *(3)* formed by cyclization of *(2)*, $n=1$. An ionic mechanism with ring cleavage is proposed for the polymerization of these cyclic monomers.

[*] Dr. H. R. Kricheldorf
Institut für makromolekulare Chemie der Universität
78 Freiburg, Stefan-Meier-Strasse 31 (Germany)

[1] Abbreviation used for compound *(1)* in Ref. [2].

[2] *T. Higashimura*, *H. Kato*, *K. Suzuoki*, and *S. Okamura*, Makromolekulare Chem. *90*, 243 (1966); *H. Kato*, *T. Higashimura*, and *S. Okamura*, *ibid. 109*, 9 (1967).

The Polymorphic Transformations II to I in Poly-1-butene

By *G. Goldbach*[*]

Of the four known crystalline forms of poly-1-butene, the tetragonal modification II and the hexagonal modification I are not only technically important but also of scientific interest. When the melt is cooled, the unstable modification II generally crystallizes out first, and then

[*] Dr. G. Goldbach
Chemische Werke Hüls AG
437 Marl (Germany)

changes more or less rapidly, depending on the experimental conditions, into the stable modification I.

The lecture dealt with the kinetics of the transformation of II into I as a function of the parameters temperature, previous thermal history, additives, and external stresses or elongations. Dilatometric, IR-spectroscopic, and mechanical-dynamic methods were used for the investigations.

The half-time of the transformation from II into I has a complicated temperature-dependence with a minimum. The temperature at which the minimum occurs depends on the chemical nature of the additives, the thermal history, and the magnitude of the applied deformation. The half-life is determined by the mobility of the molecules in the *amorphous* regions and by internal stresses. The participation of the amorphous regions in the transformation is shown by IR-spectroscopic, caloric, and mechanical-dynamic measurements.

The investigations on the influence of mechanical stresses, which were carried out over a wide temperature range extending from −196 °C to the melting point of modification II (approx. 115 °C), showed that the uniaxial deformation below the brittle fracture or yield stress proceeds mainly in the amorphous regions. Appreciable deformation of the crystallites occurs only when the yield stress is reached. There is thus a (lower) critical elongation below which (for a given short time) no transformation from II into I takes place. The critical elongation has a complicated but interpretable temperature dependence.

The Shear-induced Crystallization of Polypropylene

By *H. J. Leugering* (lecturer) and *G. Kirsch*[*]

A melt of isotactic polypropylene oriented by shearing crystallizes in band spherulites, which consist of the pseudohexagonal (β) or of the monoclinic (α) modification, depending on the crystallization temperature. Band spherulites in which both modifications occur are formed at medium temperatures. By crystallization with simultaneous shearing, contents of more than 30% of the β modification can be obtained, as has been shown by differential calorimetry. When such samples are heated, the β components exhibit characteristic melting and transformation phenomena, which are discussed in detail.

[*] Dr. H. J. Leugering and Dr. G. Kirsch
Farbwerke Hoechst AG., vormals Meister Lucius & Brüning
623 Frankfurt (Main) 80 (Germany)

The Dynamic Structure of a Synthetic Deoxyribonucleic Acid

By *A. Lezius*[*]

The enzymatic copolymerization of deoxyadenosine triphosphate (dATP) and 4-thiothymidine triphosphate (s^4dTTP) by DNA polymerase from *Bacillus subtilis* yields a polydeoxynucleotide, poly[d(A-s^4T)·d(A-s^4T)] having a high molecular weight [$M_2^{s=0} = 1.2 \times 10^6$; $S_{20,w} = 10-14$ S] and a strictly alternating base sequence[1].

[*] Dr. A. Lezius
Max-Planck-Institut für experimentelle Medizin
34 Göttingen, Hermann-Rein-Strasse 3 (Germany)

The spectra of the optical rotatory dispersion (ORD) and of the circular dichroism (CD) show a strong negative Cotton effect around 400 nm, which can be assigned to an $n \rightarrow \pi^*$ transition of the thioamide chromophore. Since this band has a positive sign in monomeric 4-thiothymidine, it is concluded that the nucleoside is probably in the unusual *syn* conformation in the polymer. A protonated form of the double-stranded polymer, in which the N-1 atoms of the deoxyadenosine act as the proton acceptors, is formed at pH = 4.2 (cooperative transition point). These properties of the polymer are incompatible with a Watson-Crick structure; the alternative is an "reversed" Hoogsteen base pairing [O-2(s^4T)———N-6(A), N-3(s^4T)———N-7(A)].

From model studies, a left-handed double helix can be predicted for this base pairing[2]. A decisive symmetry property of the model has been confirmed by X-ray fiber diagrams[3].

The polymer exhibits cooperative temperature-dependent and salt-dependent helix-helix transitions, in which structure-induced hysteresis phenomena may occur[2]. These transitions are accompanied by changes in the hydrodynamic properties, such as the sedimentation coefficient, the buoyant density, and the partial specific volume.

[1] *A. Lezius* and *U. Rath*, Eur. J. Biochem. *24*, 163 (1971).

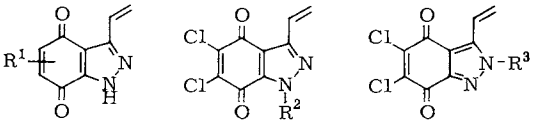
[2] *E. M. Gottschalk, E. Kopp*, and *A. Lezius*, Eur. J. Biochem. *24*, 168, (1971).

[3] *W. Saenger*, private communication.

Some New Redox Polymers Containing Nitrogen

By *G. Manecke* (lecturer), *W. Hübner*, and *H.-J. Kretzschmar*[*]

In a continuation of our studies on redox polymers, substituted vinylindazole-4,7-quinones were prepared by 1,3-dipolar addition of vinyldiazomethane to 1,4-benzoquinones. The object was in particular to synthesize quinone systems with higher redox potentials. Systems of the types *(1)*—*(3)* with redox potentials of 340—460 mV were obtained.



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

R^1 = H, Cl, CH_3, OCH_3
R^2 = H, CH_3, $CH{=}CH_2$
R^3 = CH_3, $CH{=}CH_2$

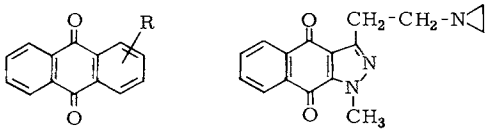
In the free-radical homopolymerization in solution, the vinylindazole-4,7-quinones and the indazolehydroquinone acetates obtained by reductive acetylation exhibited different polymerization properties.

5,6-Dichloro-3-vinylindazolehydroquinone triacetate with 5,6-dichloro-1,3-divinylindazolehydroquinone diacetate as the crosslinking agent gave a copolymer, from which hydrolysis and sulfalkylation gave a chemically and

[*] Prof. Dr. G. Manecke, Dr. W. Hübner, and Dr. H.-J. Kretzschmar
Institut für Organische Chemie der Freien Universität
1 Berlin 33, Thielallee 63—67 (Germany)

mechanically stable redox polymer that was swellable in aqueous media and had a redox capacity of 4.25 mequivalent/g; the redox potential and swellability of the polymer were measured.

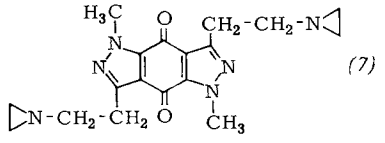
Since vinylquinones often polymerize poorly, polymerizable aziridinylquinones with redox potentials of 100—230 mV, *e.g. (4)—(7)*, were prepared by addition of aziridine to the vinyl group.



(4), R = 1-CH_2-CH_2-N△

(5), R = 2-CH_2-CH_2-N△

(6)



(7)

Their cationic homopolymerization was investigated. The monomers *(4)—(6)* were also copolymerized with 1,4-bis[2-(1-aziridinyl)ethyl]benzene as the crosslinking agent in various molar ratios. The redox polymers obtained in this way swelled readily in aqueous acid because of their tertiary amino group. The redox capacities of the chemically stable copolymers were 3.6—5.3 mequivalent/g. The redox potentials and the pH dependence of the bulk density were also investigated.

Chemical Reactions on Polymethyl Methacrylate

By *F. Arranz, J. J. Bourguignon, J. C. Galin*, and *P. Rempp* (lecturer)[*]

When reactions are carried out on high polymers, it is advisable to characterize the resulting products chemically and physico-chemically as far as possible, to establish whether the desired reactions take place on the side groups, and to what extent the reacted side groups can influence those which have not yet reacted. Great importance was placed on these questions in the study of the nucleophilic substitution of polymethyl methacrylate (PMMA).

It was found that bases such as the following carbanions: the dimsyl anion CH_3—SO—$CH_2^{\ominus}$, the dimethylsulfonyl anion CH_3—SO_2—$CH_2^{\ominus}$, and the dimethylaminosulfonyl anion $(CH_3)_2N$—SO_2—$CH_2^{\ominus}$ react with the ester functions of PMMA with conversions of up to about 50%. Cyclizations may occur when the mixture is heated. It should be emphasized that in the case of random copolymers of 54% styrene and 46% methyl methacrylate, the conversion based on the ester functions can be as high as 100%. This shows that the reacted groups protect the neighboring ester functions against substitution.

[*] Dr. F. Arranz, Dipl.-Chem. J. J. Bourguignon, Dr. J. C. Galin, and Prof. Dr. P. Rempp
Centre de Recherches sur les Macromolécules C.N.R.S.
6, rue Boussingault, F-67 Strasbourg (France)

Another feature of the products of this substitution reaction is the great lability of the C—H bond on the C atom between the carbonyl and the sulfonyl or sulfinyl groups. These are true "carbon acids". This can also be seen from the stoichiometry of the substitution reaction: two equivalents of the carbanion are required to substitute one ester group.

High-Impact Plastics Formed by Two Phases. Adjustment of the Degree of Dispersion and of the Interfacial Adhesion by Block Copolymers

By *G. Riess* (lecturer), *J. Periard*, and *Y. Jolivet*[*]

It has been shown that the degree of dispersion in high-impact plastics based on a soft dispersed rubber (*e.g.* polyisoprene) in a hard phase (polystyrene) can be adjusted by block or graft copolymers. This oil-in-oil emulsifier action of a block copolymer A—B for the incompatible homopolymers A and B or for two immiscible solvents depends both on the concentration of copolymer and on its molecular weight, structure, and composition.

It was also found that the block copolymer causes interfacial adhesion in such two-phase systems. In a certain range of particle diameters, therefore, the impact strength is directly dependent on the concentration of the copolymer at the phase boundary.

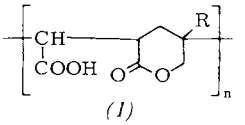
Several methods have been developed for localizing the copolymer in such two-phase systems. These include interference and UV fluorescence microscopy, analysis after irradiation, and investigations with the electron microprobe.

[*] Prof. Dr. G. Riess, Dr. J. Periard, and Dr. Y. Jolivet
Ecole Supérieure de Chimie de Mulhouse
3, rue A. Werner, F-68 Mulhouse (France)

Cyclocopolymerization with Intramolecular Formation of Lactone Rings

By *G. Sackmann* (lecturer) and *G. Kolb*[*]

The radical-initiated copolymerization of maleic anhydride with allylic hydroxyl compounds such as allyl alcohol or methallyl alcohol between −10 and +70°C yields linear and soluble (1:1) copolymers. These consist to an extent of about 90% of lactone ring structures, and contain free carboxyl groups.



R = H, CH_3

(1)

The alternating copolymers *(1)* are probably formed under the influence of a free-radical initiator by homopolymerization of EDA complexes formed from maleic anhydride and the allyl compound. Intramolecular esterification then gives the lactone ring structure. By choice of suitable initiator systems, it is possible, *e.g.*

[*] Dr. G. Sackmann and Dr. G. Kolb
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG
509 Leverkusen-Bayerwerk (Germany)

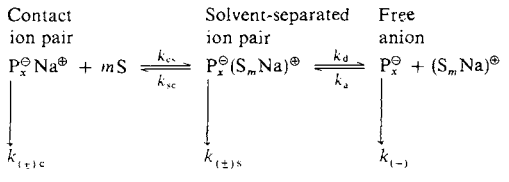
with methallyl alcohol, to obtain copolymers having molecular weights of more than 100000.

The partial replacement of the allyl or methallyl alcohol by a third copolymerizable compound leads to terpolymers that contain cyclic anhydride groups besides lactone rings.

The Analysis of Narrow Molecular Weight Distributions as an Aid to the Kinetic Investigation of Ionic Polymerization Processes

By *G. V. Schulz* (lecturer), *L. L. Böhm*, and *G. Löhr*[*]

Anionic polymerization processes can be controlled by the flow tube or stop-flow technique in such a way that all the polymer molecules formed have an equally long growth time available under identical conditions. The molecular weight distribution under these conditions should be a Poisson distribution *(Flory)*, whose nonuniformity $U = 1/\overline{P}_n$ (when $\overline{P}_n \gg 1$). Even under the most precise conditions, however, broader distributions are in fact frequently produced. This is because the polymerization has a multipath mechanism, since the reactive end *e.g.* of polystyrylsodium occurs in three forms, which exist in a dynamic equilibrium and add on monomer with very different rate constants $k_{(\pm)c}$, $k_{(\pm)s}$ and $k_{(-)}$, as shown in the following scheme:



Poisson distributions occur only if there is only *one* form of the "living" end present or if the transition is considerably faster than the addition, *i.e.* $k_{sc} \gg k_{(\pm)s}$ or $k_a \gg k_{(-)}$.

If the rates of the transition and of the addition are comparable, multipath mechanisms lead to broadening of the molecular weight distribution, and this broadening can be used to calculate the rate constants k_{sc} and k_{cs} as well as k_a and k_d with the equations given by *Figini*[1] and *Böhm*[2]. Dr. *Chmelíř*[3-5] reported to last year's Colloquium that in a series of solvents (including THP, THF, and DME), the three propagation rate constants and the equilibrium constants $K_{cs} = k_{cs}/k_{sc}$ and $K^*_{Diss} = k_d/k_a$ are known as functions of temperature. A series of experiments will now be reported in which the molecular weight distributions are determined so accurately that the rate constants of the transitions can be calculated.

The kinetic data allow the calculation of the conditions of temperature and ionic strength in which the addition proceeds by the one-path mechanism, *i.e. via* the contact ion pair, and so gives a Poisson distribution. Such polymers can be used for the development of methods for determining the nonuniformity of narrow distributions with the accuracy necessary for our purpose. We use the precipitation chromatography method, the fractions being checked by gel permeation chromatography. The width of the fractions, and hence the effectiveness of the fractionation, can be quantitatively estimated by overlapping experiments. These experiments show that the inhomogeneity of polymers in the range 0.5 to 2.0×10^{-2} can be determined with an error of less than $\pm 0.2 \times 10^{-2}$.

The temperature dependence of the rate constants determined by this method for the transition reactions for polystyrylsodium in THP and THF can be used to find their Arrhenius parameters. In DME, on the other hand, the inhomogeneity is very close to that of the Poisson distribution over the whole temperature range, so that it must be concluded that the transition rates in this solvent are greater than the addition rates.

[*] Prof. Dr. G. V. Schulz, Dr. L. L. Böhm, and Dr. G. Löhr
Institut für physikalische Chemie der Universität
65 Mainz, Jakob-Welder-Weg 15 (Germany)

[1] *R. V. Figini*, Makromolekulare Chem. *71*, 193 (1964); *107*, 170 (1967).

[2] *L. L. Böhm*, Z. Phys. Chem. N.F. *72*, 199 (1970).

[3] *M. Chmelíř, B. J. Schmitt*, and *G. V. Schulz*, Makromolekulares Kolloquium Freiburg 1971, Angew. Chem. *83*, 371 (1971); Angew. Chem. internat. Edit. *10*, 354 (1971).

[4] *B. J. Schmitt* and *G. V. Schulz*, Makromolekulare Chem. *142*, 325 (1971).

[5] *L. L. Böhm* and *G. V. Schulz*, Makromolekulare Chem. *153*, 5 (1972).

Chemical Reactions on Single Crystals of Copolymers

By *N. Wiemers* (lecturer), *H. J. Sterzel*, *E. W. Fischer*, and *G. Wegner*[*]

Polymer single crystals serve as important models for the solid state of crystalline high polymers. Because of the phenomenon of chain folding, these lamellar single crystals consist of an inner region of high crystallinity and amorphous surface regions in which the chain folds are localized. Chemical reactions proceed more rapidly in the amorphous, liquid-like surface layers than in the crystalline inner regions. This is the basis of experiments by which the structure of the amorphous surface layer can be elucidated.

A problem that can be solved by chemical methods is the structure of single crystals of copolymers. During the crystallization, a sort of phase separation may occur between the comonomer units. To be able to describe the thermodynamic properties of such crystals correctly, it is important to know whether the comonomer units accumulate in the amorphous surface layers or are incorporated into the crystalline regions.

Investigations of this type have been carried out on copolymers of 3,3-bis(chloromethyl)oxetane and propiolactone and on copolymers of L-(−)- and DL-lactide. By selective hydrolysis of ester linkages in the amorphous surface layers, it was possible to determine the number of comonomer units in these regions from a comparison of the analytical data before and after chemical treatment of the suspended single crystals. A correlation is possible between these data and results of X-ray small angle scattering, electron microscopy, and differential calorimetry.

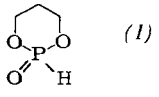
In the copolymers investigated, enrichment of the comonomer units always occurs in the surface layers. There is practically no incorporation into the crystalline regions. The distribution of the uncrystallizable comonomer units can also be investigated under different crystallization and annealing conditions by the methods developed. The application of these methods to the determination of sequence lengths was discussed.

[*] Dipl.-Chem. N. Wiemers, Dipl.-Ing. H. J. Sterzel, Prof. Dr. E. W. Fischer, and Prof. Dr. G. Wegner
Institut für Physikalische Chemie der Universität
65 Mainz, Jakob-Welder-Weg 15 (Germany)

The Polycondensation of Diethyl Phosphite with Aliphatic Diols

By *W. Vogt* and *S. Balasubramanian*[*]

The condensation reaction of diethyl phosphite with aliphatic diols of the type HO—$(CH_2)_x$—OH ($x = 2$—6 and 8) was investigated. It was found that very different products were obtained according to the number x of methylene groups between the two OH groups. Polymers with degrees of condensation greater than 10 are formed only with $x \geqslant 6$. When $x < 6$, the molecular weights are kept low by an ether formation that proceeds simultaneously with the polytransesterification; the formation of an ether linkage is formally equivalent to the removal of a molecule of water, which ultimately appears in the form of acidic P-OH groups, which are incapable of condensation with the diols under the conditions used. This ether formation is particularly pronounced in the reactions with 1,5-pentanediol and 1,4-butanediol, in the course of which large quantities of the cyclic ether tetrahydropyran (approx. 30 mole %) or tetrahydrofuran (approx. 80 mole %) are formed. The use of 1,3-propanediol leads to an entirely different main product, *i.e.* 2-hydro-2-oxoperhydro-1,3,2-dioxaphosphorin *(1)* (approx. 80 mole %).



(1)

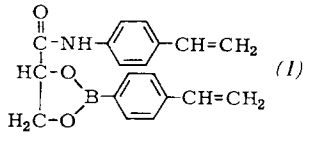
The formation of all these reaction products can be readily explained with the plausible assumption that those reactions that can proceed *via* five-membered or six-membered intermediates are always preferred.

[*] Dr. W. Vogt and S. Balasubramanian
1. Ordinariat des Organisch-Chemischen Institutes der Universität
65 Mainz, Johann-Joachim-Becher-Weg 18—20 (Germany)

The Use of Polymers with Enzyme-Analogous Structures for the Resolution of Racemates

By *G. Wulff* (lecturer) and *A. Sarhan*[*]

A new method has been investigated for the introduction of functional groups into polymers with a fixed, predetermined stereochemistry. The functional groups to be introduced were bonded, in the form of polymerizable vinyl compounds, to a suitable template molecule, and this was copolymerized *e.g.* with divinylbenzene under conditions such that macroporous, non-swellable polymers were formed. It was expected that after removal of the template, the functional groups would be present in a stereochemistry fixed by the template. With chiral templates, the arrangement of the functional groups in the surrounding polymer



(1)

[*] Prof. Dr. G. Wulff and Dr. A. Sarhan
Organisch-Chemisches Institut der Universität
53 Bonn, Meckenheimer Allee 168 (Germany)

cavity should also be asymmetric. A very sensitive method of testing for the stereochemically correct introduction of the functional groups in this case is testing for the ability of such polymers to resolve racemates, *e.g.* of the template used.

For example, the 2,3-*O*-*p*-vinylphenylboronic ester of D-glyceric acid *p*-vinylanilide *(1)* is copolymerized with divinylbenzene in the presence of acetonitrile. At most about 50% of the D-glyceric acid could be split off again. The polymer prepared in this way contained free boronic acid and amino groups, and had a capacity for the uptake of glyceric acid that corresponded to the quantity originally split off. On reaction with D,L-glyceric acid, binding of the D-form was significantly better, so that L-glyceric acid accumulated in the solution. A significant enrichment of the antipodes was also possible in the case of D,L-glyceraldehyde. As expected, the ability to resolve racemates was totally and irreversibly lost in solvents that swell the polymer.

Determination of Kinetic Constants of Homopolymerization by Measurement of Copolymerizations

By *P. Wittmer*[*]

In the determination of *r*-values, the measurements frequently also yield data that can be used for the calculation of the copolymerization rate.

It was shown how copolymerization rates can be calculated from dilatometrically measured volume contraction-time curves. The molar volume contraction consists of three increments for the two homopolymerization steps and the alternation step.

A new equation proposed by *Russo* and *Munari* was used to describe the copolymerization rate. The quantity $k_p/k_t^{1\backslash 2}$ for the homopolymerization of one of the two monomers can be determined from copolymerization rates.

The calculations were illustrated by examples from the copolymerization system ethyl acrylate/styrene.

[*] Dr. P. Wittmer
Badische Anilin- & Soda-Fabrik AG, Kunststofflaboratorium
67 Ludwigshafen (Germany)

Structural Investigations on Polymethyl Methacrylate and Methyl Methacrylate Copolymers in Solution

By *W. Wunderlich* (lecturer) and *D. Panke*[*]

Light scattering and viscosity measurements were carried out on solutions of copolymers of methyl methacrylate with methyl, ethyl, and *n*-butyl acrylate and *n*-butyl methacrylate, as well as on the corresponding homopolymers. The unperturbed dimensions and the excluded volume (acetone, 20 °C) were calculated from the experimental results. Comparison of the results obtained by the two methods shows that the Flory constant Φ_0 for copolymers is greater than the calculated and experimentally confirmed value for binary polymer solutions. This is also true of solutions of polymethyl methacrylate in a mixed solvent.

[*] Dr. W. Wunderlich and Dr. D. Panke
Röhm GmbH, Chemische Fabrik
61 Darmstadt, Postfach 4166 (Germany)

In the calculation of chain flexibility (persistence length) of ternary polymer systems, viscosity data evidently yield misleading values. Only the results of scattering experiments should be taken into account.

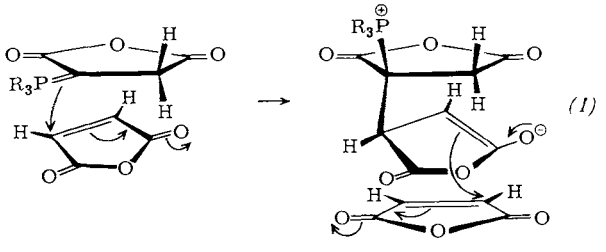
For the copolymers investigated, these show that the flexibility decreases on combination of an α-substituted monomer with an unsubstituted monomer. The contribution of hetero-contacts to the excluded volume can be determined quantitatively and correlated with the incompatibility of the corresponding homopolymers.

The Anionic Polymerization of Maleic Anhydride with Tertiary Phosphanes

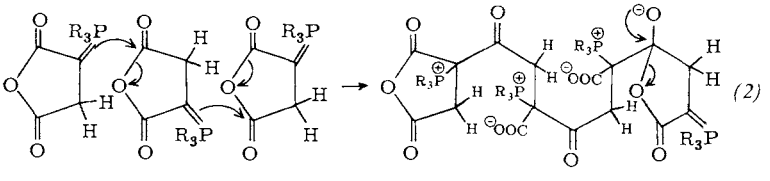
By *H. Zweifel* (lecturer) and *Th. Völker*[*]

Braun et al.[1], *Schopov*[2], and *Zweifel, Völker*, and *Giovannini*[3] found that maleic anhydride polymerizes spontaneously in the presence of *e.g.* pyridine bases and trialkylamines. *Zweifel, Löliger*, and *Völker*[4] investigated this polymerization and formulated two reaction models to explain it on the basis of the experimental findings. Their investigations also included the initiation of the polymerization of maleic anhydride by triphenylphosphane or tributylphosphane, since these phosphanes may be compared with pyridine bases in their reactivity.

The polymerization proceeds *via* zwitterions in accordance with the reactions (1) and (2).



(1)



(2)

Phosphonium groups were detected in the fractions obtained on fractional precipitation, extraction, column chromatography, and gel permeation chromatography, and the structure of the polymers was investigated spectroscopically. Kinetic measurements were also carried out on the polymerization of maleic anhydride with triphenylphosphane in dimethyl sulfoxide.

German version: Angew. Chem. *84*, 356 (1972) [VB 329 IE]

[*] Dr. H. Zweifel and Dr. Th. Völker
Lonza AG, Forschungslaboratorium
CH-1700 Fribourg (Switzerland)

[1] *D. Braun, I. A. Azid el Sayed*, and *J. Pomakis*, Makromolekulare Chem. *124*, 249 (1969).

[2] *I. Schopov*, Makromolekulare Chem. *137*, 293 (1970).

[3] *H. Zweifel*, Dissertation No. 669, Universität Fribourg (Switzerland) 1970.

[4] *H. Zweifel, J. Löliger*, and *Th. Völker*, Makromolekulare Chem., in press.

Mineralogy and Chemistry

The 49th Annual Conference of the German Mineralogical Society (DMG) was held in Kiel, September 6—9, 1971. Eight plenary lectures and 77 short lectures were presented.

Crystal chemistry formed a focal point of the lectures. Problems were dealt with concerning the structure and formation of silicates. *F. Liebau* (Kiel) reported on further progress made in the *Systematic Compilation of Silicate Structures*. They are classified according to chain type and degree of condensation, since in this way their salient characteristics can be readily compared from a crystallochemical point of view.

G. Gottardi (Modena) gave a review of the *Crystal Chemistry of the Zeolites* and their synthetic representatives.

The Feldspars were comprehensively reviewed in a plenary lecture delivered by *F. Laves* (Zürich), this year's DMG prizewinner (A. G. Werner medal), and in a series of short lectures by *H. U. Baumbauer, H. Kroll, G. Voll, H. Pentinghaus, H.-E. Nager*, and *H. H. Steuhl* (all from Münster). The feldspars constitute an important group of silicates having a framework structure of three-dimensionally connected SiO_4 tetrahedra, in which 1/3 to 1/2 of the silicon positions are replaced by aluminum, the charge being balanced by univalent or divalent cations. Ga^{3+}, Fe^{3+}, and Ge^{4+} may also replace Si^{4+}. The more or less random distribution of Al and Si in the tetrahedral sites changes the structural parameters of the univalent and divalent cations, and thus alters the symmetry of the structure. The order/disorder of the feldspars reflects their temperature of formation and can thus be used as an indicator of thermal prehistory. Accurate and detailed investigations of feldspars can be of great value as model studies for other classes of compounds.

In his plenary lecture on the *Formation of New Phases in Lattice Defects*, *E. Hornbogen* (Bochum) showed how recent progress made in the theoretical understanding of internal stress in metals can give renewed impetus to the clarification of complex oxide structures. *G. Voll* (Münster) indicated the *Analogies between the Texture of Metals during Crystallization and the Texture of Rocks*.

Industrial mineralogy commanded a great deal more attention at the Kiel conference than at previous conferences. *J. Petzold* and *K. Schilling* (Mainz) gave an insight into the recent developments that have been made in, and the present state of industrial production of *Glass Ceramics*. *H. G. Kurczyk* and *W. Münchberg* (Hagen) reported on the most promising utilizability of *Synthetic Wollastonite in Ceramics*. *R. Beising* (Karlsruhe), and *R. Singh Dev, H. Kautz*, and *H. Kirsch* (Essen) discussed the problems associated with the combustion of sulfur-containing lignites, and of fuels containing inorganic components, in conventional power stations. Methods for the chemical binding and separation of SO_2 and SO_3 in flue gases were outlined.

R. Kranz (Jülich) dealt with the question of analysis in connection with *Methods of Measuring Radioactive Equili-*

bria. H. Köster (München) reported on the separation of cations on citrate-loaded Dowex 1 anion exchanger. *M. Pavicevic* and *A. el Goresy* (Heidelberg) described the use of the electron microprobe for the *Determination of the Valency of Fe and Ti* in the system Fe—Ti—O; *M. Gramse* (Göttingen) has used the same technique for the investigation of the chemistry of basaltic glasses. *A. Schneider* and *B. Schulz-Dobrick* (Göttingen) reported on the *Use of the ARL 72000 Simultan X-ray Quantometer in Automatic X-ray Fluorescence Analysis.* Scanning electron photomicrographs of the early stages of surface alteration of silicates in presence of supercritical aqueous solutions were shown by *K. F. Riedl* and *K. Jasmund* (Köln). *K. M. Sylla* (Köln) reported the synthesis of iron chrysotile in asbestos-like fibers.

A plenary lecture delivered by *W. Noll* (Leverkusen) was devoted to the future role of the *Mineralogist in Industry.* The various possible openings for the mineralogist in the chemical industry—particularly in the field of solid-state chemistry—were outlined, and it was pointed out that mineralogy is not just an academic discipline but also an integral part of the "industrial sciences" and should receive more recognition as such than hithertofore.

Friedemann Freund [VB 333 IE]
German version: Angew. Chem. *84*, 267 (1972)

REVIEW ABSTRACTS

The mode of action of amino acid antagonists of biological origin is surveyed in a review by *G. Nass, K. Poralla,* and *H. Zähner.* There is a small group of antibiotics whose growth-inhibiting activity can be counteracted by one or more amino acids and which thus act as amino acid antagonists. In some cases the biosynthetic precursors of amino acids or their conversion products also act as antagonists. (Antibiotics inactivated by direct interaction with an amino acid do not belong to the antagonists.) Enzymatic reactions in which antagonists interfere are described. Their modes of action include feedback inhibition, inhibition of cellular amino acid uptake, influence on the incorporation of amino acids into peptide chains and on the function of proteins, and inhibition of oligopeptide synthesis and purine synthesis. [Biogenetic Amino Acid Antagonists. Naturwissenschaften *58*, 603—610 (1971); 110 references]

[Rd 472 IE –M]

Some recent trends in the chemotaxonomy of plants are reviewed by *R. Hegnauer.* It is often difficult to assess the significance of chemical characteristics because of our incomplete knowledge about the occurrence, biosynthesis, and function of most phytoconstituents. Three patterns of distribution can be distinguished, namely general occurrence, "asystematic" occurrence, and systematic occurrence, which enable assessment of the taxonomic possibilities and their limitations. By way of preference the natural products of vascular plants are dealt with in order to illustrate these patterns. The comparative chemistry of macromolecules and phytoserology also affords results which can have phytotaxonomical significance. [Pflanzenstoffe und Pflanzensystematik. Naturwissenschaften *58*, 585—595 (1971); 88 references]

[Rd 473 IE –M]

High molecular polyphenylenes, which are of interest with regard to the development of heat-resistant materials, are the subject of a review by *G. K. Noren* and *J. K. Stille.* They can be synthesized, *inter alia,* by oxidative cationic polymerization, dehydrogenation of poly-1,3-cyclohexadienes, metal-catalyzed coupling reactions, and Diels-Alder polymerization. The spectra, crystallinity, solubility and solution properties, semi-conducting properties, irradiation stability, thermal stability, and reactions of polyphenylenes are discussed. Because of their insolubility and since they are difficult to prepare, polyphenylenes have so far found only limited application. [Polyphenylenes. Macromol. Rev. *5*, 385—430 (1971); 129 references]

[Rd 474 IE –M]

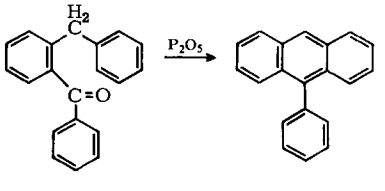
Ion binding by synthetic macrocyclic compounds is discussed in a paper by *J. J. Christensen, J. O. Hill,* and *R. M. Izatt.* The existence of macrocycles with hydrophilic cavities containing multiply binding atoms and having exterior frameworks exhibiting hydrophobic behavior, opens up a number of possibilities with regard to the development and synthesis of molecules having specific cation and anion binding properties. The metal-ligand binding in cyclic polyethers appears to be predominantly ionic but the covalent character increases on substitution of sulfur or nitrogen for oxygen atoms. The hydrophobic exterior of the macrocycles can be modified by the addition of side-chains or functional groups to facilitate the solubilization of salts in organic solvents. The macrocyclic compounds serve as models for the investigation of the interaction of metal ions with biological systems. [Ion Binding by Synthetic Macrocyclic Compounds. Science *174*, 459—467 (1971); 50 references]

[Rd 475 IE –M]

Recent developments in the synthesis of organic compounds in liquid sulfur dioxide are described in a review by *N. Tokura.* The reactions proceed *via* carbenium ion intermediates. In most cases, SO_2 forms a charge-transfer complex in

$$R\text{-}X + CO + H_2O \longrightarrow R\text{-}COOH + HX$$

$$R\text{-}OH + H^{\oplus} \longrightarrow R\text{-}\overset{\oplus}{O}H_2 \xrightarrow{+H^{\oplus}} R^{\oplus} + H_3O^{\oplus}$$



which it acts either as an electron acceptor or an electrophile. Typical examples are those given in the accompanying scheme.

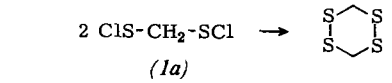
Other examples mentioned are Beckmann rearrangements and rearrangements of epoxides into ketones. [Recent Developments in Organic Synthesis in Liquid Sulfur Dioxide. Synthesis *1971*, 639—645; 56 references]

[Rd 471 IE –M]

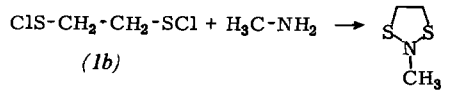
The stereochemistry of cobalt complexes with flexible tetradentate ligands is the subject of a review by *G. R. Brubaker, D. P. Schaefer, J. H. Worrell,* and *J. I. Legg.* The ligands treated are tetraamines and dithiadiamines with their donor atoms located in a straight chain, and ethylenediamine-*N,N'*-diacetate. The preparation of stereoisomers and the determination of their configurations, especially by the measurement of circular dichroism or optical rotatory dispersion, are described in detail. The importance of cobalt complexes of these ligands is due to their comparatively high kinetic stability against substitution reactions; it is conceivable, therefore, that knowledge gained from the study of cobalt complexes can be used for the determination of configurations of other transition metal complexes which cannot be isolated readily. [Complexes of Cobalt(III) with Flexible Tetradentate Ligands. Coord. Chem. Rev. *7*, 161—195 (1971); 102 references, 8 figures, 10 tables]

[Rd 477 IE –H]

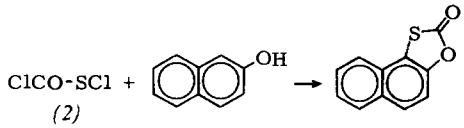
Substitution and cyclization reactions of sulfenyl halides are treated comprehensively in a review by *E. Kühle.* The main substitution reactions dealt with are the sulfenylations of hydroxy compounds, sulfinic acids, thioles, amines, NH acidic compounds, organophosphorus compounds, Grignard reagents, active methylene- and methine compounds, aromatics, phenols, and *N,N*-dialkylanilines. Bis(sulfenyl chlorides) such as *(1)*, ω-chlorocarbonylsulfenyl chlorides



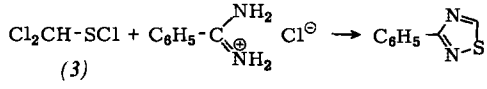
(1a)



(1b)



(2)



(3)

such as *(2)*, and substituted chloromethanesulfenyl chlorides such as *(3)* undergo cyclization reactions. Experimental details are given for individual reactions. [One Hundred Years of Sulfenic Acid Chemistry. Substitution and Cyclization Reactions of Sulfenyl Halides. Synthesis *1971*, 617 to 638; 325 references]

[Rd 470 IE –M]

BOOK REVIEWS

Titrationen in nichtwässrigen Medien (Titrations in Nonaqueous Media). By *I. Gyenes.* Ferdinand Enke Verlag, Stuttgart 1970. 701 pp., 206 figs., 108 tables, DM 84.—.

The book opens with an exposition of the various acid-base theories, together with discussions on the problems of acid and base strength and its dependence on the nature of the solvent. This gives a basis on which the processes occurring during titrations in nonaqueous media may be explained (120 pages). Some 70 pages are devoted to the solvents themselves, with particular reference to their properties, their behavior, and their purification; the titrants concerned, both acidic and basic, are dealt with in 35 pages or so.

End-point determination in titrations takes 140 pages. Descriptions are given of visual and photometric methods using color indicators, and also instrumental methods such as potentiometry, conductometry, oscillometry, voltametry, amperometry, and thermometry. In each case particular attention is paid to examples of application, without going into the fundamentals of the method.

The titrations themselves occupy 250 pages. Details are given of the determination of acidic substances, such as acids, acid anhydrides, acyl, alkyl, and aralkyl halides, enolic hydroxy and imide groups, phenolic and alcoholic hydroxy groups, nitro compounds, and acid salts. In the section on basic compounds, aliphatic, aromatic, and cycloaliphatic nitrogen-containing compounds and their salts are discussed. Methods are also given for the titration of carbonyl groups, sulfur-containing compounds, and organometallics.

This book has much of value to offer both to those concerned with theoretical aspects and those concerned with practical aspects. The latter will find very many specific analytical procedures and numerous useful tips. The book can be warmly recommended to anyone concerned with this subject area.

Günther Kraft [NB 17 IE]

Chemistry of Acetylenes. By *H. G. Viehe.* Marcel Dekker Inc., New York 1969, 1st edit., xv, 1298 pp., numerous tables and formulas, bound, $ 59.50.

This brilliantly successful book shows in clear and readily comprehensible form the rich and diverse nature of acety-

lene chemistry, and the extent to which acetylene derivatives occur in many fields of organic chemistry. Though intended primarily for research workers and chemistry students, it can also be used as a wide-ranging source of information to stimulate new ideas and as an easily understandable introduction to the individual topics of acetylene chemistry.

In the production of this book the author had the collaboration of 22 subject specialists from seven countries, and many other scientists. They have succeeded in creating a comprehensive survey of the chemistry of acetylene and its derivatives, thereby meeting a long-felt need of organic chemists. Topics not dealt with in detail in the text are completely covered by the approximately 4150 literature references, which contain practically all that is known and is worth knowing about the chemistry and reactions of acetylenes.

The book consists of 22 chapters, which deal with the following individual themes: theoretical considerations on the structure and physical properties of acetylenic compounds and the nature of the triple bond; preparation of acetylenes and polyacetylenes by dehydrohalogenation and other elimination reactions, and also by substitution reactions, starting with acetylenic compounds; ionic additions to acetylenes; radical additions; partial hydrogenation of acetylenes; rearrangement of alkynes to allenes; synthesis of cyclic and heterocyclic compounds by cycloaddition to acetylenes and cyclization reactions; coupling of acetylenes; preparation of halogenated acetylenes, alkynyl ethers and thioethers; ynamines; acetylene derivatives of elements of Groups III b, IV, and V of the periodic table; description of naturally occurring acetylenes; cyclic acetylenes; dehydrobenzene and dehydrohetarenes.

In order to achieve the desired degree of completeness, the book ought to contain a related section on the work carried out by *Reppe* with acetylene under pressure and a detailed description of *Reppe*'s discovery of the carbonylation of acetylenes. Some of these reactions are carried out today on an industrial scale, and have led to such valuable intermediates as acrylic acid and acrylic esters. The topics concerned are certainly covered by the literature references, but their description in the text would be an added boon for the reader.

Anyone concerned with the practical applications of acetylene chemistry should have this book close at hand. It is therefore to be hoped that this book, which by reason of its arrangement and its content is an irreplaceable reference work for the whole field of acetylene chemistry, will maintain its value in the future by revised editions, each of which will need to be brought up to the current state of the art.

Nikolaus von Kutepow [NB 18 IE]

Milk Proteins. Chemistry and Molecular Biology. Vol. 1. Edited by *H. A. McKenzie*. Academic Press, New York–London 1970, 1st edit., xvii, 519 pp., numerous figs., bound, $ 28.50.

Only about a quarter of this book, the first of a two-volume work, is devoted exclusively to milk proteins, and this consists of a brief historical and a longer chemical survey, which is also concerned with fractionation, nomenclature, biosynthesis, and biological functions, together with an extensive chapter on immunological studies. The main part of the book is concerned with the general chemical and physical methods of protein chemistry, and in particular with elemental analysis, the analysis of the functional groups of the amino acid, peptide, and carbohydrate residues, chromatography and electrophoresis (with particular regard to the interactions between the components of the mixture to be analyzed), spectrophotometry, and the other physical methods used to study changes in the degree of association, conformation, and structure.

The basic problem here is whether there is much point in describing general techniques in a book on specific substances. The answer in this case cannot be an unqualified no, since most of the techniques are illustrated with examples involving milk proteins, and in some (possibly too few) cases there are discussions on the method most applicable in the case in question. For the protein chemist, most of the chapters could have been shortened or replaced by references to appropriate monographs; however, the worker who is only occasionally concerned with proteins will welcome the explanations of the individual methods. For complete information it will be necessary to refer also to the second volume, which, according to the publisher's announcement, will deal with individual milk proteins and also the casein micelles and rennin. If the second volume matches the first in quality and attractive layout, this could be the best and most detailed work on milk proteins. The problems are discussed critically and precisely, and the literature has been surveyed up to 1970. The work is highly recommended.

H. G. Maier [NB 19 IE]

Lehrbuch der Pharmazeutischen Chemie (Textbook of Pharmaceutical Chemistry). By *H. Auterhoff*, with the collaboration of *J. Knabe*, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1971. 6th, revised and amplified edition, xii, 636 pp., 1 fold-out table, cloth-bound, DM 54.—.

This was the first German textbook of pharmaceutical chemistry that attempted to present the fundamentals of general inorganic and organic chemistry, in order to discuss more thoroughly the chemistry of compounds relevant to pharmaceutics, their analysis, and medical applications. The success of this approach is shown by the otherwise inexplicable fact that six editions of *Auterhoff*'s book have appeared within eight years. At present, the work has no rival. The present edition is arranged in the way that has proved so satisfactory in the past. The inorganic section, about 100 pages long, is arranged in accordance with the periodic table. The organization of the organic chemistry section presented considerable problems, and so a compromise has been arrived at; first of all the pharmaceuticals from the simple and more complex chemical classes are dealt with (*e.g.* hydrocarbons, alkyl halides, alcohols, phenols, carboxylic acids, amines, proteins, carbohydrates, steroids, alkaloids), followed by groups of pharmaceuticals arranged by their pharmacological or therapeutic properties (*e.g.* analgesics, psychotropics, coronary dilators, hypnotics, antihypertensives, cytostatics, chemotherapeutics, antibiotics, hormones, vitamins). This brief selection may show how wide a range of compounds is covered.

The sixth edition has not only been amplified to bring it as up to date as possible, but in addition some completely new chapters have been added, *e.g.* on the absorption, distribution, and biotransformation of pharmaceuticals and on enzymatic analysis. Particular care has been taken

with the redrawing of the structural formulas which are used to clarify the stereochemical relationships. In many cases references are also given to literature which will lead the reader deeper into the subject; the increase in this literature will have to be taken into consideration in further editions of this work.

Horst Böhme [NB 20 IE]

Einführung in die Optimierung (Introduction to Optimization). By *U. Hoffmann* and *H. Hofmann*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 1st Edit., xvi, 260 pp., 114 figures, 61 tables, paper DM 48.—.

The present book deals with methods for the optimization of parameters. The well arranged subject matter leads through linear programming (*Dantzig*'s simplex method) and dynamic programming *(Bellmann)* to the "hill climbing" methods of optimization, to which considerable space is devoted. Starting with one-dimensional search methods, all the important search methods for several variables with and without secondary conditions are discussed. A chapter on minimizing sums of squares follows.

The book is an explicit textbook. It is up to date and comprehensible, and is intended mainly for those who have no special mathematical knowledge. The material is backed up by simple but appropriate examples from the field of application and by many figures and tables. The student is practically forced to cooperate. Questions are interspersed to enable him to check whether he has understood the material. The flow diagrams of the various methods are also very useful, since the thought processes are repeated here. The necessary mathematical principles are presented in an appendix. This avoids any interference with the intuitive presentation of the problems.

Problems from chemical engineering are discussed at the end of the book in the chapter on examples of applications.

The aim of the authors was to present an intuitive introduction to optimization for the practical user, and in this they have succeeded. The book will undoubtedly win many friends.

H. Bakemeier [NB 27 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 40 36/40 37, Telex 46 55 16 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (0 62 01) 40 31, Telex 46 55 16 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 5
May 1972
Pages 347–450

International Edition in English

The Computer in Chemical Research—An Introduction

By Günther Wilke

With the appearance of this issue of Angewandte Chemie, an anniversary could be celebrated in the Mülheim Institute: twenty years ago the first commercially available IR spectrometer (Perkin Elmer) was put into operation. Presumably in a large number of other research laboratories in Europe, the same date marked the beginning of a new era during which a kind of revolution in chemical research began, initiating fundamental changes in the process of structural determination. Very soon UV and Raman spectroscopy, mass spectroscopy and gas chromatography, NMR and ESR spectroscopy, and finally X-ray structural analysis followed IR spectroscopy. Photoelectron spectroscopy can be cited as the newest development.

In the framework of preparative chemistry, the required tasks can be subdivided into the two fields of synthesis and analysis; clearly, the above physical methods have expedited primarily the secondary field—analysis (*viz.*, in particular, structural determination)—so that it can be approached today with a speed and accuracy that were not imaginable twenty years ago. At the same time it is also clear that in comparison the methods in the primary field of synthesis have developed comparatively little. The time requirements invested in the two areas have often been reversed by these developments, as is readily illustrated by an example of an olefin synthesis leading to a mixture of products. Formerly analytical fractional distillation required days, in some cases, weeks—out of all proportion to the time required for the synthesis—while today the gas chromatographic determination of the composition is obtained in a matter of minutes and much more accurately than was possible by distillation.

One could conclude from this reversal that the chemist is under pressure to produce ideas for new syntheses in faster succession than before. To a certain degree that is in fact the case; however, resources that were earlier dedicated to the second field are now at his disposal. One should not forget, however, that the physical methods not only provide the desired information previously obtained only by tedious chemical steps, but, in addition, yield an abundance of detailed information which must also be processed by the chemist. In any case an increased volume of information is produced which can only be evaluated through close cooperation of scientists from the two fields.

The next step of the development—the use of a relatively large computer in chemical research[*]—is described in the following six reports by different groups of the Mülheim Institute. Out of the structure of the Institute has evolved a system which is occasionally referred to as the "Mülheim System". Thus a few details about the Institute are appropriate. The Max-Planck-Institut für Kohlenforschung consists of two parts, the main institute (founded 1914) and the independent division for radiation chemistry (founded 1958). The principal areas of study concern general organometallic chemistry, electrochemistry, catalysis, photochemistry, as well as theoretical and radiation chemistry. Altogether about 120 scientists (including graduate students) are employed.

The X-ray structural analysis group, which had difficulties in obtaining adequate facilities in computer centers, initiated the discussions about acquiring a computer. A committee was formed including all parties concerned. After considerable discussion the committee established

[*] Prof. Dr. G. Wilke
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

[*] Determining synthetic routes with a computer will not be discussed here: *E. J. Corey* and *W. Todd Wipke* have already treated this topic in an interesting article (Science *166*, 178 (1969)).

all the demands to be made of the computer in "off-line" and "on-line" operation and finally contacted numerous computer manufacturers. It was soon apparent that one of the manufacturers was able to satisfy the special needs of "on-line" operation at a reasonable price. The decision for this system was made by the members of the committee and the purchase was financed by the Max-Planck-Gesellschaft and, supplementarily, out of the resources of the Institute.

Experience gained with the system since 1968 is described in the following reports from the standpoints of the different groups. The preparative chemist, even though he himself is least directly involved, usually benefits from the advantages of the system. Accordingly, the secondary field defined above was developed further. There are good prospects that the new system will benefit the primary field not only indirectly but directly if it is possible to link the computer with an analytical system (*i.e.*, a gas chromatograph) and reactor to control the reaction process. Such a mode of operation would extend the available laboratory techniques. In the Mülheim Institute the first attempts of this kind have already been successful.

For the theoretician, on the other hand, direct access to a computer installation is absolutely essential for fruitful work.

A few remarks on the following progress reports appear to be in order:

The reports are by no means written only for the specialist. The chemist not familiar with data processing should also take an interest in these problems; even without a detailed knowledge he will quickly appreciate what possibilities exist. A certain amount of repetition was unavoidable. Also, one must become accustomed to computer terminology; a few technical terms are explained in a glossary.

Finally, a word of warning: The methods of experimental analysis available today entice us to work on and to solve problems at great expense which, with regard to the real worth of the knowledge obtained, can in no way be justified. The analytical apparatus can soon become overburdened without really achieving anything new. A critical evaluation and selection of the problems to be treated with these tremendous resources is more important than ever before. In the enthusiasm over our present facilities, we should never forget the outstanding achievements of those who worked without these resources, *i.e.* before 1952.

Received: November 18, 1971 [A 865 IE]

German version: Angew. Chem. *84*, 370 (1972)

Computer Systems for Chemical Research

By Engelbert Ziegler, Dieter Henneberg, and Gerhard Schomburg[*]

1. Introduction

As in almost all areas of our daily lives, digital computers have also invaded the field of chemical research. If one thinks of the first successes of *Corey* and *Wipke*[1], who used a computer system for the determination and optimization of synthesis paths in preparative chemistry, or of the development of documentation systems for chemical literature or for molecular spectra, one can imagine the new possibilities which will become available to the chemist in the future through the increased use of computers and how the chemist's way of working could be affected.

The purpose of this paper is not so much to give a picture of future developments in the field but rather to serve as a brief survey of the current uses of digital computers in chemical research and of the corresponding computer systems. The system developed at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr, Germany, is described.

[*] Dr. E. Ziegler, Dr. D. Henneberg, and Dr. G. Schomburg
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

2. Applications in Chemical Research

The customary applications of computers can be divided into two areas:

1. Computational tasks ("off-line" operation) and

2. connection of analytical measuring instruments to a computer system ("on-line" operation).

2.1. Off-line Applications

Calculation problems from theoretical chemistry, such as those arising in the various computational approaches to MO theory or in reaction kinetics, are usually solved in off-line operation. Also falling into this category are the various kinds of computations in the field of spectroscopy and for literature and spectra documentation.

Many of these computer programs place considerable demands on the efficiency and capacity of the computer. A core memory of 32 K 36-bit (or at least 32-bit) words is a typical requirement. Aside from this, extensive computing time requirements are characteristic for such off-line pro-

grams. Even on large computers, computing times of an hour or more are by no means a rarity. (For example, evaluation programs for X-ray structure analysis run particularly long.) A further characteristic of most of these programs (exception: documentation systems) is the relatively low number of input and output operations.

As long as the programs have been tested out and average turn-around times of several hours or even days are considered tolerable, then conventional batch operation, in which the programs are processed one after another, is suitable.

For small calculations of all types, however, like those which can occur in the daily laboratory routine, a faster access to the computer and fast reporting of the results are desirable. An input-output teleprinter terminal located in the laboratory and connected to a computer considerably facilitates the use of the computer for such tasks.

2.2. On-line Applications

A completely different type of use for a computer is the real-time acquisition of data from analytical instruments coupled to the computer. The data occur either in digital form or—more frequently—as analog values, normally a voltage. For computer processing these voltages must first be digitized with an analog-to-digital (A/D) converter. An interface between the A/D converter and the computer allows proper mutual communication.

One could consider it irrelevant whether a card reader, a magnetic tape, or an A/D converter is connected to the computer. Viewed from this angle the interface to an analytical instrument would merely be an additional peripheral unit in a normal computer system such as is used for the previously mentioned off-line computations.

However, whereas conventional peripheral devices like magnetic tapes or card readers transmit data to the computer according to the needs of the program, the data from an analytical instrument must be taken by the computer at the points in time which are determined by the on-line experiment (real-time data acquisition).

The typical demands on an on-line system cannot be specified without going deeper into the individual problems. The structure of an on-line system is essentially determined by:

Data rate (data points per second)

Data volume (number of data points)

Precision of measured values

Reduction of data in real-time

Extent of closed-loop operation

Number of analytical methods to be served simultaneously

Number of analytical devices of the same type to be served simultaneously

Storage and temporary storage of data

Complexity of data evaluation

Type and speed of parameter input and result output

Requisite flexibility of hardware and software

Frequency of changes in problem specifications

Degree of operational reliability required

Existing laboratory structure and the possible extent of reorganization necessary

Available financial means for purchase and maintenance

Available personnel.

Besides the computer, an A/D converter, a real-time clock as an external timer, as well as relay inputs and outputs for registration and control of start/stop events normally make up the hardware of an on-line system. In almost all cases a peripheral data storage medium (preferably disk or tape) is indispensable. Closed-loop systems often also need a D/A converter.

3. On-line Systems for Analysis

Spectroscopic and analytical instruments have been continually improved; they have usually also become correspondingly more complicated and more expensive. The direct connection of these instruments to a digital computer is a further step in this direction. However, for the analyst and the spectroscopist this step is in no way unproblematic. On the one hand they are offered tempting new possibilities; on the other hand they see themselves confronted with, for them, a new and multifariously complicated subject. Moreover, since the purchase costs for an on-line system are at least as high as for a large analytical instrument, one should consider the installation of such a computer system especially thoroughly. For that reason several arguments for the computerization of analytical instruments are enumerated here. Their weights depend on the specific requirements of a laboratory and must be discussed for the individual case:

Increase in the accuracy and precision of analysis

Speeding up of the evaluation

Increase in analysis through-put

Gain of more information

Performing new types of experiments

Control of an experiment

Processing of spectra for documentation purposes

Saving of personnel

Supervision of personnel.

The multiplicity of measuring instruments on the market, the tasks which vary considerably from laboratory to laboratory, the differing forms of organization of the analytical work, and finally the large number of computer types which come into question have brought about the development of many very different on-line systems. Most of the present systems can be placed in one of the following categories:

1. dedicated (single-purpose) systems

2. multi-method systems

3. mixed systems (both on-line and off-line processing), with satellite computers or without.

Table 1. Areas of application for the various types of on-line systems.

System	Typical computer requirements	Especially suited for	Typical environment
Dedicated systems 1. one instrument per computer	small computer, 4—8 K	instrument control, fast data acquisition, long running experiments	largely independent of laboratory type
2. variable-purpose dedicated system	small computer, 4—8 K	alternative connection to one of several instruments	research lab (university)
3. several instruments of the same type per computer	small to medium-sized computer 8—16 K	slow data acquisition, simple evaluation, limited instrument control	routine industrial lab (*e.g.* quality control)
Multi-method systems (small or medium-sized computer)	usually medium-sized computer, 8—16 K		routine lab with essentially unchanging demands
Mixed system (with conversational time-sharing operation)	large computer, 32 K; extensive periphery	real-time data acquisition, processing of large volumes of data, complicated evaluation procedures, limited instrument control functions	research and industrial labs with many analytical methods
Satellite systems (with dedicated satellites)	large computer, 48 K; several small computers; extensive periphery; possibly complicated data transmission	instrument control, many devices with high data rates, complicated evaluation procedures, off-line calculations	large institutions with a wide range of analytical methods, large computer centers with some real-time applications

The areas of application of these three categories of on-line systems are summarized in Table 1. Their essential characteristics will be briefly described below.

3.1. Dedicated Systems

To this group belong the computer systems that serve either one single instrument or several instruments of the same type (such as a group of gas chromatographs). It is essential that the computer work with a uniform programming system ("software").

3.1.1. Computer Systems for a Single Instrument

Measuring devices for fast-running physical events (for instance a Fourier-transform NMR spectrometer or a fast-scan mass spectrometer) produce very many digitized values in a short time (data rates in the kHz region) that have to

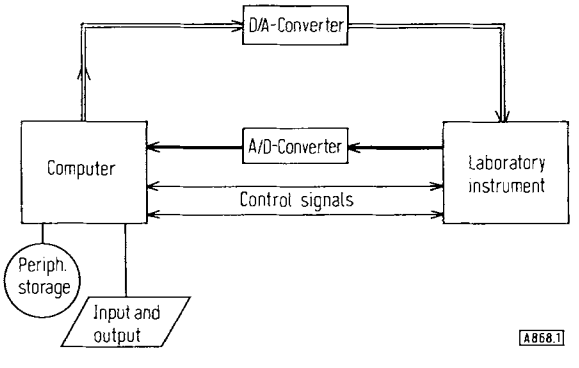


Fig. 1. Block diagram of a single-purpose ("dedicated") system in which a computer is used for the data acquisition and control of a single analytical instrument.

be accepted by the computer and further processed or stored away. In addition to the high data rates, complicated evaluation programs are frequently necessary. Therefore, a small dedicated computer may be necessary for devices with such demands.

Single-instrument computer systems (Fig. 1) can be adapted to the requirements of the respective instruments and are particularly suited for experiments that require many feedback control operations from the computer, for example the computer-controlled single-crystal diffractometer. With this latter application a measurement usually extends over several days; therefore, a particularly high system reliability, usually not achieved by complicated computer systems, is required.

From an economical standpoint such on-line systems are still very unfavorable; normally the computer together with peripherals and interface is more expensive than the measuring instrument itself. However, the development of "integrated" measuring instruments is foreseeable. Here the computer hardware is distributed as an integral constituent over the components of the instrument. This, of course, entails a completely new construction of conventional analytical instruments. As a consequence of continuing further development and reduction in cost of components such instruments with a "built-in" computer need not necessarily be more expensive than the currently existing instrument without computer.

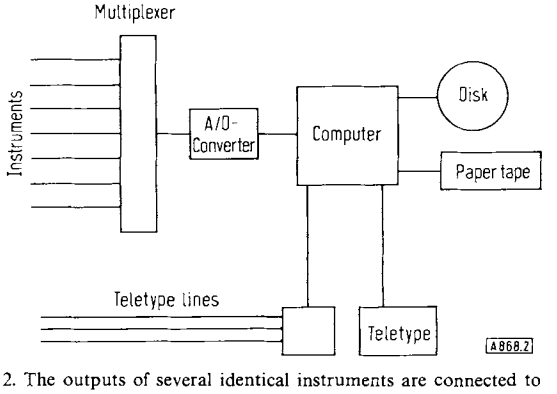


Fig. 2. The outputs of several identical instruments are connected to the computer through a multiplexer.

3.1.2. Multiple Instruments of the Same Type on one System

For economic reasons one would today still try to serve as many instruments as possible simultaneously with one computer (Fig. 2). If it is a question of devices all of one type, like a number of gas chromatographs, then it is relatively simple for all of the instruments to work with the same programming system; this means that only one copy of the data acquisition routines and evaluation programs need be in the computer.

3.2. Multi-method Systems

If different types of instruments (for instance gas chromatographs and IR, NMR, or mass spectrometers) are connected to the same computer systems for simultaneous service, then different evaluation programs and often also different data acquisition programs are required, depending on the application. In such a system a monitor program is necessary; it is reponsible for distributing the central processor time among the programs.

In order to be able also to gather the data from active instruments during data processing, the computer must operate with an "interrupt system" with several priority levels. With this system an external real-time clock can interrupt the currently running program by an electronic impulse. On such an interrupt, the monitor program decides which instrument takes its turn for the acquisition of data next, switches the multiplexer to the corresponding channel, and starts the A/D conversion. Until the completion of this activity (signaled by another interrupt), the computer can return to the previously interrupted program or switch to another one.

The programming effort for such a multi-method system is quite considerable. The parallel measurements must be tuned to each other in relation to memory requirements, external storage demands, data rates, and computing times.

Program maintenance (removal of programming errors, technical programming improvements, installation of new evaluation algorithms) can become quite a serious problem in such a system. During alteration of a program only relatively large "nice" computers prevent any influence (for instance through faulty programming) on parallel running programs. Therefore all program changes must be tested out on the total system, which is frequently quite troublesome. However, the more instruments of different types are connected to the computer system simultaneously, the more frequent such changes will be, which then disturbs the total operation considerably.

For this reason, multi-method systems are not suited for use with small or medium-sized computers, in particular for research laboratories with frequently changing problems. However, such systems could be useful for some industrial laboratories working with a set of tested programs for an extended period.

The advantage of a multi-method system over several dedicated systems lies in a saving of hardware. Only one central processor is required and duplication of some peripheral units (which therefore can be of better quality) is avoided.

3.3. Mixed Systems (Simultaneous On-line and Off-line Processing)

If a computer system serves not only several directly connected analytical instruments, but also concurrently runs one or more off-line programs ("background processing"), then it may be called a "mixed system".

If such a system is to work effectively, then an efficient central computer is required, the hardware of which guarantees that individual programs are completely protected from one another. Since many off-line programs are not completely tested and are therefore potentially faulty, such program protection is indispensable.

A mixed system offers the advantage that the many peripherals usually associated with a large computer, like line printers, card readers, disks and magnetic tapes, offer on-line users possibilities which do not exist with small computer systems.

Besides the large central computer some mixed systems employ several subordinate small computers ("satellites") for the acquisition of data from the connected analytical instruments and for pre-processing of these data. Through the satellite computers the central computer can be relieved of the pure "bookkeeping" tasks and need only occupy itself with the extensive calculations of the data evaluation work.

A variant of the satellite system is the "multi-mini" system in which a small computer (if possible of the same type as the satellites) is used as the central computer, or in which there is no central computer. In the latter case the small dedicated computers are connected with each other in a network fashion. The lack of an efficient central computer means, however, that heavily computational programs cannot be accommodated. In addition, the operating system of the small central computer, which must organize the data communication to the satellites, clearly cannot be so flexible and efficient as is possible with a large computer.

Section 4 presents a general discussion of the advantages and disadvantages of a mixed system taking the Mülheim Computer System as a typical example.

3.4. Failsafe Systems

The computerization of analytical instruments makes analytical laboratories largely dependent on the computer; therefore the greater the number of instruments connected to the system, the more serious a system breakdown can be.

The most certain measure against such "disasters" would be an identical second system that processes the same data in parallel with the first system. However, such an expenditure is normally justified only for some process-control computer installations supervising manufacturing processes. Obviously in this case one would try to keep the duplicate system as small as possible.

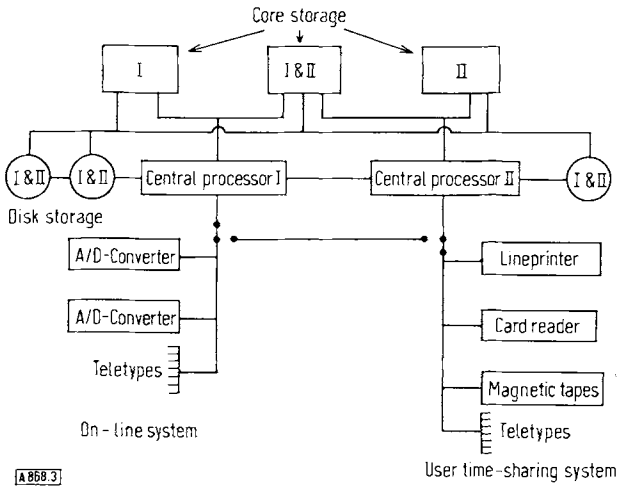


Fig. 3. The Du Pont company's failsafe system. On failure of the central processor responsible for the real-time processing, the other processor automatically takes over the duties of the first one.

For the computerized experiments in the field of chemical research no such high operational reliability is required; partial security against the worst failures is sufficient.

Interesting in this respect is a failsafe-system being built at the Du Pont company's Experimental Station in Wilmington, Delaware, USA[*]. This system consists of two coupled (PDP-10) central processors, one of which normally serves exclusively for the real-time acquisition of data from the analytical instruments, while the other is used for the evaluation of the real-time data and the execution of off-line programs (Fig. 3). Part of the memory and some of the peripheral units are commonly accessible to both central processors. Should the central processor responsible for the real-time data acquisition fail, then the other one takes over this task automatically.

4. The Mülheim Computer System

4.1. Computer Applications at the Max-Planck-Institut in Mülheim/Ruhr

At the Max-Planck-Institut für Kohlenforschung, including the radiation chemistry division, in Mülheim/Ruhr, almost all possible applications for computers in chemical research are represented. Among the off-line tasks programs exist for:

X-ray structure analysis

MO theory

Reaction kinetics

Simulation and iteration of spectra

Evaluation of spectra

Spectra documentation

Literature documentation

Support of the Institute's administration.

[*] Dr. *E. A. Abrahamson*, Dr. *J. Fok*, and Dr. *J. Read*, Wilmington, Delaware, private communication.

In addition to these there are smaller labor-saving programs of all types.

The extensive spectroscopic, analytic, and physical chemistry laboratories of the Institute have at their disposal a large number of analytical instruments, some of which should be connected directly to a computer (for the current state see Section 4.6):

1. "Slow" instruments (data rate *ca.* 20 Hz)

20—30 gas chromatographs

1 mass spectrometer

2—3 NMR instruments

1 IR spectrometer

1 ESR instrument

1 spectral polarimeter

2. "Fast" instruments (data rate 1 to 20 kHz)

2 low-resolution fast-scan mass spectrometers

1 pulse NMR instrument

While the purchase of one or more computer systems for all of these areas of application was under discussion in 1967, two alternatives were open to the Institute:

1. The purchase of a medium to large computer that would be used in batch mode for all off-line computing problems, supplemented by a number of small computers for several dedicated on-line systems for the analytical instruments.

2. The purchase of a single, more capable computer possessing both the hardware and software for a multiprogramming time-sharing system and simultaneous off-line and on-line operation.

4.2. Hardware Configuration of the PDP 10

For financial and organizational reasons the second alternative was chosen.

In December 1968, the first part of a PDP10 installation[*] was put into operation; in April and September 1969, the additional hardware required for the on-line applications was installed; in July 1970, the system was expanded by the addition of 32 K of core memory and a disk pack unit. The present system configuration is represented in Figure 4.

The hardware of the PDP10 central processor includes 366 machine instructions (including floating-point and byte instructions), an interrupt system with seven priority levels, as well as memory protection registers. The present memory capacity is 64 K 36-bit words. Two channels for fast data transmission connect the memory with a fixed-head disk (average access time 17 ms, transmission rate 77 K words/s, capacity 500 K words) and a disk pack (average access time 60 ms, transmission rate 62 K words/s, capacity 5000 K words).

A part of the fixed-head disk is used for temporary copies of the core image of running programs ("swapping" operation) if the memory is not sufficient to hold all parallel

[*] Producer: Digital Equipment Corporation, Maynard, Mass. (USA).

running programs. However, the major portion of disk space serves for storage of programs and data.

Additional peripheral units include a line printer, a card reader, magnetic tape units, a plotter, paper tape reader and punch, as well as 22 input/output teleprinters which serve as user terminals for time-sharing operation.

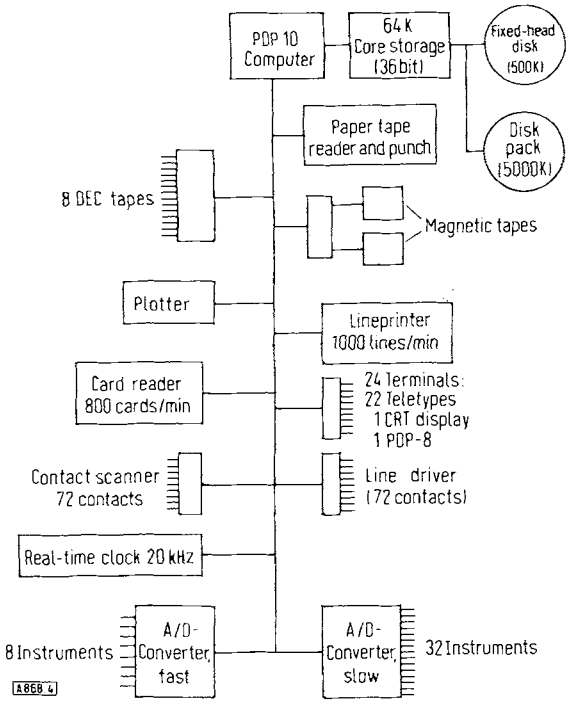


Fig. 4. Hardware configuration of the PDP10 installation at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr, Germany.

Several special units serve as interfaces between the computer system and the directly connected analytical instruments: Up to 32 "slow" instruments can be connected to a high quality A/D converter by means of a multiplexer unit. This A/D converter works with a 13-bit resolution in 11 amplification ranges, and therefore has a dynamic range of nearly 10^7. The total data rate amounts to 3.3 kHz with automatic range selection.

For the "fast" instruments another A/D converter is used that can work with data rates between 1.25 and 20 kHz. The resolution is 10 bits; the dynamic range 2.5×10^5, and is subdivided into three ranges of amplification. Up to eight instruments can be connected to this A/D converter by means of a multiplexer. However, in order not to disturb the normal time-sharing operation and the simultaneous data acquisition from the "slow" instruments only one of the eight possible "fast" instruments is allowed to be active at any one time. Due to the short recording times of about 2—3 seconds for such instruments, this restriction is no serious hindrance.

The clocking of the data for each of the two A/D converters is done by a real-time clock (quartz oscillator, 20 kHz) and two digital counters.

72 contact inputs allow the recognition of the closing and opening of external circuits; 72 relay drivers permit external relays to be opened and closed by the computer. With this equipment the computer recognizes start and stop commands for the real-time data acquisition and can control external events. Non time-linear registering instruments like IR spectrometers notify the operating system of the time for every A/D conversion by closing an external contact.

4.3. Time-sharing Operation

In the current version of the operating system up to 23 jobs can be handled simultaneously. The jobs are initialized by the users at any time from the teletype stations distributed throughout the Institute. The jobs each control the running of one program that the user has started by typing a command at the teletype. Data can be entered and the results printed out *via* the teletype. (Any other peripheral units can naturally also be used for data input/output.)

```
STATUS OF MUELHEIM 4S72R.1AM AT 15:21:50 ON 03-SEP-70

UPTIME 165:01:50, 54% NULL TIME = IDLE+LOST = 51% + 3%

JOB   WHO      WHERE   WHAT    SIZE   STATE      RUNTIME

1     **,**    DET     SELDAT  2K     SL         00:04:59
2     **,**    DET     MSDAT   4K     SL         00:00:00
3     1,2      TTY26   ORGANI  1K     SL         00:36:42
4     13,33    TTY17   ADSTAT  4K     ↑C SW      00:05:04
5     56,102   TTY11   PIP     1K     TT         00:00:42
6     5,21     TTY7    SYSTAT  2K     RN         00:00:15
7     11,30    TTY15   TECO    2K     TT         00:07:12
8     11,30    TTY1    REFREP  11K    TT         00:04:13
9     13,33    TTY5    TECO    2K     TT SW      00:00:48
10    150,45   TTY2    PIP     1K     IO         00:01:39
11    200,202  TTY6    TECO    2K     TT         00:00:01
12    11,30    CTY     PARAM   6K     TT         00:00:00
13    5,14     TTY4    ADSTAT  4K     TT SW      00:00:00
14    **,**    DET     OPFILE  3K     ↑C SW      00:00:38
15    40,60    TTY16   HEY11   8K     TT         00:01:17
16    **,**    DET     HIP     4K     ↑C SW      00:00:49
18    22,40    TTY10   NMRCAT  8K     ↑C SW      00:00:02
```

A868.5

Fig. 5. "Snapshot" of the state of the simultaneously processed jobs in the Mülheim System: SELDAT (Job 1) is the data acquisition program for the "slow" on-line instruments, MSDAT (Job 2) the data acquisition and pre-reduction program for the mass spectrometer; ORGANI (Job 3) is a control program that initializes several programs; REFREP (Job 8) produces outputs of gas chromatograms; PARAM (Job 12) is used to input parameters for on-line runs of "slow" instruments; NMRCAT (Job 18) is a time-averaging program for NMR spectra.

The commands typed in on the teletype are interpreted by the operating system. The operating system also determines the distribution of central processor computing time, the allocation of memory, and the assignment of peripheral units to the individual jobs. Whenever a job begins an input or output operation *via* one of the seven priority levels of the interrupt system, or after the apportioned amount of computing time ("time slice"—from 0.5 to 2 seconds) has run out, the operating system searches for another job to occupy the central computing unit. Figure 5 shows a representative "snapshot" of computer operation.

The time-sharing mode of operation allows a regular dialog between a program and a user. Figure 6 is an example of such a dialog; here the input of parameters for a plotting program is presented. Explanations and warnings for the inexperienced user have been provided in the program.

The scientist who has immediate access to the computer and the banks of data stored there by way of a teletype located at his place of work can use the computer as a constantly available thinking aid just as on a less sophisticated level he uses a slide rule or mathematical tables.

```
.R DATPLT

ANSCHLUSSNR.: 15

KEIN DATENSATZ FUER ANSCHLUSS 15 VORHANDEN!

ANSCHLUSSNR.: 14

X-ANFANGS- UND ENDWERT: ?

ANFANG UND ENDE DES GEWUENSCHTEN AUSSCHNITTS MUESSEN DURCH
DIE DAZUGEHOERIGEN PUNKTNUMMERN SPEZIFIZIERT WERDEN.
SOLL DIE GESAMTE MESSKURVE GEZEICHNET WERDEN, SO GENUEGT
EIN <CR>.

X-ANFANGS- UND ENDWERT: 1000,3000

DEHNUNG (PUNKTE/ZOLL): 5

WARNUNG! DIE ZEICHNUNG WIRD 10.16 M LANG! OK?: NEIN

DEHNUNG (PUNKTE/ZOLL): 100

MAXIMALAMPLITUDE (ZOLL): ?

DIE NUTZBARE ZEICHENHOEHE BETRAEGT 10 ZOLL.
FUER BELIEBIGE DEHNUNGEN KOENNEN JEDOCH AUCH GROESSERE
AMPLITUDEN ANGEGEBEN WERDEN.

MAXIMALAMPLITUDE (ZOLL): 20

TEXT: DEMONSTRATION                                    A 868.6
```

Fig. 6. Example of a programmed dialog: By typing the command "R DATPLT" the user starts a program for plotter representation of a spectrum which was measured on-line; he specifies necessary parameters in a dialog with the program. (For clarity, all user responses appear underlined.)

4.4. Organization of Real-time Data Acquisition

The dynamic time-sharing operation enables on-line and off-line jobs to be run simultaneously. For the real-time data acquisition a common data-job is needed for all "slow" instruments and one data-job for each active "fast" instrument. These are programs which essentially contain data buffers for the individual instruments. The individual data are read in by the computer on one of the interrupt levels, so that the running programs are only interrupted for several microseconds. As long as instruments are actively transmitting data, the corresponding data-jobs must remain in the core, *i.e.*, they may not be moved out to the disk during monitor swapping operations. This feature and a preferential allocation of computing time distinguish the data-jobs from the other user programs.

For the "slow" instruments the data are transmitted buffer-wise to the disk without any pre-processing; separate data sets are used for each device. For the "fast" mass spectrometers a pre-reduction of the data is carried out by the data-jobs; only reduced data reach the disk.

After the stop command the data belonging to each instrument are further processed by analysis programs (which run as separate jobs). If several instruments (for example a group of gas chromatographs) use the same analysis program, then this program can be initialized to check the status of all instruments in question at regular time intervals; on completion of a data acquisition experiment the evaluation is carried out automatically. (For a detailed description of the software organization see [2, 3].)

4.5. Flexibility of the System

The time-sharing system allows a very flexible, stepwise evaluation of the measured data. An evaluation program can be organized in dialog form so that the user can receive intermediate results over the teletype and can be questioned as to further steps in the evaluation. The individual steps of the evaluation can also be carried out with several sequentially callable programs. According to the intermediate results the user can decide freely which programs to use for further processing. For example, for a molecular spectrum, procedures for smoothing and for improving the resolution, peak searching algorithms, and so on, could be used in any sequence depending on the results of the experiment. The freedom of the user is not affected in any way by other users who are working with the computer at the same time—apart from the competition for common peripheral units such as line printers and plotters.

This high degree of flexibility is not only advantageous but necessary for analytical laboratories in a research institute with frequently changing analytical problems[4, 5]. However, a standard program can still be used for certain routine analyses with fixed evaluation procedures. This program needs no parameter input and supplies the final result in the form of a report on the teletype.

The time-sharing mode of operation proves especially advantageous in the development and check-out of new programs. As an example, new evaluation programs can be tested out without the danger of disturbing other users. With text editors it is possible to modify programs over the teletype and to immediately try out the corrected programs —without the long turn-around times associated with batch

systems. This direct contact between the programmer and the computer has considerably accelerated the development of programs for on-line application.

4.6. Current State and Reliability of the Mülheim System

So far, 23 gas chromatographs, an NMR spectrometer, an IR spectrometer, a spectral polarimeter ("Cary 60"), an ESR instrument, and a slow mass spectrometer are connected *via* the "slow" A/D converter; a fast-scan mass spectrometer and a pulsed NMR instrument are connected through the "fast" A/D converter.

Of the currently used computing capacity (in 24 hour operation 20 to 25%) almost 90% are off-line calculations and only about 10% are for the acquisition and processing of on-line data.

Off-line programs requiring more than 28 K of core must run at night, *i.e.* between 5 p.m. and 8 a.m. One reason for this is that they would cause an unreasonable amount of swapping activity during daytime operation; a second reason is that for very large programs the amount of core left free by the resident monitor (presently 41 K) is not sufficient, so a special operating system must be loaded.

The reliability of the operating system has increased through continual improvements in the course of time, so that practically no software crashes occur any more.

However, there are still occasional hardware failures that usually result in down-times of an hour to one or two days (maximum to date).

4.7. Disadvantages of the Mülheim System

A large computer system such as the Mülheim system is always unflexible if changes are necessary in the very complex operating system. Besides the interrupt routines for the real-time data acquisition, all the controlling routines necessary in real-time for a connected instrument must be present as subroutines in the operating system. For this reason it is impossible to provide for real-time control of cases in which the operating system would have to be changed too frequently because of changing experimental requirements. Additionally, the "book-keeping" cost of real-time routines in a time-sharing system is substantial. In particular, however, no real-time experiments that run over very long periods, for example several days, should be connected to a large system; the normal operation can be interrupted not only by regular maintenance work, but also by unforeseeable system failures. For this reason no attempt was made to have the Institute's automatic X-ray diffractometer controlled by the PDP 10[6].

4.8. Personnel Requirements

The Mülheim computer installation is run by a physicist, a mathematician, two programmers, an operator, and a maintenance engineer. This group also developed the major portion of the software for on-line applications. Members of most of the analytical groups of the Institute are also involved to some extent with program development.

Good teamwork between the computer personnel and the analysts proved to be an essential prerequisite for the successful construction of the system. Cooperation is also necessary with the electronics engineers to ensure trouble-free connection of analytical instruments.

5. Comparison of Computer Systems for Chemical Research

Since most research laboratories have access to a large computing center where off-line programs can be run, the main interest is usually focused on the purchase of an on-line system (see however Sections 5.6 and 5.7). The scopes of the various types of on-line systems have already been discussed in Section 3. It is, however, fitting to consider once more the advantages and disadvantages of small dedicated systems and large mixed systems.

5.1. Programming

The parts of programs for real-time data acquisition and possibly real-time control are easier to develop and in most cases also easier to modify in dedicated systems than in large ones with complicated operating systems.

On the other hand, the analysis programs are simpler to produce in large systems because they can usually be written in a high-level programming language such as FORTRAN. Programs for debugging and text editing are available for fast program modification as well as labor-saving peripheral devices (listings, copying programs). (See also Table 2.)

5.2. Computing Capacity

For some evaluation procedures (for example in mass spectroscopy) the greater computing power and larger storage capacity of a large system are desirable and sometimes also essential. In such cases the use of small systems is often limited to pure data acquisition or limited preprocessing, so that the stored data must be evaluated later off-line in a computing center.

5.3. Flexibility

As already emphasized elsewhere, a large mixed system which makes possible a conversational time-sharing mode is in many respects more flexible for the user than a dedicated system.

This holds for the programming as well as for the handling of data. The possibility of modifying programs without great difficulty and adapting them to new demands is especially important for laboratories with frequently changing tasks.

Table 2. Programming of on-line systems.

System	Real-time data acquisition and processing	Evaluation	Testing and editing of evaluation programs	Flexible use of different evaluation programs
Dedicated systems 1. one instrument per computer 2. variable-purpose dedicated system	very simple (no overlapping of different analytical methods)	troublesome (normally done in assembly language)	difficult (small memory, few testing aids, program	possible with extensive periphery
3. several instruments of the same type per computer	simple (but possibly complicated scanning algorithms)	very troublesome (assembly language, several instruments)		
Multi-method systems	difficult (timing correlation)	very difficult (assembly language, different analytical methods)	very tedious (a change for one method influences all the others)	
Mixed systems	very difficult (implementation within a complete operating system); time-sharing operating system from the manufacturer is a prerequisite	very simple (FORTRAN, no overlapping of evaluation programs of different instruments or of data acquisition parts, complicated evaluation procedures can be employed, access to extensive banks of data)	very simple (no influencing of other users, fast work with text editors, efficient testing aids, ease of use because of extensive periphery)	extremely simple (because of possibility of time-sharing dialogs!), stepwise evaluation possible depending on intermediate results
Satellite systems	simple for dedicated satellites, but conflicts with operating system possible			

In contrast, dedicated systems are more flexible in their hardware composition. They are therefore better suited for laboratories tending to experiment with hardware.

5.4. Maintenance and Operation

No maintenance personnel is normally required for a dedicated system and the user need not make allowances for other users. Small systems are also usually more reliable than complicated large systems.

Although failures are more frequent with large systems, they usually do not last so long since a maintenance engineer is invariably close at hand.

5.5. Laboratory Organization

Only dedicated systems come into question for small, individual laboratories. Also laboratories with several analytical instruments but only infrequent analyses can work with a dedicated system connected to one instrument at a time depending on requirements (standard interface essential!). Such a "multi-purpose" small-computer system, which might be transportable between laboratories, is loaded with a different programming system according to the particular analytical instrument connected to it. "Interpreter" languages (BASIC, FOCAL, *etc.*) or languages especially developed for analytical methods can be used for a relatively simple data evaluation.

However, for larger laboratories or for a number of neighboring small laboratories the advantages of a large computer system cannot be ignored.

5.6. The Decision to Buy

The decision to buy a small system is easier to make because of the lower costs and the corresponding lower risks. The purchase of a large system may require the collaboration of many interested parties. Any agreement must be based not only on financing, type, and size of the system to be

Table 3. Management considerations concerning on-line systems.

System	Typical price (DM)	Decision to buy	Operational costs
Dedicated systems 1. one instrument per computer 2. variable-purpose dedicated system 3. several instruments of the same type per computer	80000 100000 200000	easy (low costs, low risk, no organizational difficulties, fast operational capability)	low
Multi-method systems	400000—1500000	not so easy (the mutual interests of several parties must be met, limited system efficiency)	low
Mixed system	2000000	difficult (high costs, many parties concerned, possible reorganization or merging of labs, time-consuming planning and development, consideration of existing computer centers, company politics, or national motives concerning computer manufacturers)	maintenance engineer and highly specialized personnel necessary
Satellite systems	3000000		

purchased, but also on the later organization and manner of operation (see Table 3).

In many cases existing computing centers hinder the purchase of a large mixed system. However, it is often overlooked that many of the existing computer installations, even without scientific or chemical applications, are running near capacity or will be within a few years. Moreover, at least in the industrial area, the computing centers are normally oriented toward commercial applications. Scientific and technical applications, for which other types of computers and other forms of organization of computing operation are more suited, often appear as intruders.

5.7. Future Developments

Large mixed systems are desirable not only because of the requirements of data acquisition and processing for the directly connected analytical instruments: As previously mentioned, the early developments of computer programs for the support of the preparative chemist, the implementation of documentation systems, as well as continuously improved methods of interpretation in spectroscopy stimulate the purchase of large computers for the field of chemical research. Moreover, since many documentation systems and complicated evaluation procedures utilize the data sets from on-line systems, the most intimate possible union—which the mixed system optimally offers—of on-line and off-line systems is desirable.

Because of the relatively low level of exploitation of a large system by on-line tasks alone, such a system becomes economical only with the inclusion of several intensive off-line computations. A similar degree of computer usage could be attained by using the computer for training students.

Received: November 18, 1971 [A 868 IE]
German version: Angew. Chem. *84*, 371 (1972)
Translated by *Allan B. Wilson*, Mülheim/Ruhr

[1] *E. J. Corey* and *W. T. Wipke*, Science *166*, 178 (1969).

[2] *E. Ziegler*, Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Cleveland 1969; *E. Ziegler, D. Henneberg*, and *G. Schomburg*: Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Cleveland 1970.

[3] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Anal. Chem. *42*, 51A Aug. (1970).

[4] *G. Schomburg, F. Weeke, B. Weimann*, and *E. Ziegler*: 8th Internat. Symposium on Gas Chromatography, Preprints, Paper 15; *G. Schomburg, F. Weeke, B. Weimann*, and *E. Ziegler*, Angew. Chem. *84*, 390 (1972); Angew. Chem. internat. Edit. *11*, 366 (1972).

[5] *D. Henneberg, K. Casper, B. Weimann*, and *E. Ziegler*, Angew. Chem. *84*, 381 (1972); Angew. Chem. internat. Edit. *11*, 357 (1972).

[6] *C. Krüger*, Angew. Chem. *84*, 412 (1972); Angew. Chem. internat. Edit. *11*, 387 (1972).

Computer-Aided Analysis of Organic Mass Spectra

By D. Henneberg, K. Casper, E. Ziegler, and B. Weimann[*]

1. Introduction

After introduction of the sample into the spectrometer, mass spectrometric analysis may be divided into three phases: Measurement of one or more spectra; evaluation or work-up of the data; and finally interpretation with a view to answering the particular question of the analysis. Evaluation means determination of the masses present und their relative intensities as well as determination of metastable ions with the assignment of their possible origins. Data work-up refers to correction of spectra by averaging and/or background subtraction and also the choice of the most suitable representation for the information, *i.e.* bar-graph spectrum, table, mass chromatogram, or element map. The last step, that of interpretation, involves identifying molecular fragments, hetero-atoms, and structural elements responsible for the observed peaks, as well as the recognition of mixtures. It requires further quantitative determinations on mixtures or isotopically labeled compounds and identification or classification by comparison with calibration spectra.

[*] Dr. D. Henneberg, K. Casper, Dr. E. Ziegler, and B. Weimann
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

We wish to demonstrate with a few examples how the use of a computer system can effectively support all three phases of mass spectrometric analysis. In order to be able to show the impressive advantages of computer use, especially in the measurement of spectra, we would first like to give a few illustrations of the possibilities of mass spectrometric analysis with special emphasis on the more recent instrumentation and methods.

Three techniques have made the application of mass spectrometry particularly interesting, and in some cases indispensable, in the analysis of organic compounds.

1. The combination of a gas chromatograph (GC) and a mass spectrometer (MS) is of particular value in the analysis of mixtures of easily vaporizable compounds. In this technique the eluate from a GC is continuously analyzed by mass spectrometry. In the course of a chromatographic analysis it is possible to obtain the mass spectra of all resolved components (see Fig. 4). It is assumed that the spectra are recorded rapidly so that distortion due to changes in the partial pressures is minimized.

2. The direct vaporization of samples having low vapor pressures results in a considerable increase in the types of analyzable compounds. Modern mass spectrometers allow

spectra to be recorded at sample pressures between 10^{-7} and 10^{-5} torr in the ion source. Systems are available where the sample temperature may be chosen as a parameter between -100 and $+500$ °C and thus for many substances a vapor pressure suitable for the ion source can be chosen. By this method it is nowadays possible to obtain spectra of compounds ranging from peptides, with molecular weights of more than 1000, to volatile transition metal complexes which decompose well below room temperature.

In general, after introduction of the sample the temperature is set so that the sample has an insignificant vapor pressure. The temperature is then increased until the vaporization process is complete. In this way, a certain amount of fractionation occurs for mixtures which can afford valuable information for use later in the interpretation. In special cases, the composition of the mixture can be quantitatively determined (Fig. 1).

3. High resolution mass spectrometry allows determination of the empirical formula of molecules and their fragments by means of very precise mass identification. Computers have been successfully used in conjunction with high resolution mass spectrometry for some time[1]. That the method is almost unthinkable without the help of computers is clear from the wealth of data that must be analyzed. Large volumes of many-digit numbers are produced whose processing culminates in the choice of the possible empirical formula from a large number of atomic combinations.

In the following article we shall discuss only the GC—MS combination and direct vaporization techniques with on-line computer operation and direct our attention solely to low resolution spectra. This area is still in its infancy. The application of high resolution mass spectrometry to the sample introduction techniques discussed in 1 and 2 above remains limited to a few special cases due to the particularly large amounts of equipment required.

In order to highlight the effect of computerization on experimental, analytical, and last but not least organizational aspects, a comprehensive description of the available software has been intentionally avoided.

2. Measurement of Mass Spectra in Conjunction with an On-line Computer

Typically, the partial pressures of the components in the ion source change as a function of time for the GC—MS combination and the direct vaporization techniques. This is particularly obvious for gas chromatographic peaks. The partial pressure of the sample changes rapidly, especially during measurements with good chromatographic separation. The first peaks in Figure 4, for example, have widths at half-maximum of about one second. Under normal conditions (fast scan of the magnetic field) it is not possible to obtain good spectra with such peaks.

For the analysis of a total chromatogram, at least one mass spectrum per chromatographic peak is necessary. If overlapping of several components occurs and the background is not constant, then many more spectra must be recorded. At best, 10 to 20 spectra per minute can be recorded with magnetic-scan spectrometers. For a 30-minute chromatogram in which a spectrum is taken every 5 seconds a total of 360 spectra will result. Experience has shown that of these 360 possible spectra only 150 to 200 are necessary to obtain the maximum amount of information. Further reduction assumes prior knowledge of which chromatogram peaks are of interest to the analysis. Two-hundred spectra correspond to about 40 m^2 of paper. It would be simply impossible in an analytical service laboratory to evaluate so many spectra manually, even to the point of deciding which spectra are important and which are not.

However, with data processing this problem is easily solved with a minimum of time and effort. For the cost of recording a single spectrum on UV-paper with a galvanometric recorder it is possible to record and store an entire series of spectra with a computer.

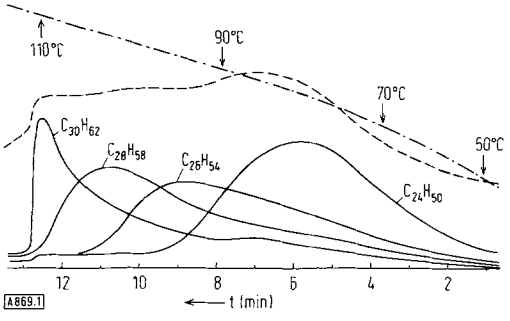


Fig. 1. Fractional vaporization of a mixture of *n*-paraffins.
Changes in the temperature (—·—) and total ionization (pressure) (– – –) were recorded with an X_1—X_2 recorder. During the total vaporization 30 spectra were measured at intervals of *ca.* 25 s. The four vaporization curves given for the separate components are obtained from the intensities of their respective parent peaks in the 30 spectra. For chemically similar compounds, the areas under the vaporization curves agree well with the known composition of the mixture in mol-percent.

Cpd.	Fraction (mol-%)	Area (%)	B. p. (°C)
$C_{24}H_{50}$	28	31	391
$C_{26}H_{54}$	22	23	412
$C_{28}H_{58}$	25	25	432
$C_{30}H_{62}$	25	21	450

The direct vaporization of a mixture of solids is shown in Figure 1. The change in the composition of the mixture with time is clearly recognizable. Although the partial pressure of each component changes relatively slowly a rapid-scan recording of the spectra is recommended. Many substances vaporize irregularly, which can result in a considerable distortion of a single spectrum. For qualitative evaluation of the analytical results shown in Figure 1, it is sufficient to record four spectra provided they are measured at favorable times for the separate components. In order to know when the spectra are best recorded and which corrections must be carried out, a prior knowledge of the shape of the vaporization curve is required. This is obtained by plotting the intensity of a chosen mass from a series of successive spectra. This technique has long been in use with the GC—MS combination and is applied in several

variations: mass chromatograms measured directly with fixed masses[2, 3] or extracted by the computer from a series of complete spectra for arbitrary masses[4]; alternating mass (AVA-technique[5]); or isotope scan[6].

The evaluation of an analysis such as that shown in Figure 1 takes several hours by hand, whereas a computer requires but a few minutes to deliver the corresponding picture.

In order to obtain such a picture for an unknown mixture, it is first necessary to know which masses are characteristic of only one component. An experienced investigator determines this by examining spectra from the beginning, middle, and end of the vaporization. We will attempt, however, to make the optimum choice with the aid of a computer program[4].

The first great advantage of measuring spectra with a computer is the ease with which a large number of spectra can be recorded and stored. Although perhaps only a few spectra are actually utilized for interpretation of the analysis, the recording of unnecessary spectra requires less effort than the repetition of an entire measurement if unsufficient spectra are available to allow interpretation.

The second advantage of using a computer is that the measurement is performed automatically and does not require supervision by a technician. In the case of a GC—MS combination without automatic measurement, the undivided attention of a technician is required to follow the chromatogram in order to measure each desired spectrum at the right moment, *i.e.* at a chromatogram peak maximum. In practice the situation is often simplified by determining the rough form of the chromatogram in a trial run. With direct vaporization prior information cannot be obtained. In this case the vaporization process is followed in successive spectra recorded at short intervals—for example with a storage oscilloscope. In order to record the "right" spectra during the fractionation of a mixture, it is necessary to recognize and interpret continuous changes in the spectra. This is, of course, only superficially possible during an experiment and requires much experience and concentration. On the other hand, with automatic recording of many spectra the technician can devote time during the measurement to other tasks such as the evaluation of previous experiments or preparation for new measurements.

3. Programs for Measurement and Evaluation of Mass Spectra

Two programs, MSDAT and MACO, developed by us, are employed in the recording and evaluation of spectra. The functions of MSDAT and MACO are discussed briefly below.

The program MSDAT facilitates the recording, reduction, and temporary storage of spectra to be evaluated. For recording of spectra it is possible to choose from three modes of operation:

1. Push-button measurement of a single spectrum.

3. Measurement of a single spectrum in a 5-s cycle of the spectrometer consisting of 2 s spectrum and 3 s pause. In this mode the start of computer measurement is synchronized with the spectrometer scan after pushing a button.

3. Automatic computer measurement in a 5-s cycle. By means of a parameter word it can be dictated whether every spectrum in the cycle or every second, third, *etc.* should be measured; in this way, spectra may be recorded every 5, 10, 15 s, *etc.*

Each spectrum is composed of 10000 digital values (2 s recording time for $m/e=20$ to 450, 5 kHz digitization frequency), which during the course of the measurement are reduced by MSDAT to the maxima contained in the spectra. Positions, intensities, and form factors of the maxima together with values for the base line and the total ionization are stored. The latter is a sum of all intensities (ITOT) which is related to the pressure in the ion source.

By comparison of the ITOT value of a spectrum with that of previous spectra MSDAT can, for example, determine whether the spectrum in a GC—MS analysis was measured on the base line or on the tail of a previous peak. In the latter case, temporary storage is pointless so that further handling of this superfluous information is eliminated (see Fig. 4)[15]. The possibility of not evaluating a spectrum can be overridden by means of the parameter word previously mentioned.

The variable operational mode of MSDAT may be adjusted to fit the particular problem:

1. For a normal GC—MS analysis, automatic measurement in 5-s cycles is chosen. Spectra for which the value of ITOT is the same as that of the immediately preceding spectrum are suppressed.

2. For vaporization of a solid sample, recording of spectra at 10-s or 15-s intervals is usually sufficient. The spectrum suppression is eliminated by the appropriate parameter word in order to obtain the complete vaporization curve from a uniform series of data points.

3. In order to obtain a good calibration spectrum of a pure substance, a number of spectra are averaged. For this purpose one chooses the fastest repetitive scan, 5 s. In this mode the spectra suppression must be turned off since it would prohibit recording repetitive spectra of a calibration substance at a constant inlet pressure.

At this point it should be clear how a single program can be flexibly adapted to perform many different tasks.

Program MACO evaluates and summarizes all spectra belonging to a particular analysis. First, the data pertinent to identification of the analysis are fed in, *i.e.* analysis number and sample designation (Fig. 2). Following this, MACO works-up the data stored by MSDAT. Normal mass peaks and metastables are recognized, noise peaks removed, and the masses calculated. In addition, MACO carries out a series of control functions which test the reliability of the mass determinations, signal intensity, position of the base line, and peak shape. Without a computer, it would be impossible to carry out all these checks for each spectrum. From each spectrum MACO stores the following list of information: integral masses; deviations from integral masses; intensities and peak type (*i.e.* sharp peak, metastables, unresolved doublets, or undetermined type of peak).

For each individual spectrum evaluated some preliminary information is printed out immediately containing the number of the spectrum, intensity and mass of the base peak, the total ionization, the largest significant observed mass, and a value which characterizes the reliability of mass determination (Fig. 2). If one of the above-mentioned control functions has discovered an abnormal situation a corresponding comment appears in addition. In Figure 2, for example, a reference is made to overloading for spectra 10 and 11. Thus it is possible to judge the correctness of the measurement from the data given in the control information immediately after the measurement of each spectrum

```
 RUN DSK MACO
VERS       710310
      ANALYSIS-FILE.   :857
      COMMENT          :SON BA 010

      TYPE NNN (FILE-NR.) OR AUTO:AUT


      NO   ITOT   BINT   BMAS    LSM    MSH
       1     60     27     28    355     74
       2     56     27     28    281     68
       3     64     27     28    355     68
       4     58     27     28    281     71
       5     61     27     28    355     66
       6     58     26     28    355     68
       7     58     25     28    355     74
       8     59     27     28    281     70
       9   1114    509     45    147     51
      OVERSHOOT
      10   4366   1073     45    102     51
      CHECK BASELINE HEAD:   -16
      OVERSHOOT
      11   6181   1073     45    103     51
      12    299    115     45    281     54
      13     99     29     28    355     64
      14    183     33     41    355     57
      15     75     29     28    354     63
FX    16     59     27     28    355     69

EXECUTION TIME:          20.80 SEC.
TOTAL ELAPSED TIME:      4 MIN. 48.38 SEC.
NO EXECUTION ERRORS DETECTED

EXIT
*C                                    A869.2
```

Fig. 2. Example of a print-out from program MACO. The underlined numbers are input data. RUN DSK MACO starts the program. 875 is the analysis number, SON BA 010 is the sample identification number. Sixteen spectra were evaluated, two of these showing warning comments. The column headings are:
ITOT: = Total ionization
BINT: = Base peak intensity
BMAS: = Mass of base peak
LSM: = Last significant mass in the spectrum
MSH: = Scale factor for mass determination

because the time-sharing operating system allows MACO to run parallel to recording of spectra. In addition to this, the teletype print-out provides a convenient record of the whole experiment.

The mass numbers are obtained with the aid of a mass/time calibration. Slow drift and small fluctuation errors are, within certain limits, corrected by MACO. The calibration table is produced automatically (9 s of computing time) by Program MASCAL from a PFK spectrum. Calibration twice a day is generally sufficient.

The program combination MSDAT and MACO is capable of recognizing peaks of the same order of magnitude as background noice (for fast scan spectra, depending upon the photomultiplier voltage, 3—5 mV). That yields a dynamic range of 3×10^4 relative to the saturation limit of the amplifier (100 V) which can be accepted by the computer. Mass peaks smaller than 0.03% of the base line are suppressed in the case of intense spectra.

In addition, MACO recognizes and evaluates metastable ions. Thus with computer techniques it is possible to obtain and correct all the available information from a spectrum, even on fast scan operation. In our experience both the masses and the intensities are more accurately determined by computer than from typical oscillographic records. This is attributable to the quality of the quartz-controlled time base and the linearity of the analog-digital converter.

We have recently installed a device which automatically switches sensitivity scales and thereby increases the dynamic range to 3×10^5. This is necessary for GC—MS analysis of mixtures whose components are present in widely differing concentrations. Otherwise, several runs with various amounts of the sample must be made.

4. Print-out of Mass Spectra

In the print-out of computerized mass spectra the most suitable form is chosen for the particular application in question. For quantitative determinations in which the composition of a mixture and/or isotope ratios are to be displayed a table is most suitable. For a qualitative interpretation, for example determination of the type of spectra and the characteristic fragmentation pattern, representation as a simple bar-graph is to be preferred. For documentation purposes, however, a bar-graph is not suitable since the dynamic range is often too small and metastable ion peaks are not easily reproduced. Analog spectra are not particularly suitable for any type of further evaluation. It is, therefore, unnecessary to record analog spectra parallel to computer measurement. Analog spectra are possibly of importance only in special analyses dealing with shapes of peaks and metastables.

Spectra evaluated by MACO, as well as any other suitably stored spectra, can be printed-out as tables with Program REMAS. For reasons of clarity and ease of filing, it is important that the print-out has a standard form. An example of such a print-out in tabular form is shown in Figure 3.

The uppermost field contains all pertinent identification information. The main field (left center) gives masses and intensities, which may be normalized to the base line or total ionization as desired. If the signal is not a normal, sharp mass peak, a symbol designating the type of peak appears (see legend of Fig. 3). The metastable ions are tabulated again to the right of the main field along with assignments of their possible origins where possible.

The capability of the program group MSDAT, MACO, and REMAS is clearly evident from the mass peaks $m/e = 86$ and 28 in Figure 3. The star alongside $m/e = 86$ indicates that the peak is broader than normal and hence may ori-

ginate from a metastable ion or unresolved doublet. The $m/e=86$ peak therefore appears once again among the metastable peaks (Fig. 3, center right). There one sees the exact mass of the ion (86.02), a possible formation route

The profile of the reduced spectrum[*] in the lower right field provides certain information important to the qualitative interpretation of the spectrum, since it is characteristic of certain classes of compounds.

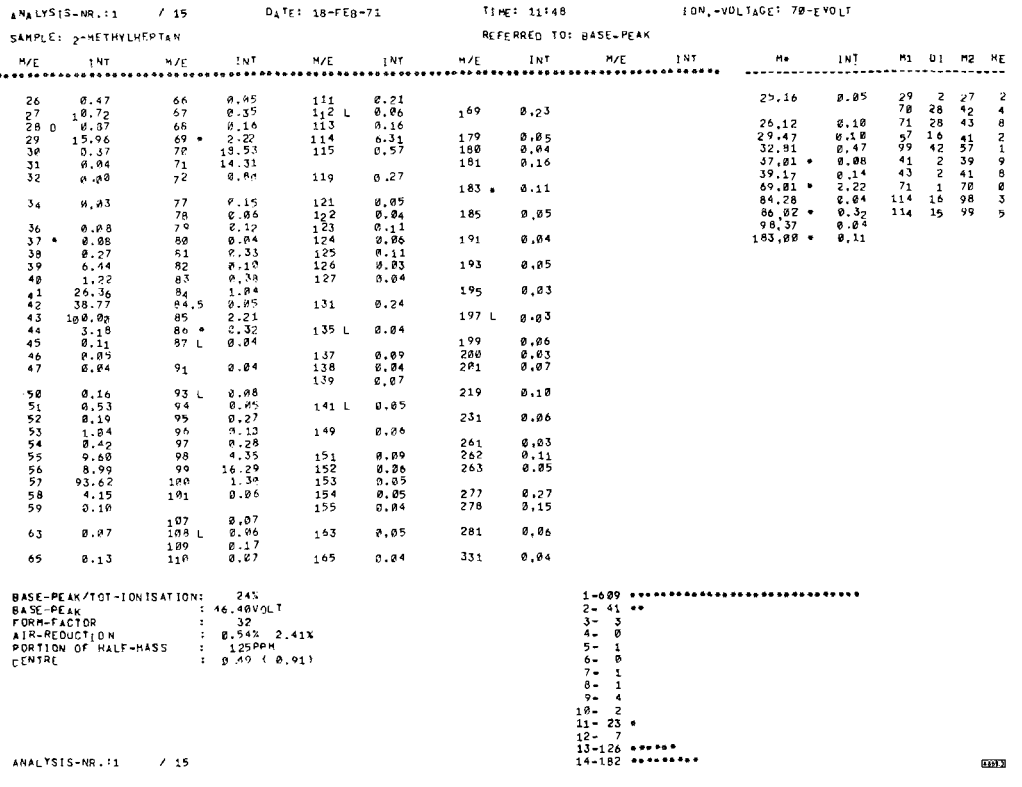


Fig. 3. Standardized print-out of a mass spectrum produced by program REMAS on a line printer. The print-out contains all values from the measured spectrum, as well as some derived information and information on the origin or measurement.
Peak type: D = unresolved doublet
.5 = doubly charged ion
* = possible metastable ion
L = small peak, type undetermined

(*i.e.* 114→99), and the deviation of the measured from the theoretical mass (5/100 mass units). This mode of degradation is resonable (loss of a methyl group from 2-methylheptane). Due to the isotopic distribution, a peak having an intensity of about 0.14% should appear at $m/e=86$ (*i.e.* 9% of $m/e=85$). It is then clear the $m/e=86$ peak arises from the superposition of this isotopic peak and the peak of the metastable ion resulting from the 114→99 decomposition. Without this superposition, the metastable ion would appear only in the metastable ion field of the REMAS print-out. At $m/e=28$ the partially resolved doublet for N_2 and C_2H_4 is shown.

Figure 3, bottom left, shows additional information such as the contribution of the base peak to total ionization, and the absolute magnitude of the base peak. The latter allows assessment of spectrum quality. If a given spectrum is the resultant of an averaging or corrective operation, this field will contain information about the way in which the spectrum was arrived at.

Should one of the control functions have responded in program MACO, the corresponding comment would be given in the blank lower center portion of Figure 3.

If a bar-graph is desired, the spectrum can be drawn by a suitable plotter. Two examples of bar-graph spectra are shown in Figure 6. The plotter requires about 1—2 minutes per spectrum and is therefore not suitable for the reproduction of series of spectra. For this reason we will soon employ a Statos recorder which requires 4 s to plot a spectrum.

5. Treatment of Spectra and Analyses

In the previous sections we have discussed how a series of spectra may be obtained as starting material for a mass spectrometric analysis. It will now be illustrated how the necessary spectra are chosen and corrected during a GC—MS analysis. It is first necessary to obtain an overall view of the chromatogram drawn by the plotter according to program DIPLO. Figure 4 shows the first part of analysis No. 875.

The times at which spectra are recorded and stored are indicated by crosses on the chromatogram. It is evident

[*] "Reduced spectrum" after *Crawford* and *Morrison* [7].

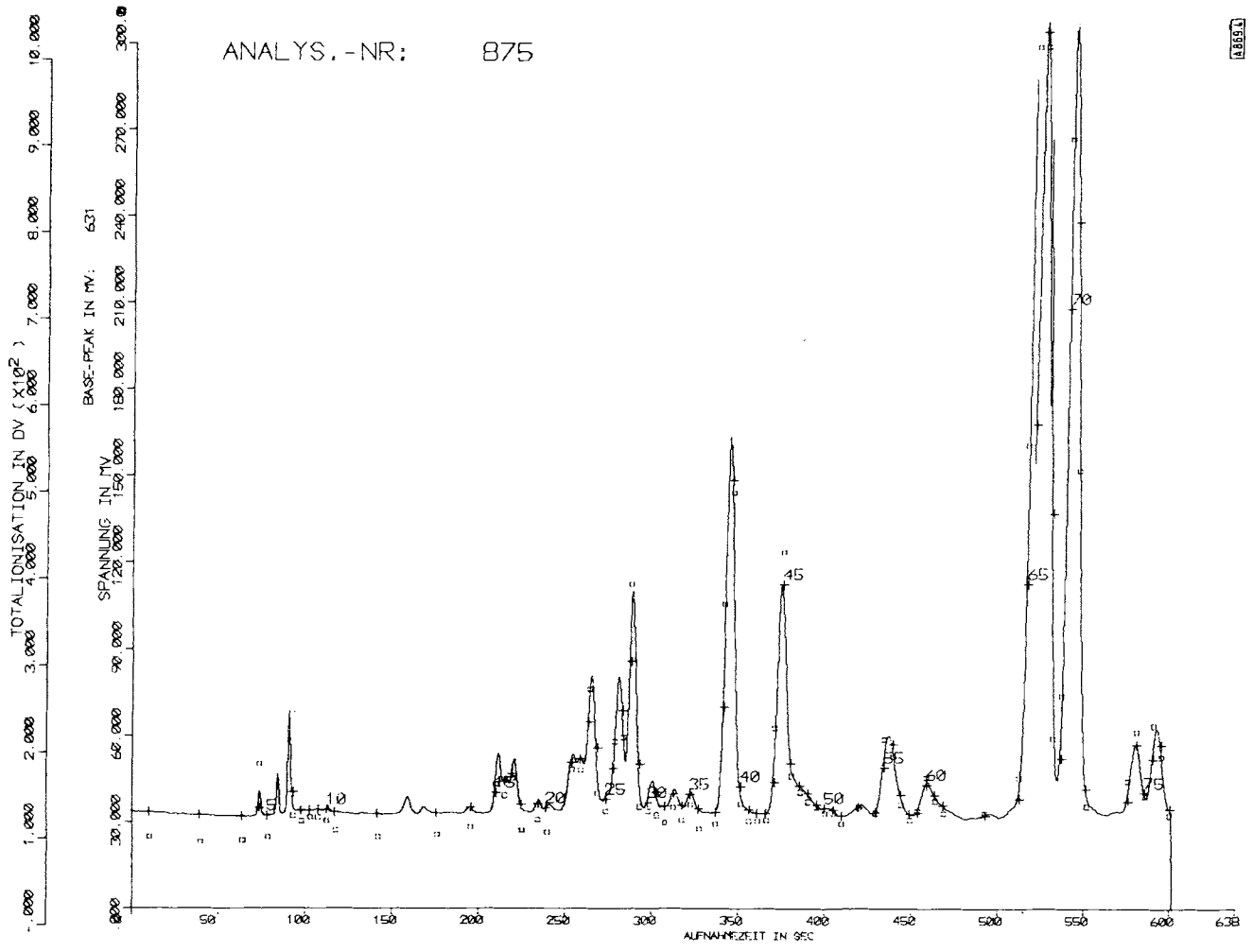


Fig. 4. Overview of the GC-MS analysis No. 875, drawn by program DIPLO with a plotter: ——, chromatogram, measured as the total current from a pressure measuring ion source at 20 eV; +, signifies measurement and storage of a mass spectrum. The number of the spectrum is printed every fifth measurement; □, total ionization values of the mass spectra.
The scale of the chromatogram is so chosen that the smaller peaks are clearly visible. Peaks too large for the chart paper are shown in reduced scale so that the largest signal appears as a full scale deflection. Its height is given alongside the scale.

that spectra recorded in peak-free regions or in flat tailing portions of the chromatogram (for example following spectrum 62) are neither stored nor further evaluated. As seen for spectra 21 and 22, however, if the ITOT value is approximately the same in a region of one or two successive GC peaks, both spectra are stored[15]. The enlargement scale for the illustration of the chromatogram as well as for the ITOT value can be chosen by a dialog after calling the program. With such a diagram, it is possible to find the spectra which are important for a particular analysis, even for a long, complicated chromatogram with many recorded spectra.

An example of a simple, straightforward trace analysis will now be described; the corresponding MACO print-out was depicted in Figure 2. In Figure 5 a portion of the DIPLO picture of the analysis is shown.

During the total running time of 250 s, spectra were measured at intervals of 5 s. Of the resulting 50 spectra, only 16 were stored and evaluated as shown in Figure 5. In this case, the GC—MS combination was connected to the computer only during the time 3 minutes before the elution of the main component until shortly after the appearance of the trace component. This limitation of the measurement was possible due to prior knowledge of the chromatogram.

The trace component is best represented in spectrum 14. As can be seen in Figure 5, about 40% of the total ionization in spectrum 14 results from the constant background and the tail of the main component. In this case, the desired correction is obtained by subtracting the arithmetic mean of spectra 13 and 15. The effect of this correction is shown in Figure 6.

After this correction, a pure hydrocarbon spectrum remains. Apart from the peaks at $m/e=28$ and 32 (due to air) the peaks removed in the corrected spectrum are mainly due to the major component, diisopropylbenzene ($m/e=45$, 59, 73, and 87).

This example shows clearly how it is possible to achieve an optimum stepwise reduction of data and applied operations: Prior knowledge of the chromatogram allowed limitation of the length of the measurement to about 4 minutes. During this time span, at 5-s intervals, a total of 50 spectra were recorded by MSDAT. Of these 50 spectra, 16 were temporarily stored and later evaluated by MACO. For solution of the analytical problem, *i.e.* determination of

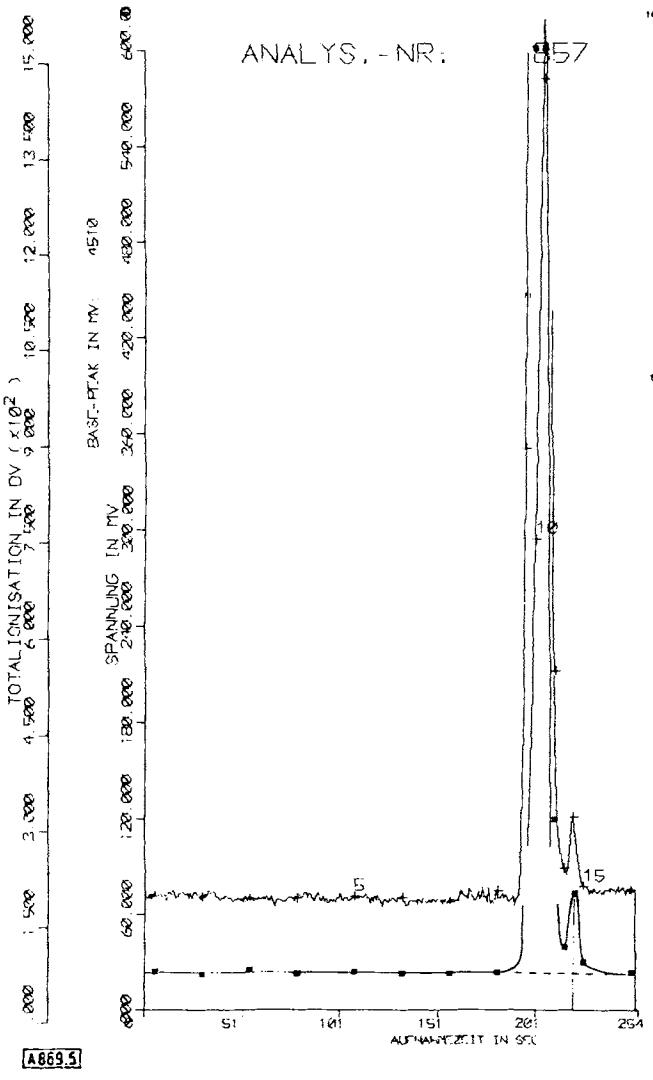


Fig. 5. Excerpt from the DIPLO display of Analysis 875 (cf. Fig. 2). In order to show more clearly how spectrum 14 of the trace component can be corrected the course of ITOT between the squares during the analysis was later added by hand.

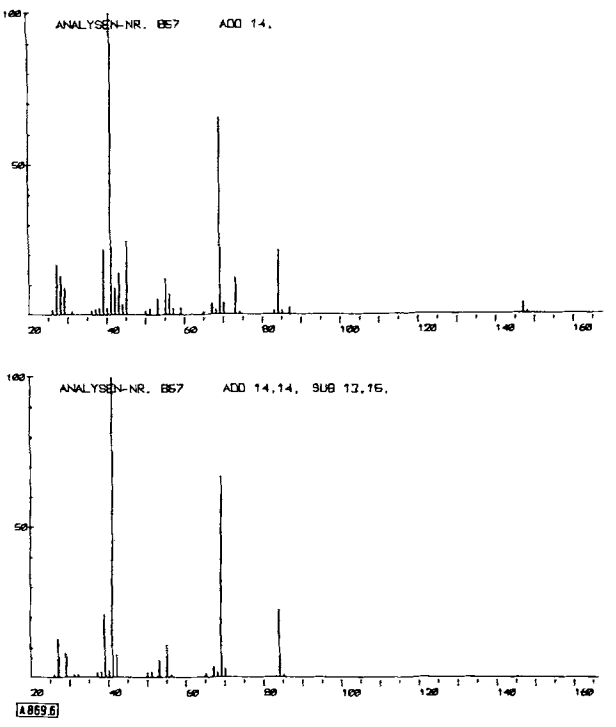


Fig. 6. Mass spectra displayed as bar-graphs drawn by a plotter. Top: Spectrum 14 of Analysis 875. Bottom: Spectrum 14 after subtraction of arithmetic mean of spectra 13 and 15 (Fig. 5).

the trace component, only 3 of the 16 spectra were necessary; apart from the uncorrected spectrum only one spectrum was finally printed out.

Only 3 operations are generally necessary for the correction of spectra: addition; weighted subtraction; and correction of intensity distortions due to pressure changes during the course of measurement (TI-correction). For example, TI-correction would be desirable for spectra 38 and 39 of Figure 4. However, before each TI-correction the constant portion of the background must be subtracted. After correction, the spectra may be compared. If the corrected spectra are not identical, then the chromatogram peak to which they belong is due to more than one component. In the case of spectra 38 and 39, a practically undistorted spectrum is obtained by simple addition since the distortions of the separate spectra tend to cancel when added.

A weighted subtraction must be applied, for instance, in order to obtain the best spectrum of the substance represented by the middle peaks of the group centered at 220 s in Figure 4: certain fractions of spectra 15 and 17 must be subtracted from spectrum 16.

Addition of spectra yields an average which is employed in cases where several weak spectra are available for one component or where a very accurate calibration spectrum of a pure substance is desired. (It is not necessary to divide by the number of spectra added together since this is already accounted for in the output program normalization.)

Without the computer, these arithmetic operations for "correction" of spectra are normally omitted since they are time-consuming and unpleasant tasks. An experienced analyst recognizes part of the "impurities" of a spectrum and disregards them during the interpretation. Since computer programs for interpretation or comparison of spectra are easily disturbed by impurities, computer interpretations therefore require background-corrected spectra.

6. Computer-Aided Interpretation of Mass Spectra

The last step of an analysis, interpretation, is particularly interesting and important. Requisite for the development of suitable methods is the availability of a comprehensive, reliable collection of computer-compatible spectra. The establishment of a collection of required magnitude will be possible in those laboratories in which spectra are directly measured and corrected with a computer. Model studies have already been carried out for limited collections at Stanford University in California[8] with programs attempting to reconstruct the decision-making process employed by an experienced analyst in spectra interpretation (Artificial Intelligence). However, this method soon runs up against the same difficulties which limit non-computerized evaluation of spectra, *i.e.* insufficient knowledge of reliable fragmentation rules.

```
RUN DSK ISOTOP
ISOTOPE PROBABILITY DISTRIBUTION
STATE TEXT:
TABLE AND GRAPH OF 1 SN,1 BR,8 C AND 18 H

SN          1
BR          1
C           8
H          18
          MASS            PROBABILITY

            305                 1.7
            306                 0.1
            307                 2.8
            308                 0.2
            309                25.8
            310                15.4
            311                66.9
            312                33.6
            313               100.0
            314                23.3
            315                65.3
            316                 5.8
            317                18.4
            318                 1.6
            319                10.1
            320                 0.9

GRAPH:
 305  X
 306
 307  X
 308
 309  XXXXXXXXXXXX
 310  XXXXXXXX
 311  XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
 312  XXXXXXXXXXXXXXXX
 313  XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
 314  XXXXXXXXXXXX
 315  XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
 316  XXX
 317  XXXXXXXXX
 318  X
 319  XXXXX
 320
      ↑    ↑    ↑    ↑    ↑    ↑    ↑    ↑    ↑    ↑    ↑
      0    10   20   30   40   50   60   70   80   90   100
STATE TEXT:
EXIT
```

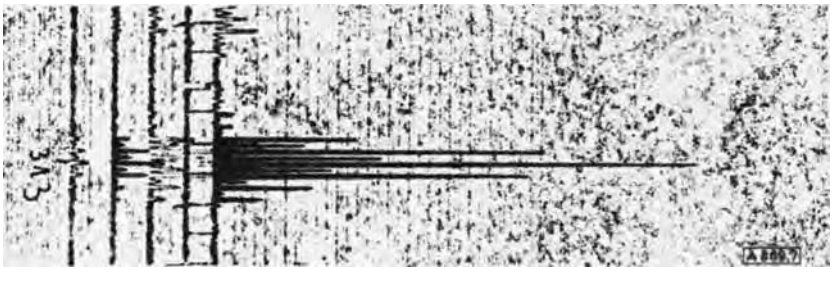


Fig. 7. Print-out from program ISOTOP. Top: Input data are underlined: program start and desired form of the print-out (TABLE AND GRAPH) of the isotope distribution for the formula $C_8H_{18}Br_1Sn_1$. Center: Mass table and bar-graph spectrum. Bottom: Molecular peak group whose hetero-atom content was to be determined.

The employment of decision vectors[9, 10] seems especially attractive where results are expected which would be inaccessible without the aid of a computer. The main task of the computer is to "train" a vector to a set of known spectra, using an iteration process within a learning program. A vector so trained is applied to a spectrum to be evaluated and a "yes—no" decision is obtained. In this way, it would be possible to determine the presence of oxygen, a vinyl group, a ring, *etc.*

An obvious type of interpretation is identification by comparison with a collection of stored spectra. Descriptions of this method have been given in some detail[11, 12]. The trace component analysis problem discussed in the previous section would be largely soluble with this method since practically all C_6H_{12} hydrocarbons are tabulated. The spectrum shown in Figure 6 could only belong to a compound of this formula. There remain, however, three alternatives whose spectra are all quite similar, 2-methyl-4-pentene, 4-methyl-2-pentene, and 2,3-dimethyl-2-butene.

A final decision in favor of 2-methyl-4-pentene is possible only when additional results from another analytical method are considered—for example, chromatographic retention times. This decision could also be made by our computer system. In the signal from the pressure-measuring ion source, the GC—MS combination delivers a chromatogram comparable with a normal chromatogram. The existing programs for evaluation of chromatograms and for determination of retention times can be called for use by the GC—MS analysis, since in the Mülheim computer system it is possible to make use of information stored by other users. These possibilities are exploited between the gas chromatography and mass spectrometry divisions and are especially advantageous for the GC—MS combination. It is possible to envision a general Laboratory Information System which would facilitate the exchange of various analytical results between analysts as well as allow access of chemists to analytical information.

The complete computer interpretation of an analysis is possible in the case of quantitative gas analyses. A program for such analyses has been in use over three years[13]. Calibration spectra of 45 inert gases, hydrocarbons, and volatile solvents are stored. Starting with the mass spectrum of a mixture the program calculates the composition of the

mixture and prints out a control slip for documentation as well as the final analysis results for the researcher. The program utilizes the method of regression analysis.

A final example of computer assistance is provided by a program which computes the isotope distribution associated with a given empirical formula (Fig. 7).

Simple isotope distributions with O, N, and up to 30 C atoms as well as the distribution of Cl and Br may be found in tables. Complicated distributions are not tabulated and cannot be calculated by hand without unreasonable effort. Therefore, such a program is indispensable in cases where isotope-rich hetero-atoms are combined with many carbon or several halogen atoms.

The future holds the promise of particularly interesting developments in the area of computerized spectra interpretation.

7. Organization of Mass Spectrometric Data Processing within the Time-sharing System

In the preceding sections it was shown that measurement and evaluation of spectra are largely automated by the computer. Interpretation of spectra, on the other hand, is accomplished on the teletype in a preprogrammed dialog using a series of programs with which the user is able to carry out only suitable and necessary operations. As a prerequisite for such a mode of operation, all spectra, regardless of origin and previous manipulating processes, must be filed in the same uniform format so that they are available for any kind of further treatment, interpretation, or output.

The logical interrelationships of the operations applied to mass spectra from the initial measurement to the final interpretation are depicted schematically in Figure 8.

In the computer system employed by us[14] all data and programs are stored on a magnetic disk, *i.e.* in a large memory with random access. All operations may be started

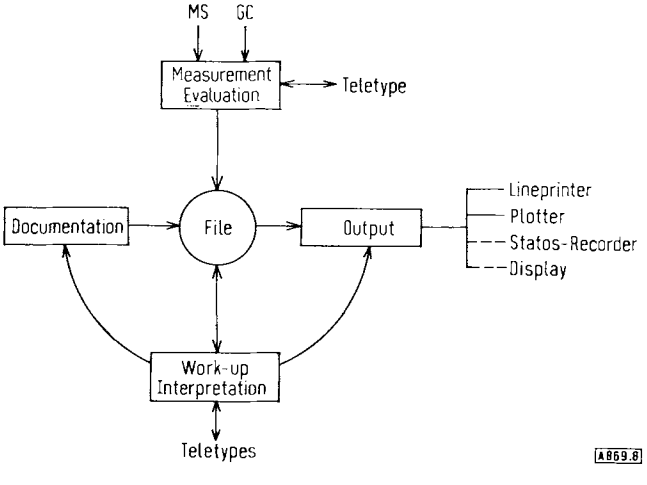


Fig. 8. Organization scheme for processing of mass spectrometric data. The file includes actual parameters, spectra, and programs, to which simultaneous, rapid access from several locations is possible in time-sharing operation.

at arbitrary times, several operations such as measuring, processing, storing, and retrieving of spectra, may be started simultaneously from different teletypes. Such a system makes for optimum flexibility and all tasks, including program development, can be economically distributed.

From the schematic diagram, and above all from the examples presented here, it is clear that the computerization of mass spectroscopic analysis does not aim at becoming a completely automated (black-box) process. Rather, the computer is used as a controllable instrumental aid whose operation is guided by the analyst and thereby adapted to fit each facet of the analytical problem. A completely automatic, combined application of all possibilities for spectral correction and interpretation for each recorded spectrum would quickly lead to the situation where the computer is overloaded with unnecessary work—not to mention the huge expenditure of programming effort. A fully automatic analysis up to the print-out of the final results would only be possible if essentially all conceivable results and associated complications were foreseeable in advance. A special case of this is the quantitative gas analysis already mentioned, *i.e.* a routine analysis the evaluation procedure of which is precisely defined and which occurs frequently enough to make the programming effort worthwhile.

Of decisive importance in the procedure described here, namely, the successive application of several programs or program modules with variable parameters, is the dialog between the program-user on the one side and the program processing the data sets on the other. This dialog takes place at the terminal from where it is possible to start and interrupt programs. The dialog, *i.e.*, the questions and answers, are appropriately preprogrammed. A simple example of such a dialog is the choice of the scales for the drawing made by program DIPLO (Figs. 4 and 5). The program determines and prints the maximum peak height in the chromatogram and the largest value of the total ionization in a given series of mass spectra. From this it is possible to specify the desired scales for the plotter diagram.

Warnings against attempts to carry out illogical operations and the possibility of terminating the program in such a case are of particular importance for a real dialog. If, for example, large negative values were produced by subtraction of background, or during an averaging an incorrect spectrum were used, warnings are issued and modifications of the processing procedure are allowed. This kind of dialog, which permits changing of the program flow during execution, is not to be confused with the input of parameters at the start of a program. These permit variation of the program flow before execution, but do not allow user interactions after the program has started.

The measurement of spectra, evaluation and interpretation of analyses, and program development are separate tasks assigned to different persons within the laboratory. Only a multi-user time-sharing system will permit the execution of these tasks simultaneously from several teletypes, or temporally independently of one another, and in the form of a dialog. Thus an optimized and economical use of a modern mass spectrometer is possible.

The time-sharing operation has worked especially well for program development. Since the use of the computer

normally does not require an operator and programs can be changed, compiled, and started at any time, it is possible to directly test and verify new ideas. Thus the computer becomes a thinking tool for the scientist.

In this connection two special types of programs should be mentioned. First, programs which serve as support for the development of optimum methods. For instance, one of these programs is written so that certain regions or peaks from the original 10000 data points of a spectrum can be quickly found and printed out *via* a teletype. For instance, this allows a user to investigate the effect of various smoothing functions or to test which algorithm or parameters give the optimum signal to noise ratio or optimum differentiation between metastable ions and partially separated doublets.

The second type of program is the test version of a regular measurement and evaluation program. Such programs print out all important intermediate results and thereby permit the location of errors in the program or spectrum.

The construction of our program system for measurement and evaluation is already substantially complete, having begun about three years ago. Two years ago automatic measurement was introduced, and automatic GC—MS analyses have been performed on a routine basis since then. In some cases, automatically measured analyses using direct vaporization are performed with the same program system and the same spectrometer.

On-line connection of additional mass spectrometers is now rapidly accomplished since the basic programs already developed can be used with only minor changes. With the exception of MSDAT, all programs are presently written in Fortran. This is feasible because of the size and speed of the computer system and has the advantage that program improvements may be easily made. Such improvements are always necessary in scientific laboratories since the problems to be solved are constantly changing and it is necessary to take instrumentational advances into account as quickly as possible.

Received: November 18, 1971 [A 869 IE]
German version: Angew. Chem. *84*, 381 (1972)
Translated by Dr. *L. C. Glasgow*, Mülheim/Ruhr

[1] See literature cited in *H. Kienitz*: Massenspektrometrie. Verlag Chemie, Weinheim 1968.

[2] *D. Henneberg* and *G. Schomburg* in *van Swaay*: Gas Chromatography, Hamburg 1962. Butterworths, London 1962, p. 191.

[3] *D. Henneberg* and *G. Schomburg*, Z. Anal. Chem. *215*, 424 (1965).

[4] *R. A. Hites* and *K. Biemann*, Anal. Chem. *42*, 855 (1970).

[5] *C. C. Sweeley, W. A. Elliot*, and *R. Ryhage*, Anal. Chem. *38*, 1549 (1966).

[6] *G. Schomburg* and *D. Henneberg*, Chromatographia *1968*, 23.

[7] *L. R. Crawford* and *J. D. Morrison*, Anal. Chem. *40*, 1465 (1968).

[8] *A. Buchs et al.*, Helv. Chim. Acta *53*, 1394 (1970); see also earlier literature cited therein.

[9] *P. C. Jurs, B. R. Kowalski, T. L. Isenhour*, and *C. N. Reilley*, Anal. Chem. *42*, 1387 (1970); see also earlier literature cited therein.

[10] *P. C. Jurs*, Anal. Chem. *43*, 22 (1971).

[11] *B. A. Knock, I. C. Smith, D. E. Wright, R. G. Ridley*, and *W. Kelly*, Anal. Chem. *42*, 1516 (1970).

[12] *H. S. Hertz, R. A. Hites*, and *K. Biemann*, Anal. Chem. *43*, 681 (1971), and further literature cited therein.

[13] *K. Casper, N. Kreitz*, and *D. Henneberg*, unpublished.

[14] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Anal. Chem. *42*, 51A (1970).

[15] *D. Henneberg, K. Casper*, and *E. Ziegler*, Chromatographia *1972*, 209.

Data Processing in Gas Chromatography

By Gerhard Schomburg, Fritz Weeke, Bruno Weimann, and Engelbert Ziegler[*]

1. Introduction

Data processing in gas chromatography is usually viewed as the execution of a large number of routine analyses—primarily analyses of mixtures whose quantitative and qualitative compositions are subject to only slight variation. However, the interest shown by industry in GC data processing has additional, "natural" motives: The large number of instruments frequently encountered in industrial laboratories and the corresponding demand for operating personnel make rationalization and automation essential for uniformity in routine analytical work.

In contrast, data processing with GC instruments employed in research or development has hitherto attracted less attention or interest. This is probably due to the lower number of instruments connected per laboratory, especially if dedicated systems for gas chromatography only are considered. Gas chromatography, however, is rarely used on its own in research and development but usually in conjunction or even in direct combination with other physical methods of analysis such as mass, NMR, and IR spectroscopy.

In these circumstances, larger computer systems having more peripheral equipment and higher efficiencies should be considered from the viewpoint of higher total cost and a better price/performance ratio. Each of the analytical methods mentioned will undoubtedly make use of electronic data processing in the future, so that each would

[*] Dr. G. Schomburg, F. Weeke, B. Weimann, and Dr. E. Ziegler
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

require its own small computer system if the philosophy of the dedicated system were to be maintained.

We believe that we will be able to show that large computers are desirable or even essential for data processing in scientific analysis, for which flexible software is a prerequisite.

These tasks, together with documentation tasks requiring extensive storage, could also be executed by computer systems consisting of a large background computer with one or more suitable satellites for real-time data acquisition[1]. In any case data acquisition from many instruments at low and high data rates must be accomplished *simultaneously*.

The importance of time-sharing, which implies an interactive or conversational mode, for "scientific" applications cannot be overemphasized because of the frequently changing problems. Such a mode not only permits stepwise data processing, but also enables the operator to make quick changes or adapt subroutines using a "high-level" programming language. Through the teletype, continuous direct contact exists between the computer and its users who thus have full access to a large computing system with all its advantages.

The following report is essentially an account of the application of the Mülheim Computer System[2-4] in the field of gas chromatography[5].

Because of the differences between industrial and scientific analyses special software has been developed for this system. This software permits flexible solution of and adaptation to any analytical problem occurring in gas chromatography with the aid of a large number of auxiliary aud subprograms, without requiring repetitive runs of the chromatogram itself. Furthermore, the data acquired in an analysis can be further processed and put into suitable form by successive application of different programs.

2. Computer Applications in Gas Chromatography

The development of gas chromatographic analysis is characterized by the continuous improvement of performance, *i.e.* resolution, symmetry of the peaks obtained, and separation rate. As the resolution improves, the analysis of complicated mixtures produces an ever-increasing number of separated species, resulting in chromatograms having a higher information content. The qualitative and quantitative interpretation of such chromatograms requires the manipulation of a large volume of data. In order to interpret and evaluate the entire data set it must also be taken into consideration that additional gas chromatographic measurements for calibration and standardization purposes must frequently be made with the same sample. Repetition of the separation with modified separation parameters, such as temperature and carrier gas flow, or in columns with different resolution or polarity of the stationary phase, also increases the amount of data. The same applies to the use of more substance-specific detectors or combined analytical methods, like reaction gas chromatography (*e.g.* on-line hydrogenation) or GC-MS coupling.

The appropriate processing of these large volumes of data is an important task. Its solution must be sought with the same intensity as the above-mentioned development of the gas chromatographic technique. High demands are also placed on the capacity and capability of the laboratory by the monitoring of chemical reactions like those already frequently carried out in industrial process chromatography. We feel that in the future equipment for automated kinetic measurements will have its place in the laboratories of research institutes.

Many chromatograms have to be processed at intervals adapted to the reaction rate. This is especially important when the results of the analysis are to be used for "closed-loop" control of reaction parameters.

The measurement of a series of analyses, where the individual samples are taken manually from the reaction vessel by an operator and transferred to an automatic device for consecutive injection of the samples also belongs to this category. (In the authors' laboratory a combination of a gas chromatograph with an automatic sampling device produced by the Hewlett-Packard company, HP-model No. 7670A and the computer system to be described was tested successfully.)

For control purposes and process chromatography it is advantageous to use small computer systems which are adapted and programmed for specific problems but can also be connected as satellites to large computers. For normal gas chromatographic work, the computing and storage capacity of a large computer is desirable or even essential if, for instance, peak overlapping calculations, comparison of retention values with tabulated data, or documentation work of any kind (including exchange of information with other analytical departments) must be carried out in parallel with data acquisition from many instruments. (For a discussion on the use of "dedicated" or "large" computer systems see [6].)

3. Information Content of Gas Chromatograms

The basic task of data processing in gas chromatography is the "evaluation" of chromatograms in both coordinates *i.e.* intensity and position of peaks. Evaluation of a chromatogram requires extraction of its information content. Essentially all the parameters required for a mathematical description of each peak must be considered, such as start, end, maximum, halfwidth, turning-point, and symmetry factors or other parameters for uncertain mathematical peak shapes, which may be due to deviations from linearity of isotherms or the influence of the geometry of the pneumatic system of the gas chromatograph. Other factors include the signal to noise ratio, base-line drift, and the start and end of the chromatogram. For all more precise analyses and calculations of, *e.g.*, overlapping peaks, it is necessary that the entire digitized chromatograms remain in internal or external storage until completion of all the desired calculation and processing operations.

Evaluation of a chromatogram therefore requires a series of steps:

1. Determination of peak height or, more often, peak area as related to a standard peak, to the amount of sample injected, or to the total quantity of all the substances contained in the chromatogram represented by the sum of the individual peak areas. (These peak areas have to be corrected with respect to detector response for each component.) For the determination of the peak area, the base-line drift and, if possible, also peak overlapping must be taken into consideration.
2. Determination of peak position as defined by the distance of the "correct" maximum from the injection point or, better, from the maximum of the "gas" peak. Automatic determination of the net retention volumes or relative retention volumes and the Kovats index is possible only in the second case.
3. Standardization, normalization, and correction of peak positions and area values; identification of peaks by additional information introduced by the operator or by automatic comparison with tabulated relative retention values.
4. Arrangement of results of series of experiments in tables and summaries, or conversion into graphical representations, *e.g.* in kinetic studies.
5. Combination of several subprograms for automatic tabulation of results of refined analysis in routine work. The operator can choose either one specialized program or a combination of several.

4. Scope of Analytical Problems and Organization of the Chromatographic Laboratories at the Mülheim Institute

Before practical examples are given to illustrate the demands on hardware and software of a computer system in a research laboratory with frequently changing gas chromatographic problems, the organization of the GC laboratories as well as the particular aspects of the analytical problems will be described as an example of centralized instrumental analysis in research and development laboratories.

The Max-Planck-Institut für Kohlenforschung consists of two divisions with different research areas; there is a gas chromatography laboratory for each division and the techniques and methods employed are adapted to the individual applications. The two laboratories—housed in two connected buildings located about 150 meters apart—are operated jointly.

The analytical problems of the divisions are very different. In the chromatography laboratories of the main institute analyses are performed primarily on mixtures of hydrocarbons or their simpler functional derivatives obtained by catalytic reactions. All physical methods are employed for rapid qualitative and quantitative analysis of the usually complicated many-component mixtures of hydrocarbon isomers. (See [7—10] for particulars of analytical problems.)

All types of chromatography including liquid chromatography are used; capillary gas chromatography plays a dominant part in analytical gas chromatography because of the difficulties usually inherent in separation of hydrocarbon isomers. The use of GC-MS combination techniques is particularly important. This method also produces an enormous amount of information. (For related software see [11].)

Finally, besides on-line hydrogenation, reaction gas chromatographic investigations are carried out in the field of heterogeneous catalysis and kinetic measurements on homogeneous catalysis.

In the radiation chemistry division, apart from normal GC analyses, qualitative and quantitative trace analyses frequently have to be done. The formation of only small concentrations of reaction products in radiation-chemical or photochemical reactions is tolerated in order to avoid the formation of secondary products.

In both divisions there is a total of 46 GC instruments (29 in the main institute and 17 in the radiation chemistry division); there are also 8 preparative GC instruments. If necessary, some of these instruments can be set up in other nonanalytical laboratories. All the analytical instruments are connected on-line over the same interface to the computer mentioned above. The interface is called "slow" because its maximum data rate is lower in comparison to the other ("fast") interface. Of the 32 channels available on the slow interface, 15 are used by the chromatography laboratories of the main institute and 7 by those of the radiation chemistry division.

5. Connection of Gas Chromatographs to the Computer

The computer and interface (analog-digital converter, multiplexer, contact-scanner, and line-driver) are separated from the gas chromatographs by about 70 to 100 meters. The analog signals are transmitted over shielded cables and registered by the computer in real time. The dynamic range, the resolution, and the data rate of the interface are sufficient for the requirements of gas chromatography.

Further connections between the GC laboratories and the computer exist with the contact-scanner and line-driver units. This control system allows the transmission of start or stop commands and the operation of relays for control functions at and in chromatographs.

By means of the contact-scanner the computer determines on which channel data acquisition is in progress or completed, while the line-driver controls opening and closing of relays. For example, with the line-driver it is possible to initialize, at pre-set time intervals after the start of a chromatogram, the following instrument operations: 1) start of a temperature program; 2) start of an inlet pressure or flow program; 3) switching of pre- or double column setups for the backflush or cutting-off of uninteresting components. Separate cables are necessary for each of these operations.

Teletypes are located in the laboratories close to the chromatographic equipment and permit the input of measurement parameters, sample identifications, *etc.* in a dialog

mode. By typing corresponding commands various programs can be called, and the computer's peripheral devices such as line printer, plotter, and magnetic tapes can be assigned to the user for convenient data output and storage.

6. Data Flow and Software Structure

An appropriate schematic representation is given in Figure 1. Gas chromatographic data from the interface are stored by the data acquisition program SELDAT in core buffers. As soon as the buffers are full the data are transferred to disk storage. Raw data are processed by the analysis program GCAN, but remain available for processing by other programs such as the plotting program GCPLOT. The use of GCAN is controlled by ORGANI, an organizing program. It checks the operating system's channel-status

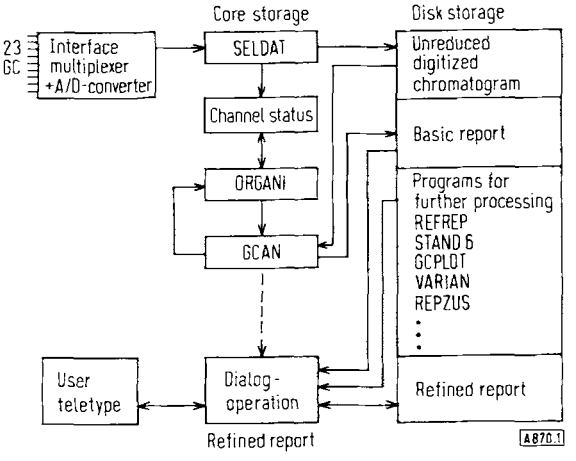


Fig. 1. Data flow and software organization for gas chromatography.

at definite time intervals. When it has detected that the data collection from a chromatograph is complete then the analysis program GCAN is called for this channel. GCAN produces a "basic report" which is written on the disk and remains there as long as desired until eventually used by other programs. While the "basic report" is produced automatically without user interaction, a "refined report" can be obtained by teletype dialog programs, thereby taking full advantage of the interactive time-sharing mode of the computer system.

7. Quantitative and Qualitative Gas Chromatographic Analysis Using Various Methods

7.1. Specification of Data Acquisition Parameters

First the GC instrument and its analog recorder are brought into the "ready" state by selecting suitable GC parameters. Such parameters are, *e. g.*, column type or stationary phase, temperature, carrier gas flow, sample load, input impedance of the amplifier, and recorder attenuation for the analog chromatogram. Subsequently the input of parameters for data acquisition is executed by the program PARAM.

A teletype dialog is used to specify several parameters of data acquisition before the sample is injected: the number of the channel on which the acquisition is to be done, the data rate (maximum of 20 points/sec), the run time (the computer stops data transmission when this time has expired if no stop signal has been given), as well as whether the raw data should be preserved for an extended period or discarded after completion of the *next* run on the same channel.

In addition, a sample identification can be entered. It is encoded to furnish information on the detailed origin of the sample.

If no new parameters are entered before the start signal (pressing the "start" button), the parameters of the previous run are used.

7.2. Data Acquisition

Special routines in the operating system (monitor) process interrupts from the real-time clock and control the analog/digital converter. The data from the A/D converter are stored in the buffers of a data job which is started automatically when the monitor is loaded; this job maintains buffers for all on-line instruments. When one of these buffers becomes full, its contents are transferred into the associated data file on the disk. It is important for the progress of the entire analysis that no data reduction or processing should occur at this stage. The data job cannot be swapped between core and disk like other time-sharing programs because data must be accepted continuously from the A/D converter. It therefore remains in the core, reducing the core capacity available to other users. When data acquisition on a certain channel is ended, either automatically or by a "stop" command, the corresponding data file on the disk is closed and becomes available for further processing.

7.3. Producing the Preliminary Basic Report with the Analysis Program GCAN

The analysis program determines the previously mentioned peak parameters such as start, end, maxima, turning points, shoulders, peak areas, and peak positions. A limit is defined for the first deviation relative to the mean signal noise, which is determined from 128 data points of the base-line before the start of the real chromatogram. Here, as with the real analysis, a special algorithm for the elimination of spikes is used. An unstable zero-line is corrected by a mathematical method in which a new base line is constructed as a polygon with minimal slope from all beginnings and ends of peaks. Peak deconvolution can be performed with special programs now under development since all raw data (unreduced A/D data) can be preserved on the disk. Very small peaks on the tails of other large ones can be treated by repeated evaluation of these data by a special version of GCAN which allows modification of the analysis parameters.

At the end of a chromatogram an organization program (ORGANI) automatically calls the evaluation program (GCAN). This program evaluates the raw data and writes the basic report on disk (Fig. 2). From there it can be recalled

```
TYPE REP22.DAT
45

11-NOV-70    10:38

KANAL          :22
INSTRUMENT     :VARIAN 1400 PPG-50M-K-S
KODE           :13

LZ             :62.3
MA             :19.1
MR             : 8.0


NR   ZEIT (MIN)  ART  HW     FLAECHE      FL. %

 1    432   2.9  BB   6.2  0.1713E+07    4.763
 2    454   3.0  BB   9.0  0.8516E+04    0.024
 3    470   3.1  BB  14.5  0.3114E+04    0.009
 4    495   3.3  BB   6.4  0.3945E+05    0.110
 *    526   3.5            0.4301E+04    0.012
 5    582   3.9  BB   6.5  0.3362E+05    0.093
 6    600   4.0  BB   5.9  0.4926E+04    0.014
 7    633   4.2  BB   8.2  0.2962E+04    0.008
        ↕                                  ↕
 *   1164   7.8            0.4309E+04    0.012
19   1215   8.1  TB        0.9427E+04    0.026
20   1267   8.4  BT  11.6  0.6148E+04    0.017
21   1311   8.7  TB  10.2  0.1827E+07    5.080
22   1350   9.0  BT   9.4  0.2734E+07    7.603
23   1404   9.4  TT        0.4397E+05    0.122
24   1438   9.6  TB        0.2961E+05    0.082
25   1644  11.0  BT        0.2046E+05    0.057
26   1730  11.5  TB  10.3  0.1239E+07    3.446
27   1808  12.1  BT  10.2  0.2446E+07    6.801
        ↕                                  ↕
39   3786  25.2  BB   5.5  0.1080E+07    3.003
 *   3852  25.7            0.7803E+04    0.022
40   4453  29.7  BB        0.2766E+05    0.077
41   5029  33.5  BB  10.7  0.2041E+07    5.676
42   6299  42.0  BB  10.4  0.1310E+07    3.642
43   6684  44.6  BB  10.6  0.1808E+07    5.029
44   8928  59.5  BT        0.3839E+04    0.011
45   9060  60.4  TB  11.1  0.2191E+07    6.093

SOM-DI-001-01                          A870.2
```

Fig. 2. Example of a preliminary report. See text for an explanation of lines 1–10.

by the operator at any time with a simple command (Fig. 2, line 1). In lines 2—9 the following information appears:

line 2: number of reported peaks
line 3: date and time
line 4: channel number on which the data acquisition has occurred
line 5: type of GC instrument and the column used on channel 22
line 6: code for data acquisition. The first figure can be 0 or 1, depending on whether the raw data are to be stored for some time or are to be deleted after the next run. The data rate is coded in the second figure
line 7: actual run-time for the chromatogram in minutes
line 8: information on the use (for the largest peak) of the linear dynamic range of the interface as percentage of full scale
line 9: information about the average noise level in μV

The sample identification is printed out at the end of the report. Many analyses can be measured on the same channel without new parameter specifications and the operator can append the corresponding sample identification at the end of each individual analysis.

The list of all the peaks found by GCAN contains the following information about each individual peak (starting at line 10):

column 1: peak number; shoulders are indicated by *
column 2: peak position as number of points between the chromatogram start and the maximum
column 3: retention time in minutes from the start to the maximum (for faster location in the analog chromatogram)
column 4: information about whether the integration, *i.e.* the determination of peak area, was from base line to base line (BB) or the minimum between two not completely separated peaks was used as the integration limit (BT for between base and valley, TB for between valley and base)
column 5: halfwidth of peak relative to retention time (in the first approximation a constant for isothermal chromatograms)
column 6: absolute area of the peak
column 7: peak area normalized over the total area

(The lines number 1—10 are not actually part of the computer output.)

This basic report serves as the basis for the refined analysis.

7.4. Refined Analysis

Like GCAN, the programs in this group have been written in FORTRAN IV by the analysts themselves, *i.e.* staff members of the chromatography laboratories. The use of a time-sharing computer facilitated their fast production. These programs serve to normalize, standardize, and correct the basic report data according to the wishes of the user, and also to plot the data (Fig. 3) and put them into the proper format. Additional information about the sample (*e.g.* numbers and/or intensities of standard peaks, concentrations and other parameters for response factor determinations, and internal standards, as well as names and response factors of identified peaks) is therefore also introduced by the operator in a teletype dialog. The operator can decide which limits should be set for the elimination of small peaks, *etc.* With the exception of the internal standard program all of these programs are subprograms of a large general program for refined analysis (REFREP) which can be called with the command RUN DSK : REFREP. Then the name of the basic report is typed in, *e.g.* REP 14 for the report for channel 14. Next the computer asks the operator at the teletype for the sample identification in case it is missing from the report. In response to the question "Auswertung" the operator can specify any of the following subroutines of program REFREP: FAKTOR, NAME, DIGFIL, ZUSFAS, NORM, INDEX, RESP.

7.5. Quantitative Analysis with the Basic Report Data

The following Section contains reproductions of teletype output from program REFREP's various subroutines working on the basic report (see Fig. 2). In the first example

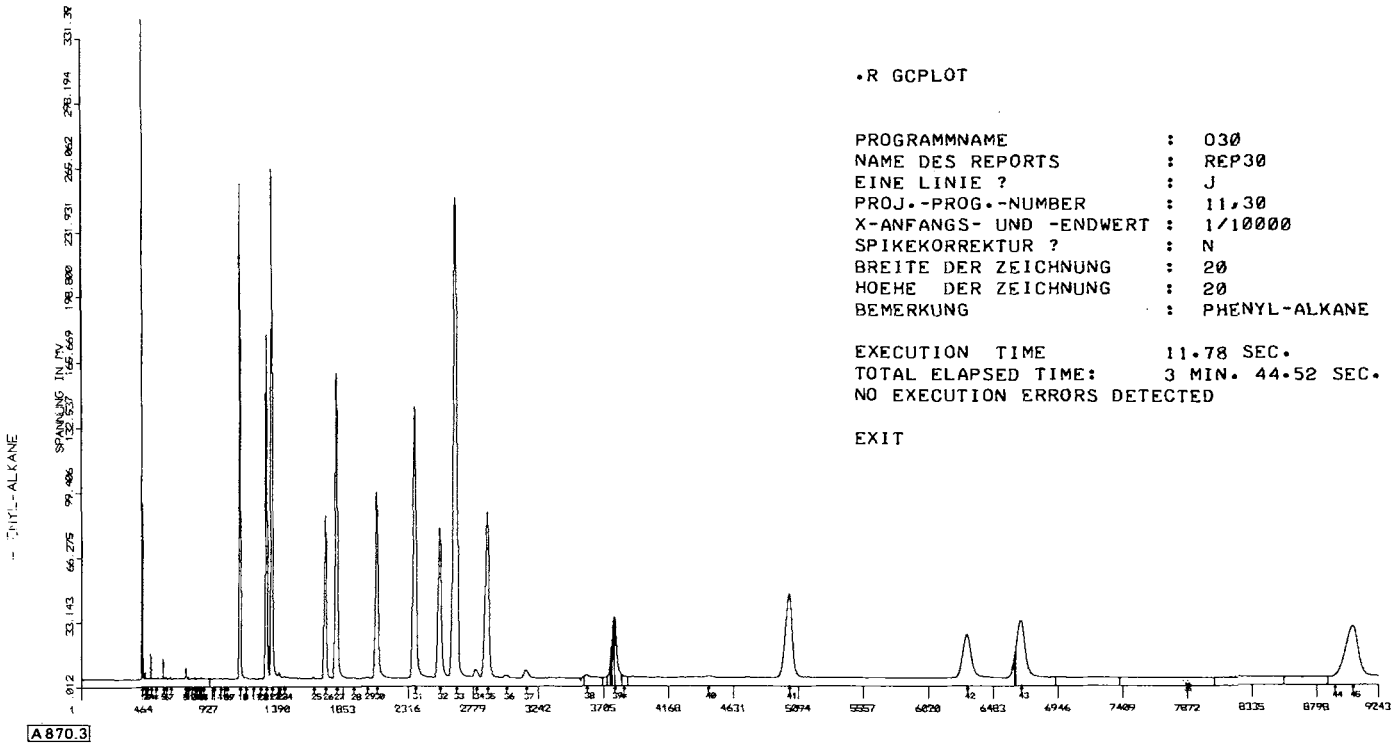


Fig. 3. Plotter representation of an analog chromatogram.

```
AUSWERTUNG :DIGFIL
SCHRANKE: 1.0
```

14-AUG-70

PROBE: SOM-DI-001-01

NR	ZEIT	%	FAKTOR	NAME
1	2.9	4.650		METHAN
18	7.5	5.874		N-NONAN
21	8.7	5.570	1.123	N-PROPYL-C°HEXAN
22	9.0	9.225	1.243	ALLYL-BENZOL
26	11.5	3.363		N-DECAN
27	12.1	6.640		3-PHENYL-BUTEN-1
30	14.0	4.680		4-PHENYL-BUTEN-1
31	15.8	7.848		TR-1-PHENYL-BUTEN-2
32	16.9	4.759		CIS-1-PHENYL-BUTEN-2
33	17.7	16.562		3-PHENYL-PENTAN
35	19.2	6.016		N-UNDECAN
39	25.2	2.932		1-PHENYL-PENTAN
41	33.5	5.540		N-DODECAN
42	42.0	3.556		6-PHENYL-HEXEN-1
43	44.6	4.908		1-PHENYL-HEXAN
45	60.4	5.948		N-TRIDECAN

SUMME DER PEAKS UNTER 1.000% = 1.929%

A870.4

Fig. 4. Subroutines FAKTOR, NAME, DIGFIL.

(Fig. 4) the operator specifies the peaks by their numbers within the basic report. Response factors are employed for the correction of peak areas.

In this example, the program DIGFIL was used as well as the programs FAKTOR and NAME (for "manual" input of response factors and substance names) to condense the final report; with DIGFIL a limit can be specified for the normalized peak areas in the basic report. All single peak areas which lie below the given value (here 1.0%) are not printed out in the new report; they are added and their sum printed out at the end of the output. After using DIGFIL, the report contains the percentage area values of the unnormalized report obtained after response factor correction.

Subroutine ZUSFAS can also be used in conjunction with REFREP's subroutines NAME and FACTOR; it allows

```
AUSWERTUNG :ZUSFAS
 1.-ABSCHNITT:4/17
 2.-ABSCHNITT:19/20
 3.-ABSCHNITT:23/25
 4.-ABSCHNITT:28/29
 5.-ABSCHNITT:36/38
 6.-ABSCHNITT:

14-AUG-70

 PROBE: SOM-DI-001-01


   NR    ZEIT      %     NAME

    1     2.9    4.650   METHAN
 4-17     3.3-   0.422
          6.9
   18     7.5    5.874   N-NONAN
19-20     8.1-   0.042
          8.4
   21     8.7    5.570   N-PROPYL-C'HEXAN
   22     9.0    9.225   ALLYL-BENZOL
23-25     9.4-   0.255
         11.0
   26    11.5    3.363   N-DECAN
   27    12.1    6.640   3-PHENYL-BUTEN-1
28-29    12.9-   0.097
         13.5
   30    14.0    4.680   4-PHENYL-BUTEN-1
   31    15.8    7.848   TR-1-PHENYL-BUTEN-2
   32    16.9    4.759   CIS-1-PHENYL-BUTEN-2
   33    17.7   16.562   3-PHENYL-PENTAN
   34    18.7    0.342
   35    19.2    6.016   N-UNDECAN
36-38    20.1-   0.685
         23.9
   39    25.2    2.932   1-PHENYL-PENTAN
   40    29.7    0.075
   41    33.5    5.540   N-DODECAN
   42    42.0    3.556   6-PHENYL-HEXEN-1
   43    44.6    4.908   1-PHENYL-HEXAN
   44    59.5    0.010
   45    60.4    5.948   N-TRIDECAN

FAKTOREN:

   21    1.123
   22    1.243                                  A870.5
```

Fig. 5. Subroutine ZUSFAS.

entire groups of small peaks to be summed as one total area leaving only the main peaks to appear individually (Fig. 5). It is used only when many small unimportant peaks occur in the chromatogram together with very few peaks of interest.

7.6. Quantitative Analysis with Internal Standard(s)

After calling the corresponding program (STAND6—see Fig. 6), the report number, calibration factors, and the names and numbers of the peaks to be identified and evaluated are given. The program asks for the weights of the sample and the standard and specifies the peak numbers of both standards (in this example).

Then the framed portion of Fig. 6 is printed out for the experimenter, the peak areas or concentrations of standards having been eliminated to calculate the concentrations of the components of the original mixture.

7.7. Qualitative Analysis

In order to identify separated species by means of their retention parameters the latter must be available in a standardized form. For this purpose either normal relative retention or Kovats indices can be used. The latter are especially suited, in keeping with the relevant thermo-

```
RUN DSK:STAND6


ANALYSENTYP:2,REP70

   NR     FAKTOR    NAME
:18//N-NONAN
:21//N-PROPYL-C'HEXAN
:26//N-DECAN
:31//TR-1-PHENYL-BUTEN-2
:32//CIS-1-PHENYL-BUTEN-2
:39//1-PHENYL-PENTAN
:43//1-PHENYL-HEXAN
:41//N-DODECAN
:

WELCHE PEAKS SOLLEN AUSGEWERTET WERDEN ?
:18/21/26/31/32/39/43/41

TARA         :19.2647
              19.2647
TARA+PROBE   :24.5525
              24.5525     5.2878 GRAMM PROBE
TARA+PR+ST   :24.9128
              24.9128     0.3603 GRAMM STANDARD 1
T+PR+ST+ST   :25.2527
              25.2527     0.3399 GRAMM STANDARD 2

NR DER BEIDEN ST-PEAKS:18/41
```

```
21-AUG-70

PROBE: SOM-DI-001-01

 NR     FLAECHE    % ST-1   % ST-2   FAKTOR   NAME

 18  0.2164E+07 STANDARD **.***            N-NONAN
 21  0.1827E+07    5.753    5.754          N-PROPYL-C'HEXAN
 26  0.1239E+07    3.901    3.902          N-DECAN
 31  0.2891E+07    9.103    9.105          TR-1-PHENYL-BUTEN-2
 32  0.1753E+07    5.520    5.521          CIS-1-PHENYL-BUTEN-2
 39  0.1080E+07    3.401    3.401          1-PHENYL-PENTAN
 41  0.2041E+07 **.***STANDARD            N-DODECAN
 43  0.1808E+07    5.693    5.694          1-PHENYL-HEXAN
                  99.988  100.012
A870.6
```

Fig. 6. Program STAND6.

dynamic principles, for a structural interpretation on the basis of increments (see, *e.g.* [7, 8, 10, 12—14]). Therefore only the use of Kovats indices is illustrated in the following.

```
RUN DSK:REFREP

REPORT:REP70.DAT


AUSWERTUNG :INDEX
NR UND INDEX DES 1. STANDARDS: 18/900
NR UND INDEX DES 2. STANDARDS: 35/1100
NORMIERT AUF PEAK NR          : 26
KODE                          :
TABELLE                       : TAB01


19-AUG-70

 PROBE: SOM-DI-001-01


 NR    POS     INDEX   TYP    FL-%     NORM   NAME

 18   1125    900.00    ST   **.**     1.75
 19   1215    919.35    IN    0.03     0.01
 20   1267    929.54    IN    0.02     0.00
 21   1311    937.68    IN    6.12     1.47
 22   1350    944.56    IN    9.15     2.21
 23   1404    953.62    IN    0.15     0.04
 24   1438    959.07    IN    0.10     0.02
 25   1644    988.59    IN    0.07     0.02
 26   1730    999.45    IN    4.15     1.00
 27   1808   1008.70    IN    8.19     1.97
 28   1930   1022.16    IN    0.06     0.02
 29   2026   1032.01    IN    0.05     0.01
 30   2095   1038.72    IN    5.77     1.39
 31   2365   1062.57    IN    9.68     2.33
 32   2542   1076.45    IN    5.87     1.41
 33   2656   1084.79    IN   20.43     4.92
 34   2800   1094.73    IN    0.42     0.10
 35   2880   1100.00    ST   **.**     1.79

SCHRANKE FUER TABELLENVERGLEICH + -:0.5


 NR   INDEX-REP  INDEX-TAB  DIFFERENZ   NAME

 21     937.68     937.89    -0.2108   N-PROPYL-C*HEXAN
 22     944.56     944.80    -0.2409   ALLYL-BENZOL
 27    1008.70    1009.20    -0.4983   3-PHENYL-BUTEN-1
 30    1038.72    1039.06    -0.3356   4-PHENYL-BUTEN-1
 31    1062.57    1062.77    -0.2025   TR-1-PHENYL-BUTEN-2
 32    1076.45    1076.58    -0.1273   CIS-1-PHENYL-BUTEN-2
 33    1084.79    1084.87    -0.0783   3-PHENYL-PENTAN

SCHRANKE FUER TABELLENVERGLEICH + -: ↑C
```

A870.7

Fig. 7. Subroutine INDEX, table look-up.

Considerable progress with regard to precision and rapid evaluation of the measurements has been made in this field by complete computerization of gas chromatography. We feel that the practical application of the Kovats index for qualitative analysis in the past essentially suffered from the fact that its calculation and determination were inaccurate, troublesome, and time consuming.

It will be shown in the following how the Kovats index can be determined from the basic report (Fig. 2).

The determination of Kovats indices of the components of a mixture requires the presence of standard compounds—*n*-paraffins in the right carbon number range—if no extrapolation of standard peak retentions is allowed. In the interests of high precision it is desirable that the standard paraffins should already be present in the sample and that the *n*-paraffin retention values for the index calculation not be determined independently through the measurement of a standard chromatogram.

The program INDEX is a subprogram of REFREP. The program asks for the peak numbers and the retention index of standards found in the mixture. It will also ask for the peak number to which all peak areas whose index values are to be determined should be normalized. The answer to the code inquiry allows different kinds of evaluation procedures, according to which Kovats indices can be calculated from one or more or whole groups of peaks in the basic report.

Fig. 7 shows the teletype output for an identification of isomeric hydrocarbons by the comparison of experimentally determined index values with tabulated ones. In answer to the question "Tabelle:", the number of the corresponding collection of data is given. Two limits are defined in the process. The first limit at the beginning of the report has the same function as the limit in program DIGFIL. All peaks of substances whose concentrations are less than, *e.g.* 1.0% are not evaluated. The second limit is defined as the "window" for data comparison with the values in the tables; *i.e.*, the tabulated index values and names of compounds whose index values are inside the limits of the measured ones are printed out. The table search can be repeated as often as desired with variations of the limits up and down in order to exclude possible isomers or include others in the comparison. Thus each qualitative analysis is accompanied by a quantitative analysis. The standard peaks are not taken into consideration on normalization of peak areas since the standards in most cases are added and do not belong to the sample.

Identification is also possible without any added standard if the sample contains components whose indices are known. The peak numbers and index values of these compounds are then specified during the TTY dialog instead of the index values of the standard *n*-paraffins, and the program calculates the index values from them.

Under the heading "Typ" (see the beginning of the index table), the standard peaks are marked with ST and the others with IN and EX to indicate whether the index values were interpolated or extrapolated. Certain errors for the index determination are to be expected for extrapolated values because of the curvature of the $\log V_R$/C-number plot of the standard paraffins.

7.8. Mean Standard Deviation of Repeatability of Qualitative and Quantitative Analyses

Not only rationalization by saving of service staff and greater analysis through-put are important arguments for the introduction of electronic data processing with on-line operation. Besides the possibility of carrying out completely new experiments (*e.g.*, in process control), a considerable increase in analytical precision and accuracy is obtainable through the elimination of subjective errors and through the use of better instruments (see description of the interface, *etc.*).

Fig. 8. gives an impression of the repeatability of quantitative analyses.

The accuracy of the evaluation of gas chromatographic analyses with such a computer system can be checked only at considerable expense since the systematic errors of sample preparation and of gas chromatographic analysis itself (sample injection, detection, *etc.*) can only be made smaller than the repeatability with extreme effort.

The repeatability of Kovats index measurements is in principle better (for instance, the standard substances are generally contained in the sample) (Fig. 9). The standard deviations of Kovats index determination on an analog diagram using logarithmic scales are three to four times larger than those observed with the computer evaluation. Such a repeatability of index measurement is of great importance for high resolution gas chromatography with capillary columns, since it is better than the resolution (0.2—0.3 IU[*] at best). Thus the full benefit of gas chromatographic separation efficiency in the interests of qualitative identification is assured. Details of the determination of the repeatability of peak areas and retention values will not be reported here. The data acquisition rate and various parameters of the program GCAN employed clearly play a role in such measurements.

TYPE ABC.DAT

REPEATIBILITY VON FLAECHENWERTEN

DATUM : 10-DEC-70
BEARBEITER : SE
KANAL : 22
DATENRATE : 5/SEC
INSTRUMENT : VARIAN 1400-2
SAEULE : PPG-50M-K-S
PROBE : SOM-SE-020-01

1	0.1635	3.3235	8.3909	0.2183	2.2653	22.0738	2.6050
2	0.1522	3.3846	8.3737	0.2164	2.2708	22.1866	2.6014
3	0.1604	3.4619	8.5666	0.2202	2.2754	21.8756	2.6057
4	0.1631	3.4292	8.4658	0.2047	2.2686	22.0263	2.6103
5	0.1778	3.3860	8.4784	0.2266	2.2832	22.1000	2.6230
6	0.1598	3.3111	8.3210	0.2236	2.2646	21.9887	2.6717
7	0.1630	3.4369	8.6384	0.2247	2.2888	21.8336	2.6114
8	0.1681	3.4259	8.5848	0.2210	2.2778	21.8872	2.5999
9	0.1571	3.4147	8.4316	0.2150	2.2696	22.1825	2.5918
10	0.1594	3.2781	8.3291	0.2196	2.2611	22.0732	2.6126
MW	0.1624	3.3852	8.4580	0.2190	2.2725	22.0227	2.6133
V	0.0069	0.0613	0.1098	0.0062	0.0087	0.1249	0.0222
VREL	4.2257	1.8102	1.2987	2.8237	0.3845	0.5672	0.8491

A870.8

Fig. 8. Repeatability of area determinations.

7.9. Additional Auxiliary and Subprograms for the Refined Analysis

The following list summarizes additional auxiliary and subprograms and their functions:

REPZUS: Compilation of the most important data of several basic reports into tables

VARIAN: Calculation of mean standard deviation for a large number of measurements

SORT: Program for production, competition, or correction of data tables with corresponding names. A table can be sorted in ascending order of data if so desired

RINGO: Program for the determination of theoretical plate numbers and K values

GCVARI: Program for repeatability measurements for the compilation of values from several basic reports

GCPLOT: Production of an analog chromatogram from the unreduced data, either completely or partially. Arrows show the positions of the peaks (Fig. 3); stars indicate shoulders

The description of the software used in gas chromatographic analysis corresponds to the state as of Summer, 1971.

[*] IU stands for Index Units.



	a	b	a	b	a	b	a	b
M =	865.23	865.77	897.16	897.62	901.16	901.67	914.44	914.88
S =	±0.2106	±0.0528	±0.2292	±0.0453	±0.1957	±0.0553	±0.1601	±0.0545

Fig. 9. Repeatability of retention-index determinations for C_9 cyclopropane hydrocarbons. Comparison of evaluation (a) by hand and (b) by computer.
M = mean of 10 measurements, S = standard deviation. Column: Squalan 100 m, 0.25 mm i. d./100 °C/1.5 atm Ar.

Received: November 18, 1971 [A 870 IE]
German version: Angew. Chem. *84*, 390 (1972)

[1] *H. Günzler*, Chem.-Ing.-Techn. *42*, 877 (1970).
[2] *E. Ziegler*, Pittsburgh Conf. Anal. Chem. Appl. Spectr., Cleveland 1969.
[3] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Pittsburgh Conf. Anal. Chem. Anal. Spectr., Cleveland 1970.
[4] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Anal. Chem. *42*, 51 A, Aug. (1970).
[5] *G. Schomburg* and *E. Ziegler*, Lecture, 152nd ACS-Meeting Washington; J. Chrom. Sci. *1971*, in press.
[6] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Angew. Chem. *84*, 371 (1972); Angew. Chem. internat. Edit. *11*, 348 (1972).
[7] *G. Schomburg*, Anal. Chim. Acta *38*, 45 (1967).
[8] *G. Schomburg* and *D. Henneberg*, Z. Anal. Chem. *236*, 279 (1968).
[9] *G. Schomburg* and *D. Henneberg*, Chromatographia *1*, 23 (1969).
[10] *G. Schomburg*, Chromatographia *4*, 286 (1971).
[11] *D. Henneberg, K. Casper, E. Ziegler*, and *B. Weimann*, Angew. Chem. *84*, 381 (1972); Angew. Chem. internat. Edit. *11*, 357 (1972).
[12] *G. Schomburg*, Adv. Chromatogr. *6*, 211 (1968).
[13] *G. Schomburg*, Separation Sci. *1*, 339 (1966).
[14] *G. Schomburg*, J. Chromatogr. *23*, 1, 18 (1966).

Use of a Computer in Nuclear Magnetic Resonance Spectroscopy

By Ernst G. Hoffmann, Werner Stempfle, Gerhard Schroth, Bruno Weimann, Engelbert Ziegler, and Josef Brandt [*]

1. Survey

1.1. On-line Data Acquisition and Direct Processing

The NMR spectroscopist has long been familiar with the connection of a computer to his spectrometer.

Specially organized small computers have been employed in on-line operation with NMR spectrometers for many years. Since the advent of spectrometers whose magnetic fields are sufficiently stable over a long period of time with regard to homogeneity and drift, spectroscopists have used multi-channel analyzers, such as were known from nuclear physics, for signal improvement by accumulation of spectra[1]. Indeed one of the greatest weaknesses of the NMR method is its low sensitivity or high sample requirement. By coherently summing the records in digital form, the signal to noise ratio can be improved by at least one order of magnitude.

These improved spectra can then be written out in *analog* fashion, or *digitally* by use of a punched tape output, for further processing in a computer center[2]. The signal averaging computers CAT® (computer for averaging transients) or TAC (time averaging computer) are hardware programmed for their particular purpose[3]. Operating synchronously with the sensor (the spectrometer) they add (or subtract) the analog data (signals) of the periodically repeated runs of spectra. In some types of correlation or signal averaging computers signal integration is also possible.

However, we soon succeeded in using such computers with further spectroscopic methods[4]. Thus, for example, an infrared analysis of complicated mixtures is possible by subtracting, in increments, the spectra of assumed components from the stored spectrum of the mixture, until even strongly overlapping absorption bands may be identified and measured. The above method can also be utilized for solvent compensation when it is impossible to use a comparison cell for optical compensation. Corresponding on-line applications in NMR spectroscopy (compensation of unavoidable solvent impurities becoming significant on accumulation) are restricted by the greater solvent and concentration dependence of the signal positions. Further, Raman spectra can be separated

[*] Prof. Dr. E. G. Hoffmann, Dipl.-Phys. W. Stempfle, Ing. G. Schroth, Dipl.-Math. B. Weimann, Dr. E. Ziegler, and Dr. J. Brandt
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

from a fluorescent background (subtraction of a "spectrum" recorded with an extremely large slit width)[2].

The small number of storage locations (usually 1024) in these now outdated instruments[*] allows full reproduction of the resolution capacity only for limited sections of the spectra. Freely programmable computers extend the on-line uses considerably as will be shown below. In particular they allow immediate flexible processing of the digitized data files.

1.2. Off-line Interpretation Aids and Evaluations

The off-line use of (albeit large) computers in NMR spectroscopy for classification and analysis of strongly coupled systems goes back even further. If the differences in the chemical shifts and the accompanying coupling constants do not differ greatly from one another then the resulting splitting pattern is very complicated and prevents direct extraction of these values. The computer allows quantum mechanical model calculations for larger spin systems too. In these calculations[6-8b] the tentative parameters of the coupled nuclear spins are varied until the simulated spectrum is sufficiently similar to that measured. Iterative calculation programs[6-8b] then optimize the agreement between the calculated and the experimental spectrum, and thus the exact parameters important for spectral assignment and interpretation of topological and stereochemical molecular properties can be determined.

With respect to the kind of assistance that a modern computer can give in *qualitative* analysis, nuclear magnetic resonance spectroscopy assumes a position intermediate between gas chromatography and molecular vibrational spectroscopy:

The parameters of a gas chromatogram can be extracted *directly* from the record in nearly all cases after only simple computational treatment. Its information content for qualitative analysis is small even when account is taken of combinations of different measuring conditions (change of columns *etc.*). In NMR and vibrational spectra, the parameters (chemical shifts and coupling constants, mass and force constants, respectively) are contained *implicitly*, and can be found for example by model calculations. In general, such calculations are practicable as an analytical tool only in NMR spectroscopy. In vibrational spectroscopy such simulations are possible in principle, but except for some useful findings on the characteristic vibrational frequencies, the molecule has to be considered as a *whole* with all the degrees of freedom that the atoms possess within its elastic system. Therefore complete calculations are possible here only for fairly small molecules, and they only yield less reliable approximations of structural parameters. These parameters are closely connected with the frequently quite arbitrary choice of model and require support from other methods. *Routine* application of model calculations when deciding about structural problems does not come into question presently because of the large number of estimated parameters necessary in the calculations. Therefore in gas chromatography as well as in vibrational spectroscopy a computer can generally only help to correlate the measured records or their characteristic data with material previously stored for comparison by use of search and library programs[9, 14].

In contrast to molecular vibrational spectroscopy, the NMR spectrum of a compound hardly depends upon the molecule as a *whole* but may be understood as a superposition of the spectra of its constituent parts because of the very limited transmission of indirect spin-spin coupling within a bond system. Model calculations with seven to nine spins or equivalent spin groups are therefore possible and permit a *unique* assignment of the molecule or a section thereof[16-21].

1.3. The Computer as a Spectrometer Component

There is a third type of computer application to NMR spectroscopy in which the NMR signal contains the spectrum in a coded form dictated by the measuring method, and the computer, acting as a translator, represents an integral component of the spectrometer. This type of computer application includes the processing of pulsed spectroscopy which has become so important recently. The information here is present initially as an intensity *vs. time* diagram from the "free induction" of the nuclear resonance signal (FID), *i.e.* as an interferogram of all the resonance frequencies present. This has to be changed by Fourier transformation into the usual form of an intensity *vs. frequency* spectrum[10] with all the resonances differentiated by chemical shifts and spin-spin couplings. The new experimental technique of Fourier transform spectroscopy offers so many advantages in increased sensitivity and measuring speed[11, 11a], that it will certainly contribute to popularization of the computer in nuclear magnetic resonance spectroscopy[27].

Because of the astoundingly rapid progress in semiconductor technology, computers of sufficient capacity for this purpose have become so cheap that instead of costing many times more than a medium priced NMR spectrometer they cost only as much as a fairly expensive spectrometer accessory.

Further computer applications of this sort are the investigation of kinetics of fast reactions by examination of the line-broadening and its variation with temperature.

The development of uniform process control especially by optimizing the spectrometer adjustments (*e.g.* continuous control of field homogeneity) and the direct control of spectral recording by computer is also progressing. Small computers[12] are now on the market which have been programmed for this purpose.

[*] It should be noted that signal averaging computers of this kind, but now normally with 4 to 8 K channels, are still on the market [5]. They can no longer compete with genuine minicomputers of similar capacity with regard to price and flexibility, and are being increasingly replaced by the latter.

2. Experience with the Mülheim Computer System

2.1. On-line Data Acquisition and Direct Processing

From what has been said above it should be clear that the aid of a computer is indispensable if one wishes to completely exploit the capability of nuclear magnetic resonance spectroscopy. Thus the emphasis lies equally on the use of a computer as a digital recorder (on-line service)—with subsequent more or less extensive processing of the information produced by the spectrometer—as on the off-line use for spectrum simulation.

A large computer system[13], which allows both possibilities to be used equally well in a time-sharing configuration, is accordingly ideal for the solving of NMR problems. However, such an investment for this purpose alone cannot be considered.

The connection of many measuring instruments, user terminals, and peripheral instruments requires, among other things, a sophisticated operating system (monitor) with high core storage requirements. The prerequisite for suitable availability of a computer system for NMR spectroscopy, especially when extensive calculations such as those encountered in Fourier transform spectroscopy have to be performed, is that the operating system should not be over-extended. If this does happen, then reduction of the calculating capacity, increased susceptibility to trouble, and discontinuous operation can result.

The digital registration of a conventional spectrum (field or frequency sweep) takes place over one of the connections of the "slow" interface (Figure 1). This reduces the continous sequence of spectral signals produced by the spectrometer into a discrete series of sampled points to which the corresponding numerical values are then assigned by an analog/digital converter. The data acquisition program SELDAT picks up these values 20 times (or less) a second and feeds them into the computer for storage. Signal searching is then carried out with the program NMRAN which, in many respects, resembles the program GCAN. However, it also takes into account some special features of NMR spectra that impede signal searches and are not easy to handle in programming.

Thus a nuclear magnetic resonance spectrum, in contrast to a gas chromatogram, can begin directly with a signal. The baseline cannot therefore be assumed (for example from the first 20 points of the record) but must be found by the program: The bottom third of the lowest 6% of the points of a spectrum are discarded, and the remainder used for an extrapolation onto the maximum of a Gaussian curve. This forms the basis for a zero-line correction.

We consider such a complicated procedure necessary because NMR signals can show oscillations ("wiggles") following the peak. These may reach far below the true baseline and would falsify it. Since the additional danger exists of mistaking the wiggles for very sharp signals, a measure for the closeness of successive signals has to be included in the evaluation. On the other hand, very broad signals may appear in an NMR spectrum which must not be interpreted as the baseline. These can be dealt with by inclusion of a further parameter. Finally transmission errors ("spikes") must be eliminated in a special program section. If desired digital filtering[*] can be introduced here for smoothing or for increasing contrast.

A subsequent integration yields the intensities of the lines or the group of lines. As each nucleus contributes equally to the signals in which it shares the line groups can be normalized with regard to the number of nuclei present, provided their total number is known. Otherwise the signal intensities are allotted as percentages. Spectral records, determination of line positions, and integration are carried out in one operation, thus saving manpower.

For further computer processing, line positioning with high precision is necessary. This requires a strict correlation between measured frequency (abscissa) and storage address. The correlation is best guaranteed if the computer itself controls the frequency or field sweep, and possibly the recorder sweep, of the spectrometer. Such control could be carried out by computer-driven stepper-motors or D/A converters, or by direct digital control of a frequency synthesizer. All this, however, places a burden on the computer and one therefore frequently proceeds in the reverse manner: The *spectrometer* induces the acceptance of a data word, usually by means of the priority interrupt system.

The following method is a compromise which we are successfully employing at present. Our NMR instruments are 300 m away from the computer so that rapid transfer of digital data is a problem. The system we have devised relies on the precision of the internal computer clock and thus saves corresponding output units on the computer and the spectrometer. While not using rigid abscissa coupling, we are able to control the spectrometer by a stepper-motor whose driving pulses are taken from the correspondingly subdivided frequency of a highly stable counter crystal oscillator. The motor simultaneously drives the spectrometer recorder and a potentiometer connected to a highly linear voltage-regulated oscillator (VCO). However, the better solution of this problem at present (Figure 1) is the use either of a sweep ramp of an externally

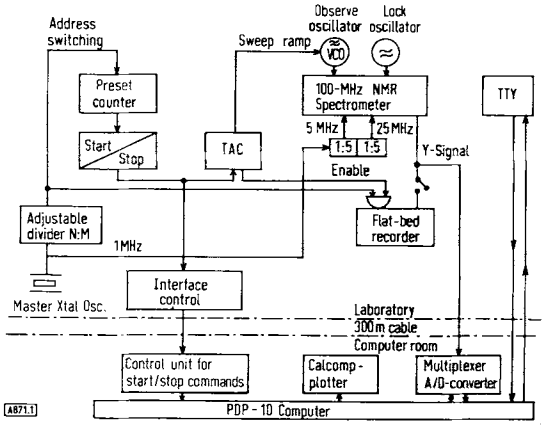


Fig. 1. Block diagram of our conventional NMR instrument (frequency sweep) in on-line operation.

[*] Unlike electronic filtering, in which the back edge of the signal is strongly spread out, *supplemental* digital filtering operates symmetrically on the signal (*i. e.* on the amplitude, not on the phase, of its high frequency components). In this way the filter characteristics can be varied *after* recording as required.

controlled signal averaging computer (TAC) or of a suitably programmed D/A converter for an automatic recording routine. The necessary start and stop impulses for the computer are produced by the start- and final frequencies preselected at the coding switches which causes the triggering through a properly modified counter.

(NMRCAT). In contrast to the signal averaging computers discussed initally, a large computer system has the advantage of being able to distribute the spectrum over *many more* storage locations with *larger* word size. This means that even *long* spectra with *high* resolution can be registered, and that one is hardly limited in the number

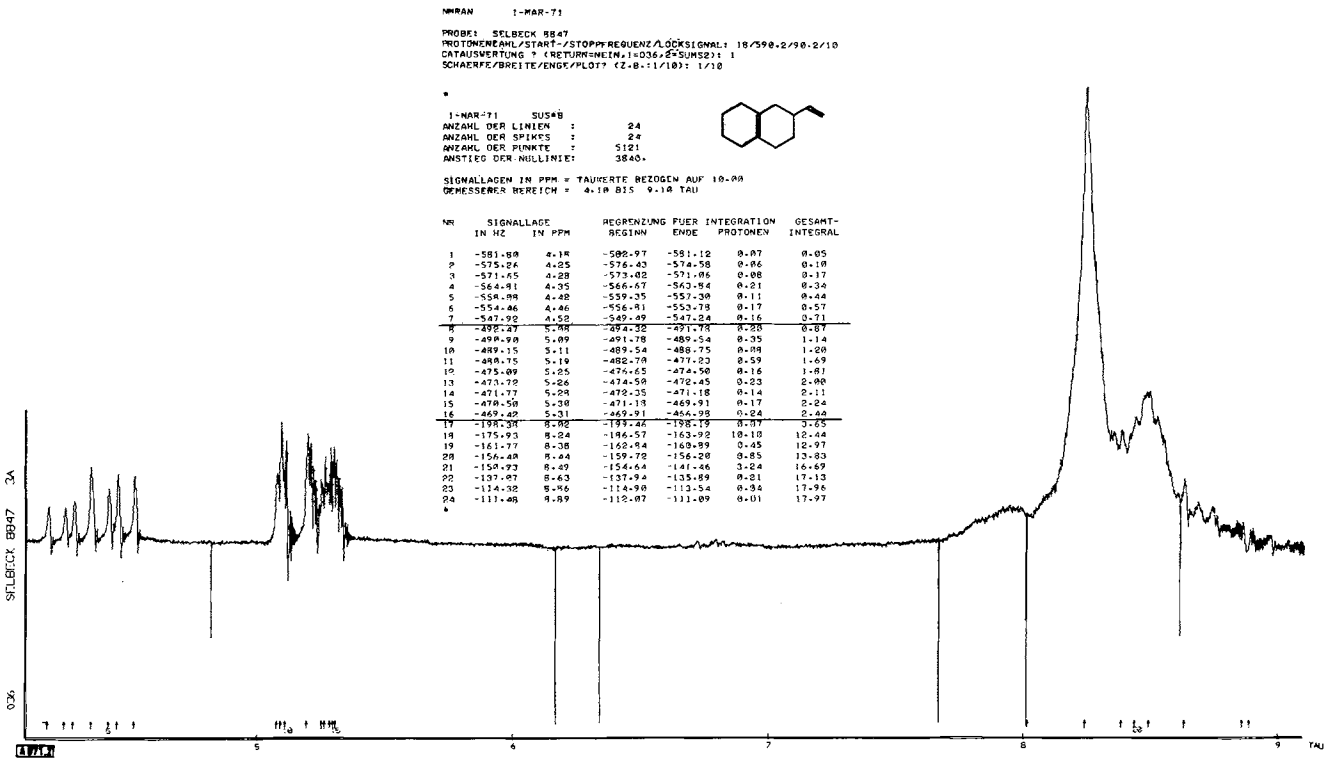
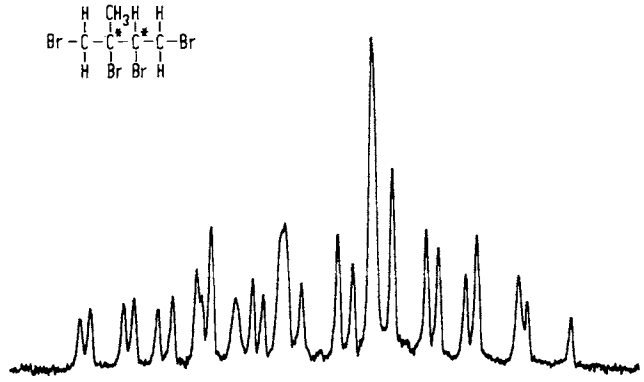


Fig. 2. Example of data acquisition and reduction: frequency range 500 Hz, data rate 10 points/s. Arrows on the abscissa mark line positions discovered by the program. Some spikes were not eliminated by the program. The uneven values on integration suggest an impurity in the sample (2-vinyl-1,2,3,4,5,6,7,8-octahydronaphthalene).

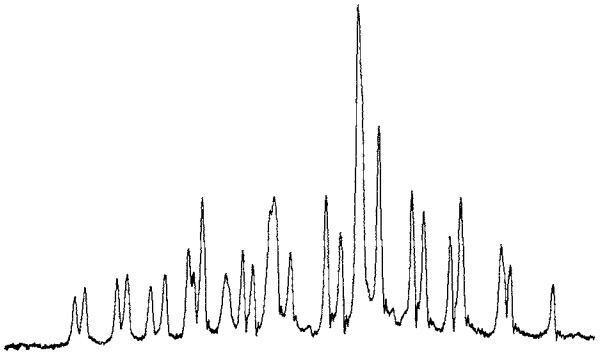
Figure 2 illustrates data processing by this method. The line positions recognized by the program NMRAN are marked by arrows on the computer diagram (consecutive program NMRPLT). The top of the list contains instructions regarding number of protons, start and stop frequencies, lock signal, *etc.*, and for the type of evaluation as mentioned above. The result, written either slowly by teleprinter in the laboratory or rapidly by line printer in the distant computer center, gives line separations in Hz from a standard line, and chemical shifts as τ or δ values. The standard line may be defined at a later time if desired. The integration proceeds in increments (*i.e.* separately for each line), at which point errors caused by signal overlap may enter, as well as cumulatively, in which defined line groups are evaluated without such errors. The processed spectrum remains on the disk file, and is ready for further processing. Its signals can be taken out by an evaluation program (NMRSIG) that searches for repeated line spacings and thus finds probable coupling constants. Also it sorts the signals into given ranges, thereby affording preliminary evidence about structural features. In its present form this program needs further improvement.

The program complex concerned with spectral data acquisition must also include an accumulation program of accumulations. ^{1}H-NMR spectroscopy thus becomes a micro method. However, it is primarily the possibility of being able to accumulate spectra thousands of times ($n \geqslant 1000$; sensitivity gain $S/N \approx \sqrt{n}$) that proves so advantageous for the recording of resonances of nuclei other than ^{1}H and ^{19}F. Because of their smaller gyromagnetic ratio and their frequently lower natural abundance, such "heteronuclei" possess considerably smaller detectabilities. In addition they exhibit very large chemical shifts and must therefore be recorded over a broad spectral range.

Figure 3 shows the possibility of data processing from a complex spectrum (the methyl signal has been omitted) recorded for a mixture of two racemates of diastereomers (two chirality centers)[15]. The spectral type of the isomers cannot therefore be very different, and an assignment of line groups to each racemate was therefore accomplished by a combination of searching for recurring line separations, and for the centers of gravity of the chemical shifts. The computer permits sufficiently accurate determination of the line positions and also yields a good estimate of the ratio of the two constituents from the calculated intensities of the single lines, even from such a complicated spectrum. An undertaking of this nature would be unthinkable



2*[A8CXY]



NR	ZEIT(MIN:SE)		FLAECHE	FL.IN %	ART	HW.-BR.SCHULT.		ZEITEN
1	1743	1:27	0.4346E+06	0.54	BB	12.79	0	0.00
2	1789	1:29	0.9694E+06	1.20	BB	22.22	0	2.31
3	1936	1:37	0.1343E+07	1.66	BB	21.25	0	9.69
4	1983	1:39	0.1554E+07	1.92	BB	23.97	0	12.04
5	2098	1:45	0.1179E+07	1.45	BB	-1.00	0	17.41
6	2156	1:48	0.1570E+07	1.94	BB	23.16	0	20.73
7	2265	1:53	0.3301E+07	4.07	BT	43.75	0	26.19
8	2331	1:57	0.3923E+07	4.84	TB	23.69	0	29.51
9	2435	2: 2	0.2629E+07	3.24	BT	-1.00	0	34.73
10	2514	2: 6	0.2419E+07	2.98	TB	24.64	0	38.69
11	2558	2: 8	0.1964E+07	2.42	BT	22.70	0	40.90
12	2584	2: 9	0.1503E+06	0.19	TB	-1.00	0	42.20
13	2659	2:13	0.8188E+07	10.10	BB	55.99	0	45.97
14	2734	2:17	0.2147E+07	2.65	BB	-1.00	0	49.73
15	2898	2:25	0.3488E+07	4.30	BT	21.69	0	57.96
16	2921	2:26	0.2029E+06	0.25	TT	-1.00	0	59.11
17	2963	2:28	0.3012E+07	3.72	TT	23.50	0	61.22
18	2988	2:29	0.2109E+06	0.26	TB	-1.00	0	62.48
19	3048	2:32	0.1521E+08	18.76	BT	-1.00	0	65.49
20	3141	2:37	0.6589E+07	8.13	TT	26.35	0	70.15
21	3168	2:38	0.2850E+06	0.35	TB	-1.00	0	71.51
22	3291	2:45	0.3658E+07	4.51	BT	23.03	0	77.68
23	3315	2:46	0.2286E+06	0.28	TT	-1.00	0	78.89
24	3345	2:47	0.3537E+07	4.36	TT	24.10	0	80.39
25	3464	2:53	0.2493E+07	3.08	BT	23.02	0	86.36
26	3515	2:56	0.4382E+07	5.41	TB	25.65	0	88.92
27	3698	3: 5	0.3238E+07	3.99	BT	32.99	0	98.11
28	3740	3: 7	0.1623E+07	2.00	TB	-1.00	0	100.21
29	3935	3:17	0.1130E+07	1.39	BB	-1.00	0	109.99

7.4% ES

•

A071.3

Fig. 3. Sections of the spectrum of a diastereomeric pair (1,2,3,4-tetrabromo-2-methylbutane). Above: recorder trace of the spectrometer. Below: computer diagram with evaluation sheet from the program GCAN (precursor of NMRAN, intensities in percentages of the total integral).

with normal analog integration. The figure shows the spectrum of the skeletal protons as recorded by the spectrometer (above), and the spectrum as acquired and plotted by the computer (below). A table of printed out values is also included.

An acceleration of data flow by more rationalized data acquisition and direct data reduction, although desirable for our considerable analysis throughputs on several instruments, can at present only be achieved to a limited extent. There are two bottlenecks which can only be partly bypassed. Firstly, much would be gained if the readiness of the spectrometer could be optimized automatically by the computer. This is particularly important for prolonged spectrum accumulation. A time-sharing computer of our type is not really suitable for process control[13]. Improvements in this direction such as have already been effected in special small computers[12] must therefore be put aside in our case (see Section 3, last paragraph).

Furthermore, the on-line *processing* of conventionally recorded spectra will remain difficult. Even on slow scanning of a spectrum, it is unavoidable that *sharp* lines will show strong wiggles whose maxima may be mistaken for further absorption lines. Even the program tricks described above prove inadequate when groups of very sharp lines predominate in the spectrum.

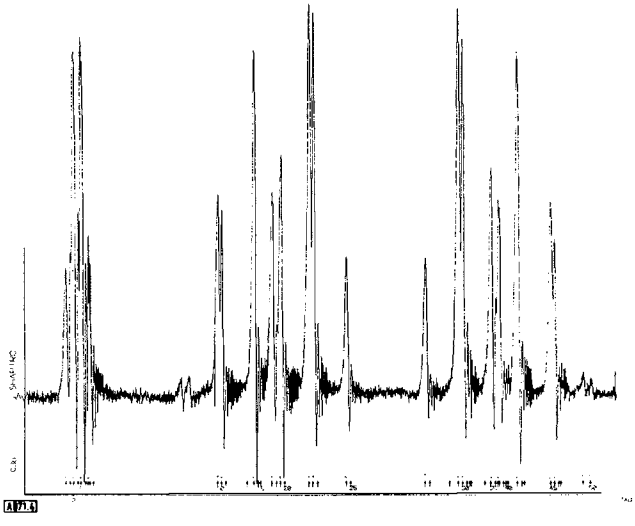


Fig. 4. 100-Hz section of the spectrum (100 MHz) of an eight-component mixture (here: signals of methyl formate and *o*-dichlorobenzene) with sharp lines. Computer diagram: data rate 20 points/s, sweep 0.2 Hz/s. Report see Figure 5.

Figures 4 and 5 illustrate this point with the aid of a typical example. The imperfection of the method is shown by the fact that 22 out of 24 lines were found correctly (×) (even with the considerable precision of ±0.03 Hz), but 28 arise from misinterpreted wiggles (/). A truly satisfactory solution is only to be expected on general application of Fourier transform spectroscopy which, owing to its principle of stationary operation, inherently gives spectra without wiggles.

2.2. Off-line Applications

Nuclear magnetic resonance spectra may show very complex splitting patterns which can no longer be analyzed by simple means. In the last ten years, a series of programs have been developed which can simulate spectra from a number of parameters (chemical shifts, coupling constants,

```
.RUN DTA6:NMRAN

NMRAN       5-FEB-71

PROBE:  SHAPIRO
PROTONENZAHL/START-/STOPPFREQUENZ/LOCKSIGNAL: 100/805/705/10
CATALOGWERTUNG ? (RETURN=NEIN,1=036,2=SUMS2): 1
SCHAERFE/BREITE/ENGE/PLOT? (Z.B.:1/10): 1/10

*


 5-FEB-71      SUS*A
ANZAHL DER LINIEN    :        50
ANZAHL DER SPIKES    :        33
ANZAHL DER PUNKTE    :     10240
ANSTIEG DER NULLINIE:     26368.

SIGNALLAGEN IN PPM = TAUWERTE BEZOGEN AUF 10.00
GEMESSENER BEREICH =  1.95 BIS  2.95 TAU
```

NR	SIGNALLAGE IN HZ	SIGNALLAGE IN PPM	BEGRENZUNG FUER INTEGRATION BEGINN	ENDE	PROTONEN	GESAMT-INTEGRAL	
1	-800.77	1.99	-801.22	-800.59	1.95	1.95	X
2	-800.28	2.00	-800.45	-800.24	1.03	3.00	
3	-799.95	2.00	-800.24	-799.75	6.22	9.22	X
4	-799.48	2.01	-799.61	-799.37	1.55	10.78	
5	-799.22	2.01	-799.38	-798.95	5.80	16.53	X
6	-798.69	2.01	-798.78	-798.59	0.70	17.25	
7	-798.43	2.02	-798.54	-798.32	1.18	18.45	X
8	-798.26	2.02	-798.33	-798.17	0.57	18.98	
9	-797.92	2.02	-797.98	-797.87	0.09	19.08	
10	-746.22	2.54	-746.80	-745.98	4.14	23.23	X
11	-745.81	2.54	-745.99	-745.68	1.83	25.02	X
12	-745.37	2.55	-745.44	-745.32	0.04	25.07	
13	-743.17	2.57	-743.23	-743.15	0.01	25.08	
14	-742.47	2.58	-743.12	-742.29	6.59	31.68	X
15	-742.01	2.58	-742.09	-741.95	0.23	31.92	
16	-741.75	2.58	-741.81	-741.69	0.07	31.99	
17	-740.60	2.59	-741.16	-740.39	4.12	36.12	X
18	-740.10	2.60	-740.22	-740.04	0.46	36.58	
19	-739.69	2.60	-740.04	-739.52	4.17	40.76	X
20	-739.24	2.61	-739.31	-739.19	0.13	40.89	
21	-736.77	2.63	-737.56	-736.51	9.47	50.38	X
22	-736.33	2.64	-736.52	-736.13	5.03	55.34	X
23	-735.86	2.64	-735.93	-735.80	0.22	55.57	
24	-732.92	2.67	-733.46	-732.74	2.26	57.33	X
25	-732.46	2.68	-732.53	-732.40	0.06	57.90	
26	-724.74	2.75	-725.28	-724.53	2.57	60.47	X
27	-724.27	2.76	-724.34	-724.20	0.03	60.50	
28	-722.20	2.78	-722.25	-722.18	0.01	60.51	
29	-721.32	2.79	-722.16	-721.05	9.73	70.27	X
30	-720.87	2.79	-721.06	-720.66	4.83	75.02	X
31	-720.39	2.80	-720.47	-720.32	0.25	75.28	
32	-720.10	2.80	-720.16	-720.06	0.09	75.38	
33	-719.94	2.80	-719.99	-719.89	0.05	75.44	
34	-718.55	2.81	-718.76	-718.51	0.17	75.61	
35	-717.94	2.82	-718.51	-717.72	4.83	80.44	X
36	-717.44	2.83	-717.59	-717.36	0.85	81.30	
37	-717.18	2.83	-717.36	-717.11	2.11	83.41	X
38	-717.07	2.83	-717.11	-716.87	1.28	84.69	
39	-716.62	2.83	-716.73	-716.56	0.10	84.79	
40	-716.35	2.84	-716.41	-716.30	0.05	84.84	
41	-716.16	2.84	-716.22	-716.10	0.06	84.91	
42	-715.22	2.85	-715.92	-714.99	7.84	92.76	X
43	-714.72	2.85	-714.81	-714.63	0.28	93.04	
44	-714.44	2.86	-714.50	-714.40	0.08	93.13	
45	-711.77	2.88	-712.46	-711.52	4.74	97.88	X
46	-711.37	2.89	-711.52	-711.22	1.72	99.60	X
47	-710.90	2.89	-711.05	-710.85	0.10	99.71	
48	-710.69	2.89	-710.74	-710.64	0.06	99.77	
49	-708.42	2.92	-708.67	-708.27	0.17	99.94	X
50	-707.63	2.92	-707.74	-707.46	0.06	100.00	X

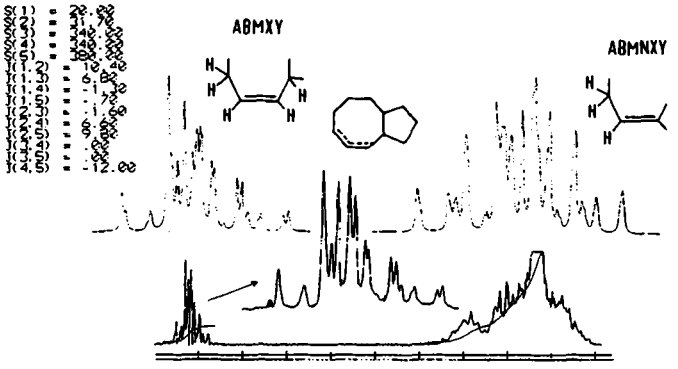
*

A871.5

Fig. 5. TTY machine report of the spectrum in Figure 4 from the program NMRAN. (×) correctly found line position; (/) wiggles misinterpreted as lines.

line widths)[*]. The appearance of the simulated spectrum depends very strongly on the choice of the initial parameters. We have therefore modified the simulation

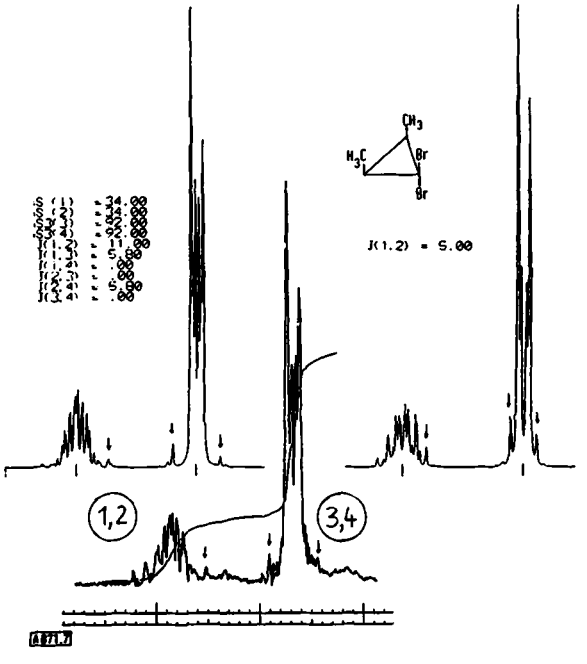
[*] NMREN, NMRIT [16, 17]; FREQUINT [18] and its further developments LAOCOON I, II, III, LAME [19] (considers *magnetically* equivalent nuclei), LACX [19] (considers *chemically* equivalent nuclei); newer programs such as LAOCOONOR [20] and LEQUOR [21] also allow the determination of direct spin-spin coupling in nematic phases. Further information from ASTM, Task Group on Computer Applications, Subcommittee E-13.7.



A871.6

Fig. 6. Spectrum simulation with VARIOS. Below: measured 100-MHz spectrum with expanded section (center) of the olefin signal. Above: simulation with *three* (left), and *four* protons (right) in the allylic position. Parameters (S = chemical shift, J = coupling constant) in Hz.

programs to make allowance for step-wise variations of the initial values (VARIOS). In this way it is normally possible to recognize the spectral type and so to decide between structural alternatives, especially if the simulated spectra are drawn out with a plotter program (POMLUX). In addition to the spectrum POMLUX writes some frequency marks, the input parameters (see Figs. 6—9), and an identification label.



A871.7

Fig. 7. Structural differentiation by model calculation (LAME) between *cis*- and *trans*-1,1-dibromo-2,3-dimethylcyclopropane. Below: measured spectrum (100 MHz) (signal groups 1,2 = ring protons, 3,4 = methyl groups). Above: simulation with *cis* (left) and *trans* couplings (right). Especially noticeable effects are marked (by hand) with arrows.

If *precise* values are to be extracted from a measured spectrum, the iteration routines contained in a second part of the programs are used. These approximate the model spectrum to the measured one with regard to the line frequencies and sometimes also to intensities. It is intended to couple the feed-in of the measured spectra for the iteration program directly to the record evaluated by NMRAN.

A typical example of a qualitative evaluation (structural elucidation) by the computer is shown in Figure 6. It is concerned with deciding on the position of the double bond in the eight-membered ring of a bicyclo[6.3.0]-undecene. From the synthesis, there was a choice between the alternatives shown having three or four allylic protons. The spectrum of the olefin part was simulated using

For the sake of illustration a particularly successful model calculation on a 1,3-dioxane is indicated in Figure 8. Here even the "W" coupling over four bonds, $^4J(1,4)$, visible in the observed spectrum was verified by line broadening of groups 1 and 4 in the model spectrum. (The spectrometer resolution was better than the line widths of 0.5 Hz used in the simulation.)

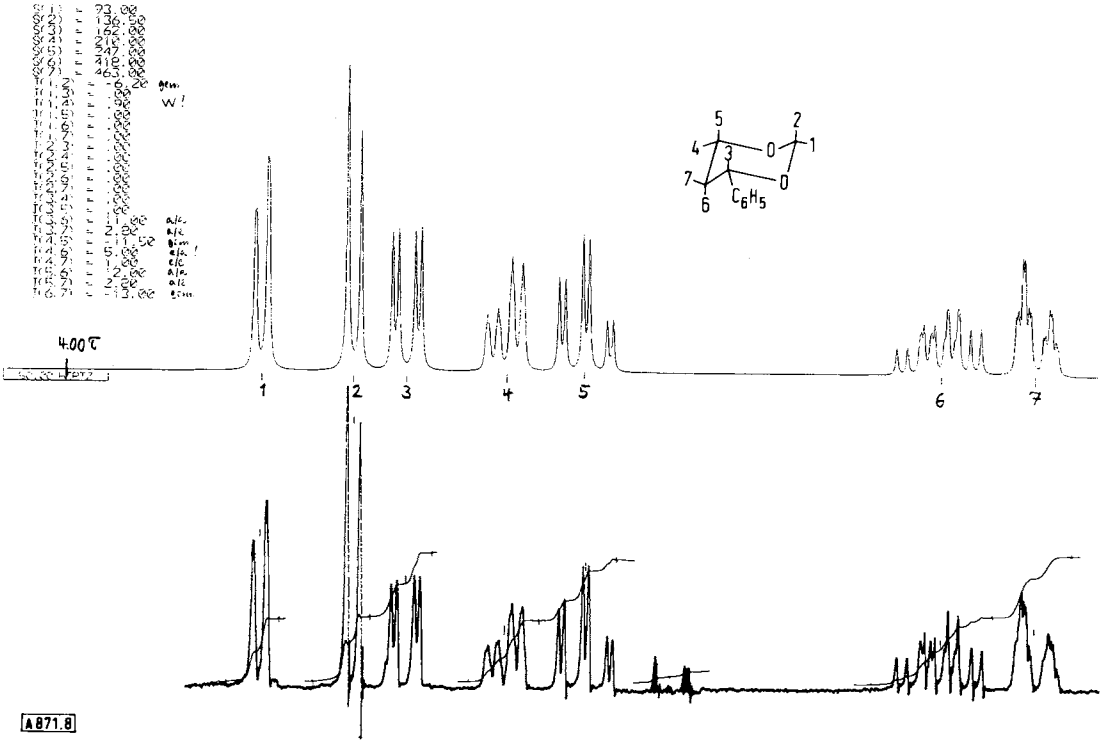


Fig. 8. Model calculation of the 100-MHz spectrum of 4-phenyl-1,3-dioxane. Below: measured spectrum. Above: simulation.

plausible coupling constants and chemical shifts. (No useful information could be obtained from the rest of the spectrum since the signals of the allylic protons are overlapped by the other ring protons.) The section on the left of the figure (three neighbors to the double bond) agrees well, as is evident from the comparison of the computer-simulated and plotted partial spectrum with the measured one (shown enlarged in the center).

A further example in which a model calculation elucidates the configuration of a compound is shown in Figure 7. It is known that in three-membered rings, *cis* vicinal protons have coupling constants between 8 and 12 Hz, while those in the *trans* configuration have constants less than 6 Hz. We had to determine the configuration of a 1,1-dibromo-2,3-dimethylcyclopropane[22]. Here the line pattern was complicated by the spin-spin interaction of the six closely neighbouring methyl protons, so that the coupling constants required to solve the problem could not be found directly. A model calculation with LAME[19] using the smaller coupling constant $J(1,2) = 5$ Hz ruled out the *trans* configuration. A calculation using $J(1,2) = 11$ Hz is however in convincing agreement with the experimental spectrum. The rather high value of 11 Hz can be explained by the known ability of neighboring halogen atoms to increase *cis* coupling constants considerably.

In Figure 9, an approximated spectrum is shown which was derived by an iteration program (LAOCOON[8]) using the method of least squares. Whenever the solution is to converge within a tolerable computing time, the application of an iteration program presupposes a successful model calcu-

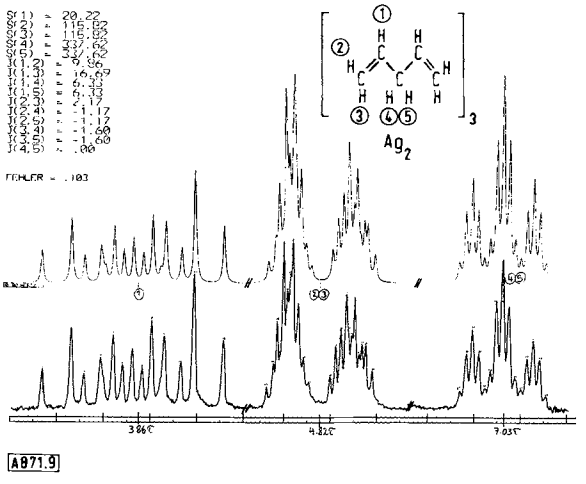


Fig. 9. Iteration with LAOCOON: 100-MHz spectrum of $Ag_2(CH_2CHCH_2CHCH_2)_3$. Below: measured spectrum. Above: best fit after 2 iterations (RMS error 0.103 Hz).

lation giving values closely approaching the real ones. This was a further reason for including automatic variation of critical parameters (VARIOS) in the simulation programs. Iteration then yields values for spin coupling and chemical shifts that are reliable enough for inclusion in tables of structural parameters in the literature. Well measured spectra are naturally essential for this purpose.

In these applications, data input normally represents a bottleneck and may give rise to errors. We have therefore modified our programs so that they can request the required data from the user (over TTY) in dialog form, thus increasing reliability, providing more flexibility, and allowing program use by less experienced persons.

2.3. The Computer as a Spectrometer Component

2.3.1. Fourier Transform Spectroscopy

One can obtain information about nuclear magnetic resonance in two complementary but different ways. The conventional manner of recording a spectrum is to scan slowly through the resonance positions by time-linear variation of the polarizing magnetic field H_0 or of the monochromatic HF measuring frequency. One can also, as was first accomplished *experimentally* by *Ernst* and *Anderson*[11], irradiate the sample (H_0 field constant) with one sufficiently broad high frequency band. All the resonances of a spectrum are then excited simultaneously. In practice irradiation is performed with short (microsecond range) intense HF square pulses having a frequency distribution given by $\sin \omega t/\omega t$. As a consequence a frequency band of several hundred to several thousand Hz at nearly constant amplitude is produced. The "free induction" signal of such an experiment is shown in Figure 12 (see also the interferogram shown in the upper left of Figure 15). It contains all the resonance frequencies superimposed upon one another and each decaying with its characteristic relaxation time, which is usually of the order of seconds ("time domain"). *Computational* frequency analysis (Fourier transformation) reproduces the spectrum in the familiar form ("frequency domain"). The result of a Fourier transformation by the computer is shown in Figure 10.

The trace—showing a 500-Hz section of a spectrum of an eight-component mixture (containing 30% v/v CCl_4) —was drawn out with the TTY plotter described below (see footnote [*] on p. 384). The spectrum originates from a single high frequency pulse, whose free induction decay (FID) was sampled for 5.7 s. The necessary phase correction was carried out automatically by a special program. In spite of the good resolution of the spectrometer, no wiggles are observed in the spectrum, so that in principle no difficulties exist in the application of the line search program. (Cf. remarks about Figure 5 in Section 2.1!)

The instrumentation (Figure 11) and computer programs will be described next:

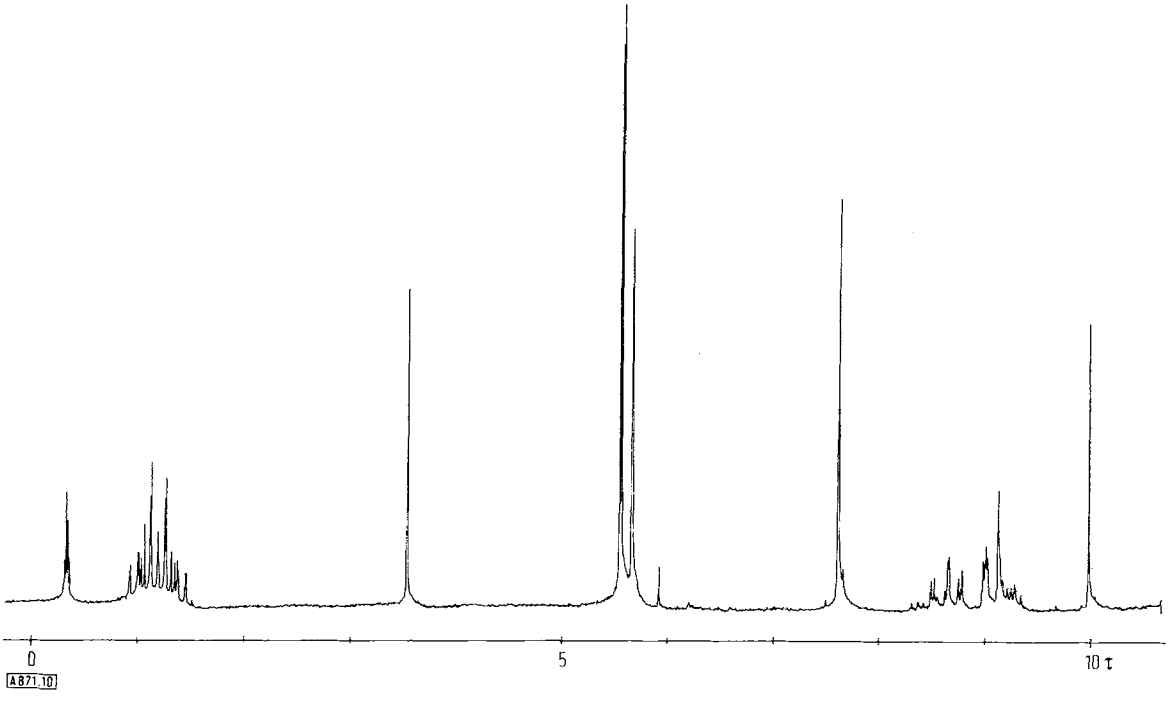


Fig. 10. Fourier transform spectrum (60 MHz) of a test sample after phase correction by the program PHASE. Signals from left to right are: Methyl formate (H),*o*-dichlorobenzene, dichloromethane, methyl formate (CH_3), methyl acetate (ester CH_3), methanol (CH_3), methyl acetate (acid CH_3), 3,3-diethylpentane, TMS. FID 5.7 s. Resolution: 4080 points/711 Hz.

For Fourier transform spectroscopy we use a multipurpose spectrometer of our own construction which can process three frequencies simultaneously. One frequency stabilizes the magnetic field on an external ^{19}F standard. The two other frequencies (ν_1, ν_2) are transmitted and received by doubly tuned networks matched to the probe coils. Thus the resonances of two kinds of nuclei can be observed simultaneously (cf. ^1H- and ^{31}P-FID of Fig. 12), or one nucleus may be observed while ν_2 is used for narrow- or broad-band double resonance experiments.

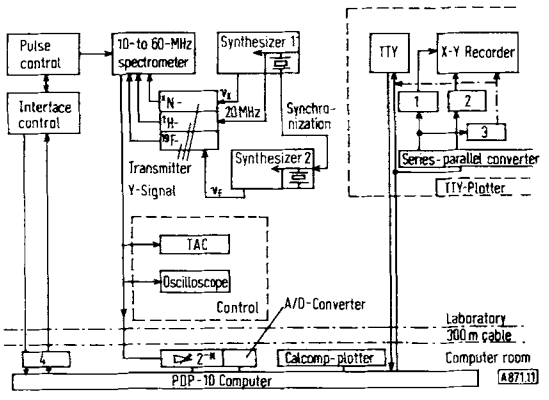


Fig. 11. Block diagram of our 14.1 kG multinuclei Fourier transform spectrometer system. See incriptions; 1, D/A converter for the ordinate (signal amplitude); 2, D/A converter for the abscissa (frequency and chemical shift respectively); 3, up/down control of the plotter pen; 4, control instrument for start/stop commands.

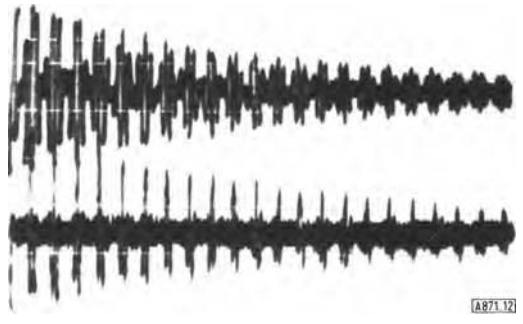


Fig. 12. Simultaneously recorded Fourier transform spectrum of $P(OCH_3)_3$. Above: Interferogram (FID) of ^1H resonance. Below: Interferogram (FID) of ^{31}P resonance. Pattern on double channel oscilloscope. Abscissa 2 s. From this $^2J_{H-P} = 10.7$ Hz. Irradiation: *ca.* 0.7 ppm off the centers of resonance.

(Examples of ^1H-$\{^{31}P\}$ experiments are shown in Figures 13 and 14.) The instrument also contains a pulse-programmer which is particularly important for spin-echo experiments and an automatic control circuit for activating fast signal sampling by the A/D-converter of the computer.

As mentioned earlier, if it is desired to measure heteroatoms with large chemical shifts, then the interface must be able to process high frequencies. For such measurements we require the "fast" interface of the computer with a maximum data rate of 20 kHz, which at present is alternatingly used for data acquisition from a rapid-scan mass spectrometer. The appropriate handling program TRADAT corresponds to the above mentioned slow acquisition program SELDAT. Like SELDAT and TRADAT, the very commonly used data accumulation program HSCAT is written in the assembler language of the PDP 10 (MACRO). The Fourier transformation is programmed in FORTRAN IV, either in the rapid version of *Cooley* and *Tuckey*[23] (FORT) or in a conventional transformation program (TRANS) of our own. Digital smoothing may also be appended (GLAETT). The method of measurement and the properties of the amplifier cause a phase rotation of the signal frequencies that varies over the whole spectrum. These phase changes are determined by the program AUTFA and correctly adjusted by the auxiliary program PHASE.

The graphical analog output on a Calcomp plotter is controlled by the program PLOTTC. The plotter allows all the calculated points to be quickly reproduced as a well-resolved spectrum. However, it is installed in the distant computer room and must be available to all users. For supervision in the laboratory, we therefore use a DAC interface, controlled by a TTY connection with an attached DIN A3 XY-recorder whose speed is limited by a teleprinter in parallel and whose resolution along both axes is only 512 points (9 bits). For this a routine PLOTTC and sub-routine TPLOT are used. Longer sets of data must be drawn out in sections (but see footnote [*] on p. 384!).

The advantages of Fourier transform spectroscopy are obvious. By suitable choice of pulse width, one can always work at maximum excitation when recording single spectra. Signal accumulation is particularly efficient because the very short sampling duration allows incomparably more records to be summed in a given time. A gain in sensitivity (signal to noise ratio) of two orders of magnitude is readily attainable. As the recording of *one* spectrum takes only seconds, kinetic phenomena extending over time intervals of 1—60 minutes can be observed by spectroscopy, and under certain conditions even very short-lived products can be detected. It may be supposed that if the computing time is too long the accomplishment of the transformation will be restricted. However, in our experience the usual time of execution (about 20 s with the fast Cooley-Tuckey algorithm) does

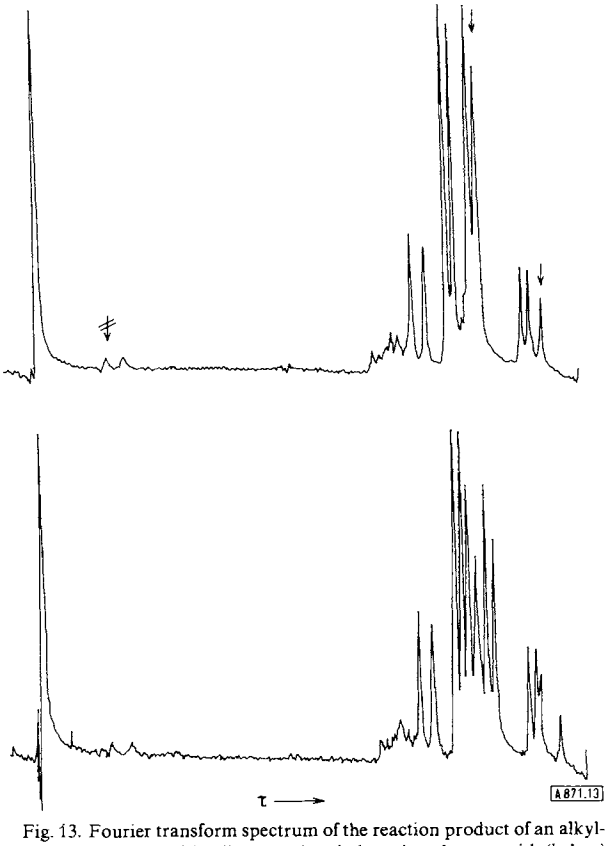


Fig. 13. Fourier transform spectrum of the reaction product of an alkylaluminum amide with triisopropylmethylenephosphorane with (below) and without (above) ^{31}P noise decoupling. Accumulated 20 and 3 times, respectively. Frequency range 500 Hz (for explanation see text). The arrows indicate the disappearance of the phosphorus coupling.

not give rise to problems, *e.g.* due to overflow of the memory.

The plotting of a transformed spectrum over a TTY recorder can take more than 20 minutes when performed under the conditions just mentioned[*]. This was the case for Figures 13 and 14. The spectrum shown in Figure 13 was recorded for the reaction product[24] of an alkylaluminum amide with triisopropylmethylenephosphorane. For the elucidation of the structure of the compound, it was important to know whether the doublet (marked with a crossed arrow) originated from ^{31}P coupling.

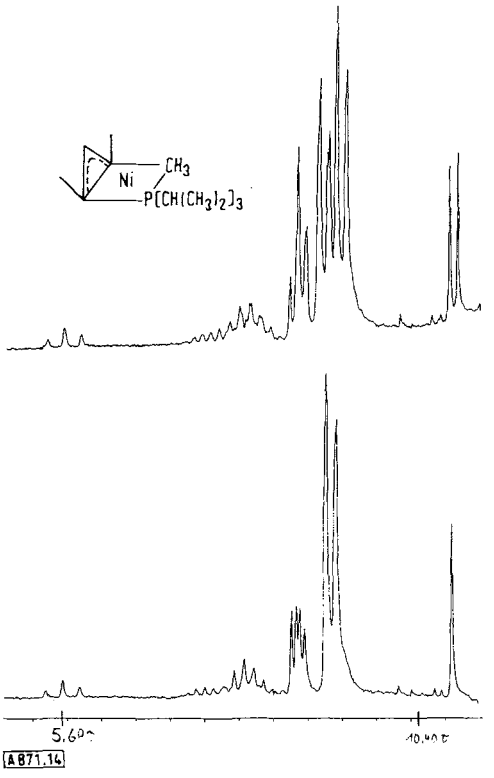


Fig. 14. Proton Fourier transform spectrum of a π-pentenylnickel complex with (below) and without (above) ^{31}P noise decoupling. Accumulated 30 and 10 times, respectively. Recording time: 2.4 s for each FID. Temperature −20°C.

Briefly the method was as follows: The region of phosphorus signals was searched for resonances with pulses while simultaneously applying spin-spin noise decoupling[26] of protons and signal accumulation. The sample gave only one phosphorus resonance which was then irradiated with a broad band. Under these conditions, the proton spectrum was pulsed and transformed. The figures show the spectra before (below) and after ^{31}P decoupling (above). The signal in question remains unchanged, and therefore does not derive from ^{31}P coupling. On the other hand the phosphorus coupling of the isopropyl signals and of the P-methylene signal (marked with arrows) are seen to disappear.

[*] In the meantime we have successfully obtained a resolution of 2^{13} (8 K) points in 12 minutes on a 60 cm flat-bed recorder by better use of the TTY code, other D/A-converters, and automatic switching to higher transfer speed (cf. Figure 10).

Another successful example of this kind is shown in Figure 14. ^{31}P decoupling made assignment straightforward. The sensitive substance[25], a π-pentenylnickel complex, was measured at low temperatures and served as a model for the assignment of a similar complex in which additional multiple splitting due to induced chirality completely obscured the line pattern.

The examples illustrate some special applications of Fourier transform spectroscopy to proton resonance at high resolution. The enormous increase in sensitivity attainable with this method, especially where an increase in signal concentration is obtained by the additional use of noise decoupling[26] and signal enhancement results from the *nuclear Overhauser effect*, makes this the method of choice for NMR spectroscopy of heteronuclei. Thus ^{13}C spectroscopy on samples with the natural isotopic abundance of only 1% has made remarkable progress despite the 6000-fold lower sensitivity compared to the case of ^{1}H-NMR[27]. However, it should not be forgotten that the nuclear Overhauser effect falsifies the relative signal intensities.

Figure 12 shows the ^{1}H and ^{31}P free induction of trimethyl phosphite, *simultaneously* displayed on an oscilloscope. The coupling constant $^{3}J_{PH}$ could easily be obtained by signal correlation[2]. Application of the method in this case would be trivial, but it is possible to think of more complicated cases for which the solution by this procedure could be of interest.

We also utilize the high sensitivity of Fourier transform spectroscopy for the detection and measurement of the ^{31}P chemical shifts of unstable transition metal complexes present in low concentrations because of their low solubility at reduced temperatures.

2.3.2. Treatment of Time-dependent Phenomena

Nuclear magnetic resonance spectra are known to be affected by rapid reactions such as ligand exchange, isomerization, and topomerization[27a] (time scale 10^2 to 10^5 μs). Changes in the number of lines and effects on the line width are possible consequences in the spectra. The transverse relaxation time T_2, whose reciprocal is a measure of the width of a spectral line, depends on the lifetime τ of the fluctuating molecular state of the chemically reacting species. Precise measurement of T_2 affords rate constants whose temperature dependence yields information about activation energy and enthalpy and entropy of reaction.

Basically two methods can be used to determine the kinetics of reactions on the NMR time scale[6, 28, 29], *viz.* the "line-shape" method and the spin-echo procedure.

The former includes the derivation of analytical expressions for the spectral pattern as functions of the different rate constants. These expressions can be very unwieldy when spin coupling is accounted for and can normally only be solved by computer[6, 29]. The observed spectra are compared with those computed either by inspection or by iteration procedures. The recent development of a so-called "direct"[31] method of calculating spectral patterns including line shapes by *Binsch et al.*[30] has made

the derivation of rate constants from spectra a very powerful method. The procedure (program DNMR 3)[32] simulates the whole spectrum, and besides having the advantage of providing spectral assignments it also yields the line shape parameters and thus kinetic data too. Since this method takes account of all lines, including those unaffected by the reaction, it is to a great extent free from systematic errors and is therefore generally applicable to NMR. Unfortunately the demand on core storage is well over 30 K, so that we use the method only occasionally. However, attempts are being made to reduce the program size by more than 9 K[33]. An iteration method has also been appended to the program[34].

3. Conclusion

The computer system of our institute is able to handle most of the qualitative requirements of the NMR spectroscopist satisfactorily. In daily practice, the dialog mode of computer usage made possible by time-sharing has been a definite advantage. Working in our laboratory we can easily write, or modify, our own programs, and adapt foreign programs. Moreover, we can simplify the data input and supervision of the execution of our programs, as well as initiate the start and control routines of the instruments operating on-line.

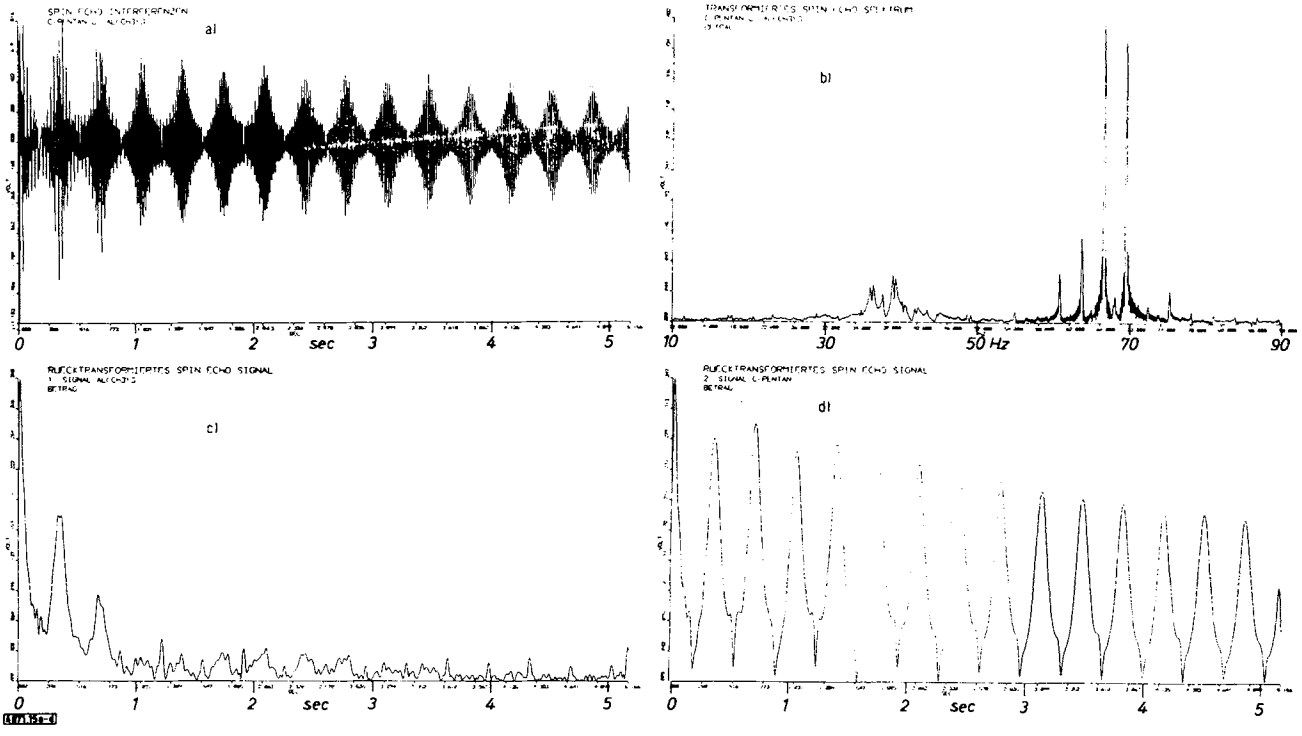


Fig. 15. 51.9% solution of $[Al(CH_3)_3]_2$ in cyclopentane as an example of simultaneous determination of two T_2 values differing considerably owing to methyl group exchange in $[Al(CH_3)_3]_2$. Recorded at 180°-pulse separation of $2\tau = 0.348$ s. Our sample gives $T_2 = 10.6$ s for cyclopentane, and 0.56 s for trimethylaluminum (from [38]). a) Spin echo interference pattern of cyclopentane and $[Al(CH_3)_3]_2$. b) Transformed spin-echo spectrum. c) Inverse transformation of the 1st signal (trimethylaluminum) of b. d) Inverse transformation of the 2nd signal (cyclopentane) of b.

(The line-shape method belongs to the type of applications described in Section 2.2.)

We have tried to master the extended application of the spin-echo method, as described by *Hahn*[35], *Carr* and *Purcell*[36], and *Meiboom* and *Gill*[37], to chemical kinetics. The spin-echo method is directly applicable only to single signals. A spin-echo record complicated by chemical shifts and/or coupling constants gives interferograms which are *a priori* not interpretable. Meanwhile, however, we have succeeded[38] in separating the signals by Fourier transformation, and reproducing the spin-echo trace for each line by inverse transformation of the frequency section of the signal groups for each line. This yields the transverse relaxation time T_2 (Figure 15). We hope in this way to be able to use the spin-echo method also for more complex systems.

The least problems are encountered on operation with the "slow interface" and the related programs. There are fundamental difficulties involved in writing an infallible evaluation program which limit the routine acquisition of spectra at slow scanning rates. In our view, *general* use of Fourier transform spectroscopy should make for completely computerized processing of the spectra once some minor difficulties with phase correction and the resulting integration error have been overcome.

For certain problems, however, the combined time-sharing and real-time processing of our computer system does not allow continuous work. Of course, some extensive programs such as relatively involved simulation and iteration programs or programs for dynamic nuclear magnetic resonance spectroscopy (DNMR), can be run off between 8 a.m. and 5 p.m. as long as they do not require

more than 28 K storage units. Larger problems must be dealt with outside these hours.

More serious is the computer processing of problems requiring long continuous operation, as for example with prolonged spectrum accumulation. Here each interruption of normal time-sharing operation (*e.g.* for routine checks) or machine failure can destroy the accumulated records. It is also difficult to apply automatic checks over short time intervals or to employ proportionality control, which is desirable for spectrometer optimization.

The greatest difficulties arise in the use of the "fast interface", which is always employed with pulsed spectroscopy. Access alternates with that by rapid mass spectroscopy[39] when the latter is coupled with gas chromatography. The interface can only be used for 2.5 to 3 s between successive mass spectrometer recordings since control of a combined GC/MS analysis requires a definite timetable and therefore has higher priority for access to the fast analog/digital converter. However, this rigid timetable is unacceptable for pulsed spectroscopy and restricts its efficiency considerably.

For the future, it will therefore be expedient to enlarge the system by inclusion of small satellite computers to relieve the central computer of limited problems concerned with process control, data transmission, and data acquisition and output, and thus allow unrestricted continuity of operation. The latter is especially important since uninterrupted, freely scheduled Fourier transform spectroscopy is accompanied by qualitative advantages such as further increases in sensitivity and selectivity by use of "driven equilibrium Fourier transform spectroscopy" (DEFT)[40] or other multiple pulse methods[40a]. We are attempting, therefore, to connect a small computer across a fast TTY input by means of a data coupler or directly at the input/output bus to the large machine. In our situation such an investment seems justified to rationalize the use of three large analytical instruments adapted for computer connection, two of which being able to perform Fourier transform spectroscopy.

We would like to thank Messrs. A. Iländer, A. Bischof, and H. Brenneke for their cooperation in electronic developments, and for the preparation of the instruments for connection to the computer.

Received: November 18, 1971 [A 871 IE]
German version: Angew. Chem. *84*, 400 (1972)

[1] *L. A. Allen* and *L. F. Johnson*, J. Amer. Chem. Soc. *85*, 2668 (1963).

[2] *E. Ziegler* and *E. G. Hoffmann*, Z. Anal. Chem. *240*, 145 (1968).

[3] Technical Measurement Corp., North Haven, Conn. (USA); Varian Ass., Palo Alto, Calif. (USA).

[4] *E. G. Hoffmann* and *E. Ziegler*, Paper read at Arbeitskreis Spektroskopie, Oct. 1966, München; *E. Ziegler* and *E. G. Hoffmann*, Paper read at Symposium über Fortschritte in der Raman-Spektroskopie, Oct. 1966, Magdeburg; *E. Ziegler* and *E. G. Hoffmann*, Österr. Chemiker-Ztg. *68*, 15 (1967).

[5] Fabri-Tek System 1070, Fabri-Tek Instruments Inc. Madison, Wisconsin (USA); Laben "Modular" 8000, Laben/Montecatini Edison Elettronica SpA, Milano (Italy); MAC 4000, Wenzel Elektronik, München; DIDAC-Systems Intertechnique, 78 Paisiv (France).

[6] *S. D. Swalen*, Progr. NMR Spectrosc. *1*, 205 (1966).

[7] *J. A. Musso* and *J. Metzger*, Bull. Soc. Chim. France *1968*, 463.

[8] *D. T. Detar*: Computer Programs for Chemists. Benjamin, New York 1968, Vol. 1.

[8a] *C. W. Haigh*, Ann. Rep. NMR Spectros. *4*, 311 (1971).

[8b] *P. Diehl, H. Kellerhals*, and *E. Lustig*: NMR Basic Principles and Progress. Springer, Heidelberg 1972, Vol. 6.

[9] *H. Schmidt*, Paper read at conference on "Datenverarbeitung in der analytischen Chemie", Nov. 1970, Basel (Switzerland); *T. Clerc*, Paper at same conference; *R. N. Jones*, Pure Appl. Chem. *18*, 303 (1969).

[10] *E. L. Hahn* and *D. E. Maxwell*, Phys. Rev. *88*, 1070 (1952).

[11] *R. R. Ernst* and *W. A. Anderson*, Rev. Sci. Instr. *37*, 93 (1966); *R. R. Ernst*, Advan. Magn. Resonance *2*, 1 (1966).

[11a] *T. C. Farrar* and *E. D. Becker*: Pulse and Fourier Transform NMR. Academic Press, New York 1972.

[12] *E. g.*, VM 620/i in "Spectrosystem 100" of Varian Ass., Palo Alto, Calif. (USA).

[13] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Angew. Chem. *84*, 371 (1972); Angew. Chem. internat. Edit. *11*, 348 (1972).

[14] *G. Schomburg, F. Weeke, B. Weimann*, and *E. Ziegler*, Angew. Chem. *84*, 390 (1972); Angew. Chem. internat. Edit. *11*, 366 (1972).

[15] We are indebted to the team of Dr. *R. Köster*, MPI Mülheim, for supplying the substance.

[16] *J. D. Swalen* and *C. A. Reilly*, J. Chem. Phys. *37*, 21 (1962); Program 33, 34, 35, 126; Quantum Chemistry Program Exchange (Q. C. P. E.) of Indiana University.

[17] *R. C. Ferguson* and *D. W. Marquardt*, J. Chem. Phys. *41*, 2087 (1964).

[18] *S. Castellano* and *A. A. Bothner-By*, J. Chem. Phys. *41*, 3863 (1964); Program LAOCN3 = Q. C. P. E. No. 111.

[19] *C. W. Haigh*, Dept. of Chemistry, Univ. Coll., Swansea SA2 8PP (U. K.).

[20] *P. Diehl, C. L. Khetrapal*, and *H. Kellerhals*, Mol. Phys. *15*, 633 (1968).

[21] *P. Diehl, H. P. Kellerhals*, and *W. Niederberger*, J. Magn. Resonance *4*, 352 (1971).

[22] Synthesized by Dr. *H. Bönnemann*, MPI Mülheim.

[23] *I. W. Cooley* and *I. W. Tuckey*, Math. Comp. *19*, 297 (1965); Program of the SHARE-Library (SDA No. 3465).

[24] *C. Konstantinovic*, Dissertation, Universität Bochum 1971.

[25] *H. Schenkluhn*, Dissertation, Universität Bochum 1971.

[26] *R. R. Ernst*, J. Chem. Phys. *45*, 3845 (1966).

[27] *E. Breitmaier, G. Jung*, and *W. Voelter*, Angew. Chem. *83*, 659 (1971); Angew. Chem. internat. Edit. *10*, 673 (1971).

[27a] *G. Binsch, E. L. Eliel*, and *H. Kessler*, Angew. Chem. *83*, 618 (1971); Angew. Chem. internat. Edit. *10*, 570 (1971).

[28] *Ch. S. Johnson jr.*, Advan. Magn. Resonance *1*, 33 (1965).

[29] *G. Binsch*, Topics Stereochem. *3*, 97 (1968).

[30] *G. Binsch*, Mol. Phys. *15*, 469 (1968); J. Amer. Chem. Soc. *91*, 1304 (1969); *D. A. Kleier* and *G. Binsch*, J. Magn. Resonance *3*, 146 (1970).

[31] Cf. [6], p. 212.

[32] *D. A. Kleier* and *G. Binsch*, Program DNMR3 = Q. C. P. E. No. 165.

[33] *W. P. A. Pascoe*, Canberra, private communication.

[34] *B. L. Hawkins* and *J. D. Roberts*, Pasadena, private communication.

[35] *E. L. Hahn*, Phys. Rev. *80*, 580 (1950).

[36] *H. Y. Carr* and *E. M. Purcell*, Phys. Rev. *94*, 630 (1954).

[37] *S. Meiboom* and *D. Gill*, Rev. Sci. Instr. *29*, 688 (1958).

[38] *W. Stempfle* and *E. G. Hoffmann*, Z. Naturforsch. *25a*, 2000 (1970).

[39] *D. Henneberg, K. Casper, E. Ziegler*, and *B. Weimann*, Angew. Chem. *84*, 381 (1972); Angew. Chem. internat. Edit. *11*, 357 (1972).

[40] *E. D. Becker, J. A. Ferretti*, and *T. C. Farrar*, J. Amer. Chem. Soc. *91*, 7784 (1969).

[40a] *J. D. Ellett jr., M. G. Gibby, U. Haeberlen, L. M. Huber, M. Mehring, A. Pines*, and *J. S. Waugh*, Advan. Magn. Resonance *5*, 117 (1971).

Automated X-Ray Structure Determination as an Analytical Method

By Carl Krüger[*]

1. Introduction

The last few years have seen such rapid advances in X-ray structure analysis, even of complicated chemical compounds, that the method now appears able to provide the preparative chemist with a valuable service as a modern analytical technique. The main reason for this development is technological progress. Firstly, large, third-generation computers, which are necessary for the time-consuming evaluation of extensive data sets, have become available; secondly, the manufacturers of analytical instruments offer fast automatic diffractometers that are necessary for the collection of these data. The working schedule for the elucidation of the exact structure of a chemical compound by three-dimensional X-ray structural analysis is therefore divided into two parts:

1. Measurement of position and intensity for a large number of diffraction data from a single crystal

2. Evaluation of these data for subsequent solution of the structure and representation of the molecule and the contents of the unit cell of the crystal.

The first part of this report describes the operational features of our diffractometer system, while the second part deals with our computational approach to the solution of structural problems. Problems that have not yet been satisfactorily solved are indicated. It should be pointed out that ours is not the only system possible, but an optimal one for our computational and operational facilities.

2. Fully Automatic Single-Crystal Diffractometers

Construction and operation of modern single-crystal diffractometers have already been described in detail[1]. As a common feature, crystals having approximate dimensions of 0.1 to 0.6 mm are mounted on a carrier and oriented in a homogeneous, monochromatic X-ray beam in reflecting positions according to *Bragg*. The integrated intensity of a reflection is measured with a scintillation counter. During the course of one analysis of average difficulty, there are more than a thousand reflecting positions for a crystal and a corresponding number of intensity measurements must be performed.

Most of the available instruments orient the crystal into reflecting positions using the so-called "Eulerian cradle" which allows the crystal to be rotated about three or four axes into any position. Control of these movements in early instruments was accomplished using stepping motors driven by paper tape. This technique relies heavily on the availability of a computer for preparing the controlling tapes. Any changes in the measuring parameters during data collection (*e.g.* crystal misalignment) were tedious and necessitated preparation of a new controlling tape. This and other similar tasks may be more flexibly performed automatically by a process-control computer.

In principle this control could also be accomplished by a time-sharing computer in on-line operation. The advantages of such a mode would include the programming facilities available in a higher-level language (FORTRAN *etc.*), fast program change, and direct data transfer to external data storage devices of the computer. An alternative would be the utilization of a small process-control computer or "dedicated computer" (see ref. [2] for the advantages and disadvantages of these two systems).

In lengthy experiments, where a relatively large computer effort is required for control, the use of a small computer appears more suitable. A small computer is independent of servicing and breakdown periods of a naturally more sensitive, large computer system. It is useful, however, to link the small computer to a large computer for rapid transfer of programs and data. Thus the external storage capacities of a large computer become accessible, while still preserving a certain independence in the data collection system. The arrangement of our diffractometer system is shown in Figure 1.

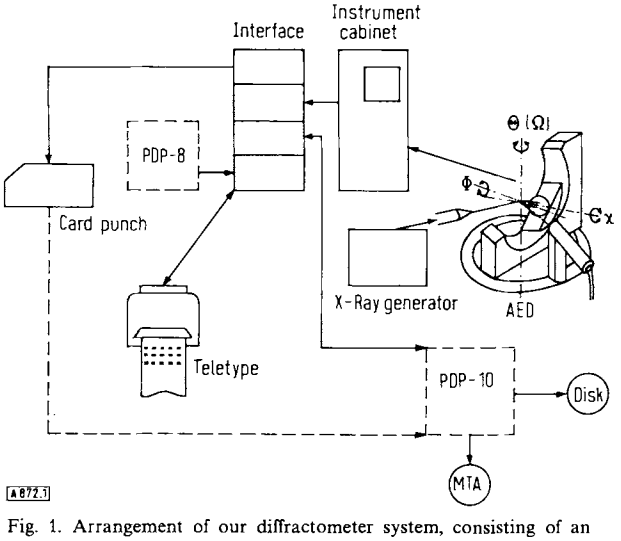


Fig. 1. Arrangement of our diffractometer system, consisting of an automatic, four-circle X-ray diffractometer, Kristalloflex 4 AED (Hoppe-Siemens), an interface, and a small computer (PDP 8) connected to a large computer (PDP 10). For further details see text.

A fully automatic four-circle diffractometer[*] (AED Siemens-Hoppe)[3] is controlled by a small PDP 8 computer (12-bit word length, 4 K memory and 32 s cycle time) using an interface linked to an IBM 026 card punch. An ASR 35

[*] Dr. C. Krüger
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

[*] In principle, all commercially available computer-controlled diffractometers can be used in the manner described here.

teletype is also connected *via* an additional link and can be used to communicate with the large computer. The connection between large and small computers is very important. For several technical reasons we chose to connect the small computer in the simplest possible manner, *i.e.* as a pseudo-teletype, which allows for selection of various data transfer rates[4][*].

This type of connection can be made without altering the operating system of the large computer. The normal data transfer rate permits operation of the teletype as a normal time-sharing terminal, but data-collection programs or data can be transferred ten times faster if desired. The experimentalist therefore enjoys the advantages of both systems.

Storage of data collection programs for a process-control computer in binary form on external devices of a large computer and loading them when needed has proved to be an optimal mode of operation. The time required for loading programs is ordinarily about two minutes. Programs which may be needed at the diffractometer in the course of the experiment may also be initialized on the large computer from the same teletype (*e.g.*, least-squares programs for cell dimensions or programs for generation of Miller indices with the corresponding angular values for the instrument).

Figure 2 gives the scheme of a routine X-ray analysis[5].

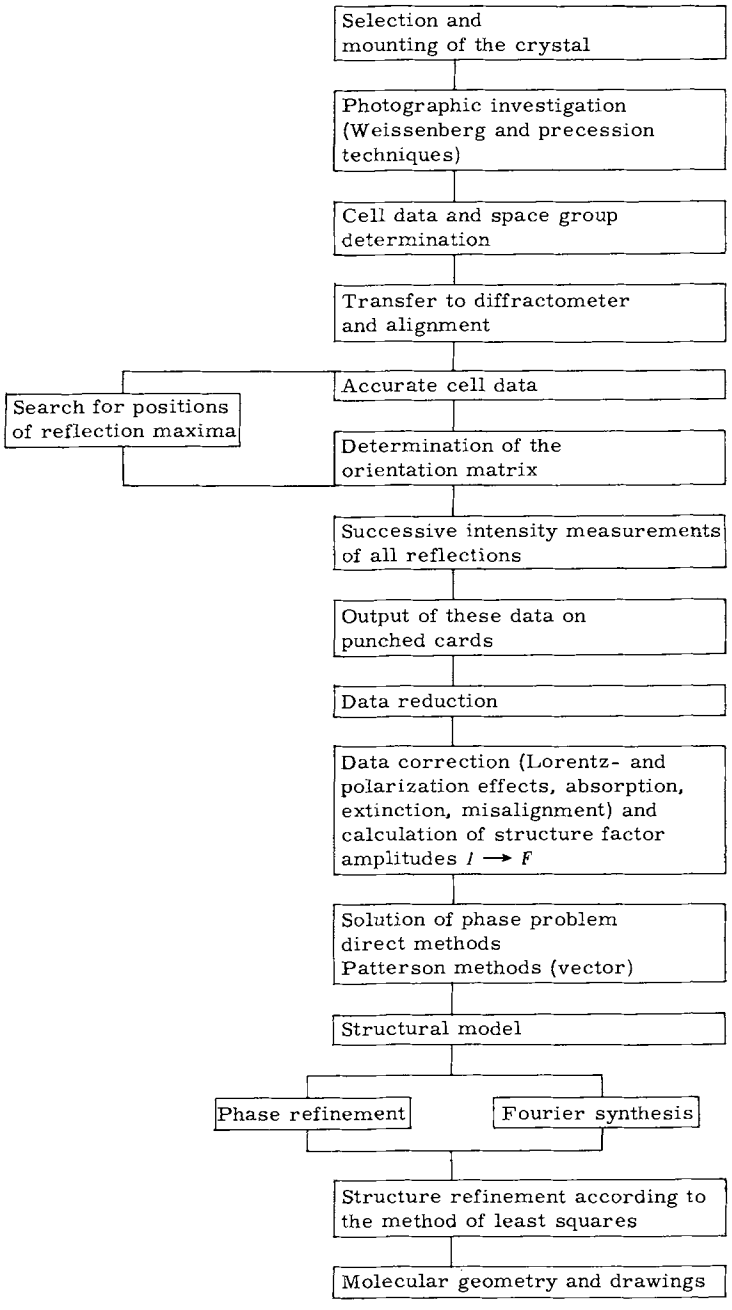


Fig. 2. Scheme of a routine automatic X-ray structural analysis.

After selection with the aid of a polarizing microscope, the crystal may be mounted on a goniometer head, if necessary under an inert gas atmosphere in a Lindemann glass capillary, centered, and adjusted optically. Determination of cell data and space group is performed by Weissenberg and precession photographic techniques, which also furnish information about the crystal quality and crystal symmetry. Crystal and goniometer head are transferred to the automatic diffractometer where the operations of centering and adjusting the crystal are computer controlled.

Crystal quality is again checked (Ω-scans, Φ-scans) before data collection. Accurate diffracting angles of several (*ca.* 50) high-angle reflections are then determined from the positions of the maxima obtained by computer controlled step-scan profiles using a receiving slit in front of the scintillation counter. These measured data are treated by the method of least squares and yield accurate unit cell parameters (± 0.001 Å) that are subsequently used for exact positioning of the crystal and counter for the determination of the intensities of the reflections.

Various programs for these operations are available for the small as well as the large computer and are accessible from the teletype. Experience has shown the availability of more than one computer system to be especially time-saving in such cases.

A possible alternative to the point-to-point search for reflections lies in the use of computer programs that determine optimum angular positions of accessible reflections within specified limits and record these values. From our experience we prefer the former method.

The actual data collection program of the controlling computer subsequently generates Miller indices of desired reflections within defined limits and excludes those that are systematically absent due to molecular arrangement (space group).

Every reflection is centered on the counter by movement of the "Eulerian cradle" and the integral intensity is determined by scanning in one angle. Each reflection has five measured values of which two are background measurements on each side of the peak (five-value measurement[6]).

There are also data collection programs employing difference filter measurement. Every reflection is scanned twice: once with a filter screening out the white radiation and a

[*] Alternatively, the diffractometer could be controlled by a small computer with an expanded memory (8 K) or a fast disk unit. These systems are relatively economical, but not in comparison to our system.

second time with another filter screening out the primary peak as well as the white radiation.

Additional characteristics of our measuring programs include the following: The scan-width for each reflection can be controlled as a function of the diffracting angle by the computer, thus reducing the overall measuring time. Furthermore, very strong reflections are scanned with attenuating filters automatically introduced into the primary beam and are marked accordingly. The intensity of a monitoring reflection is determined with a slit system at the end of a cycle (about 20 to 40 reflections) and indicates possible misalignment or decomposition of the crystal. Misalignment errors are reported. Output of the measured intensity as well as the diffractometer parameters for each reflection are printed out on the teletype and punched on cards. The remainder of the calculations for the structural analysis is done off-line on the large computer.

3. Determination of the Structure

After data collection the measured intensities are prepared for evaluation. The relevant program[7] utilizes the five measurements of each reflection, determines probable errors and indicates possible reasons, scales the data with respect to the initial monitoring reflection, and then writes the results onto a magnetic tape that is used for the actual data reduction. Most of our programs write data onto magnetic tapes that are subsequently read by other programs. Data reduction first corrects the measured intensities (I) for Lorentz and polarization effects and for absorption, and then converts them into the required amplitudes (structure factor amplitudes, F)[8].

The crucial and remaining problem of an X-ray crystal structure analysis is to derive the electron density distribution of the unit cell, which means computing the parameters that define the geometry and vibrational characteristics of the molecule. Given the measured amplitudes (structure factor amplitudes ($|F|$)) and the corresponding phases, this computation is relatively simple. However, the necessary phase angles (zero and π for centrosymmetric space groups) are neither known nor measurable.

The subsequent mathematical treatment of the structural analysis is divided into three parts:

1. Solution of the phase problem by finding parts of the molecule

2. Construction of the complete molecule

3. Adjusting the molecular parameters to the measured data.

For practical solutions to the phase problem the methods described in Sections 3.1 and 3.2 have been applied successfully.

3.1. Heavy Atom Method

In this method the larger electron density of a heavy atom is utilized to ascertain the spatial position of the heavy atom by Patterson methods with the squared amplitudes ($|F^2|$) and does not require any knowledge of the phases. A sufficient number of phases are then known so that a Fourier synthesis will establish the remainder of the molecule more or less completely.

Similar results are obtained by the convolution method[9]. The geometry of a known molecular fragment (*e.g.* one or more benzene rings) generates a vector set which is optimally adjusted to the observed vector set. Phases obtained from the located molecular fragment are then applied as a pseudo heavy atom.

3.2. Direct Methods

Direct methods[10] are structural solving processes which furnish structural models directly from structure factor amplitudes and not from information about heavy atoms *etc.* These methods employ statistical relationships between the phases of certain reflections (triple-product relationship). For centrosymmetric space groups there are computer programs that yield probable solutions by iterative techniques. This method is best applied to molecules with atoms of similar atomic number. The program set (FAME-MAGIC)[11] which we use works automatically in most centrosymmetric problems. Structures in acentric space groups require considerably more mathematical treatment, but computer programs for these situations are in an advanced testing stage in several laboratories.

Apart from these principal methods, crystal structures can also be solved by anomalous dispersion effects or by isomorphous replacement of heavy atoms where the space group symmetry remains the same. Another, "trial and error" method which adjusts a given model to the unit cell has received only limited attention.

4. Structural Refinement

After a sufficient part of the molecule has been ascertained, the complete construction of the unit cell is determined by successive Fourier and difference Fourier syntheses. Proposals have also been made for automation of this time-consuming part of structural analysis[12]. One method which appears very promising refines the occupancy factors of all atoms according to a third order polynomial equation (phase refinement). Also included in this refinement are positions which may eventually prove to be false. The method works in reciprocal space as well as real space[13] and is being automated.

The last step, which requires the most computer time, adjusts the atomic positions and vibrational parameters to the observed data by the method of least squares[8]. The subsequent calculation of inter- and intramolecular distances and planes or drawing of the molecule, as shown in several examples, requires comparatively less computing time.

The program system which we apply to structural determinations has been developed around the operational mode of the available computer. All of the necessary programs are stored on a disk unit and are individually accessible from a teletype at any time. Input data for these programs

can also be given from the teletype, while all other information is stored on mini-magnetic tapes or on disk units and are retrievable when needed. Systems for other computers work similarly, but input control for programs is generally by punched cards[14][*].

5. Examples

The following typical examples illustrate how efficient these present methods are in application to routine operations.

The drawings were prepared with a local modification of the program ORTEP[15] on an x-y plotter.

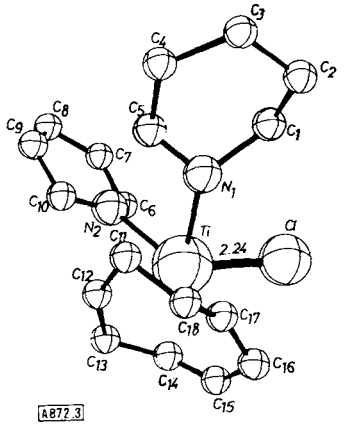


Fig. 3. Structure of a pyridine adduct to cyclooctatetraenechlorotitanium.

Figure 3 shows the geometrical arrangement of a pyridine adduct to a cyclooctatetraenechlorotitanium. The gross features of the structure were obtained by direct methods, even though the cyclooctatetraene fragment was disordered about the transition metal atom and the pyridine rings occupy two statistically disordered orientations. Several examples of similar disorder are known[16].

A further example indicates the present limits of our operation with respect to molecular size and is depicted in the stereoscopic drawing of Figure 4. This structure is a nitrogen adduct to bis(tricyclohexylphosphane)nickel(0) and is a molecule with 80 atoms[17].

In this analysis 5977 reflections were measured with the following cell data: $P2_1/n$, $a=21.83$, $b=16.54$, $c=21.24$ Å, $\beta=102.7°$, $Z=4$, d(X-ray)$=1.12$, d(observed)$=1.13$ g cm^{-3}. The positions of the heavy atoms were determined by direct methods; all subsequent C and N atom positions were established through ten cycles of phase refinement in direct space. The following refinement of the molecular parameters had to be divided into several parts, because the size of the problem far exceeded the capacities of the computer.

In view of this situation, the resulting computing time for the anisotropic refinement of the vibrational parameters

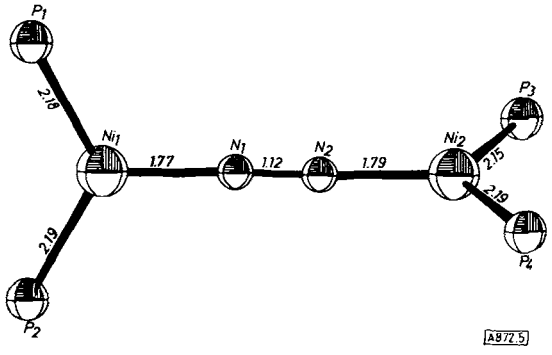


Fig. 5. Illustration of the group $P_2Ni—N{\equiv}N—NiP_2$ in the nitrogen adduct to bis(tricyclohexylphosphane)nickel(0) shown in Fig. 4.

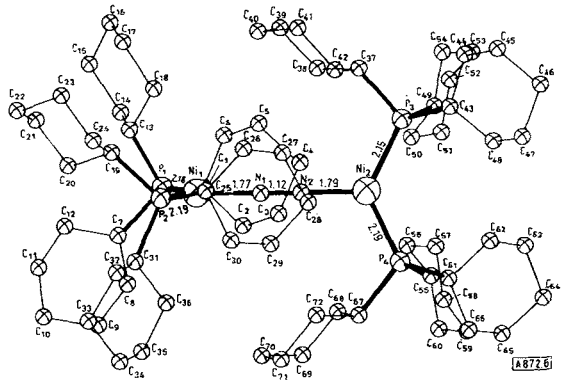


Fig. 6. Structure of the nitrogen adduct to bis(tricyclohexylphosphane)-nickel(0) depicting the enclosure of the nitrogen molecule by the cyclohexyl rings.

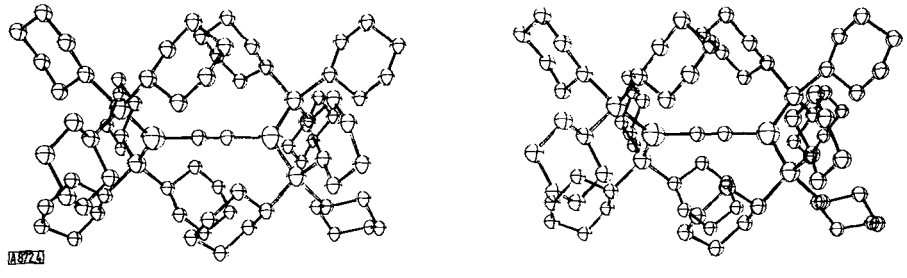
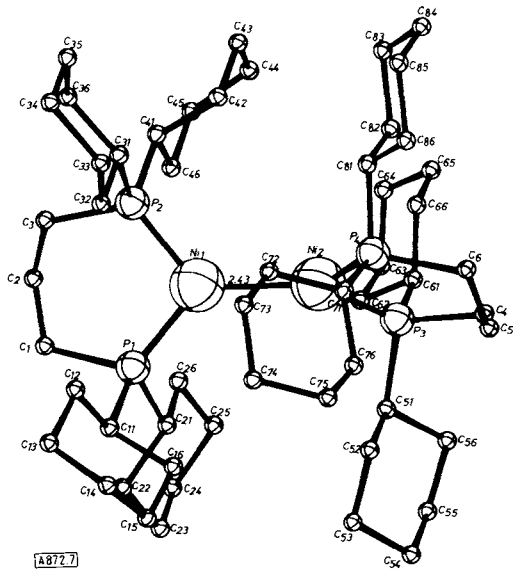


Fig. 4. Structure of a nitrogen adduct to bis(tricyclohexylphosphane)nickel(0) illustrated by a stereoscopic drawing.

[*] The system described in [14a], which contains all necessary programs, is available from Deutsches Rechenzentrum Darmstadt. An expanded version is in use at the Max-Planck-Institut for Eiweiss- und Lederforschung, Abteilung für Röntgen-Strukturforschung, München.

indicated termination of the refinement at the agreement value of $R=0.11$. Figure 5 shows the geometry for an important section of the molecular grouping $P_2Ni—N{\equiv}N—NiP_2$.



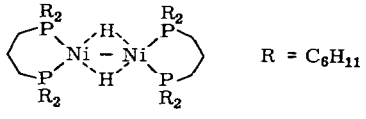


Fig. 7. Structure of di-μ-hydridobis[1,3-trimethylenebis(dicyclohexylphosphane)nickel] *(Ni-Ni)* and structural formula.

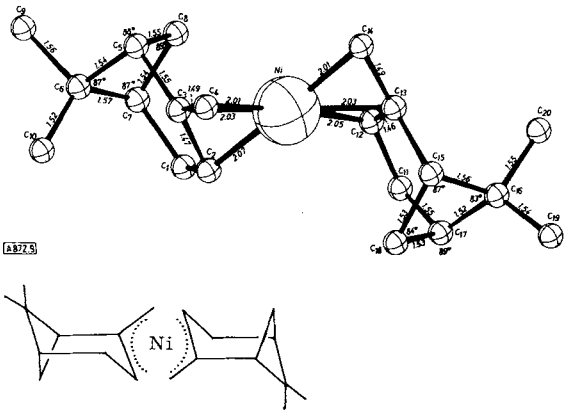


Fig. 9. Structure of bis(π-pinenyl)nickel and structural formula.

symmetry axis can be seen parallel to the *c* axis. The molecular structure is also illustrated stereoscopically in Figure 9 and Figure 10.

The last example, the structure determination of a compound prepared by the displacement of one carbonyl from $Ni(CO)_4$ by the ylide tricyclohexylethylidenephosphorane, will also illustrate the costs incurred by a three-dimensional structural analysis. The molecular arrangement is shown in Figure 11[20].

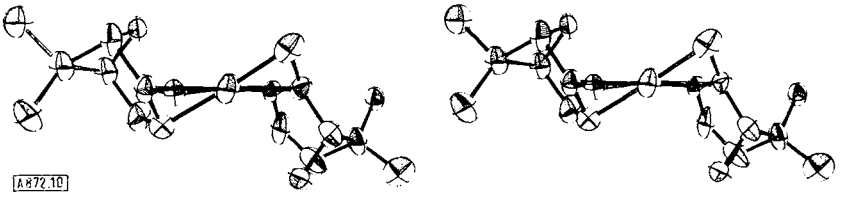


Fig. 10. Stereoscopic drawing of bis(π-pinenyl)nickel.

From Figure 6 it is evident that the effective stability of this compound is primarily dependent on the molecular nitrogen being enclosed by the cyclohexyl rings. This steric arrangement is also evident in the dihedral angle of 96.7° between P—Ni—P planes (see also Fig. 4).

A similar torsion (116.7°) between opposite P—Ni—P groups can also be observed in di-μ-hydridobis[1,3-trimethylenebis(dicyclohexylphosphane)nickel] *(Ni-Ni)* (Fig. 7[18]). The bond distance of the complexed nitrogen is slightly lengthened (0.01 Å) compared to that in the free state.

Another form used to illustrate the molecular parameters with the plotter program ORTEP is shown in Figure 8 for the unit cell of bis(π-pinenyl)nickel[19]. A two-fold screw

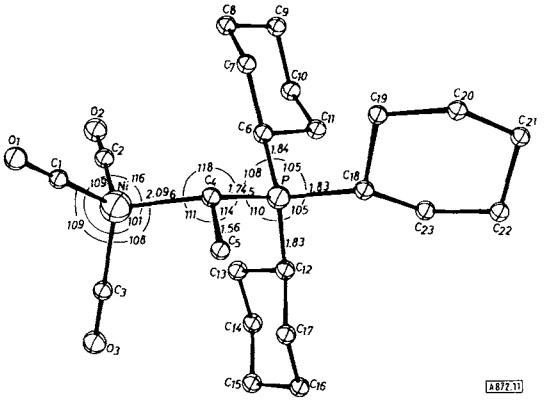


Fig. 11. Structure of the compound $(CO)_3Ni{-}CH(CH_3){-}P(C_6H_{11})_3$.

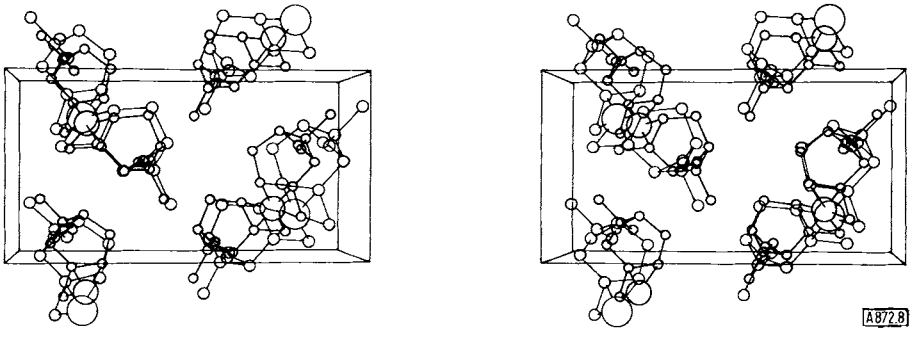


Fig. 8. Stereoscopic drawing of the unit cell of bis(π-pinenyl)nickel. *a* axis horizontal, *b* axis vertical.

The formation of a sigma Ni—C bond between the sp^3 carbon (C4) of the ylide and the transition metal is of interest. This bond is noticeably longer than several other σ-Ni—C bonds[17, 21] which we have recently investigated (Figs. 12 and 13). The phosphorus-carbon distance is relatively short, although longer than that found in free ylides[22], but is similar to the P—C distance found in phosphonium compounds[23].

According to our present experience three-dimensional structural analyses of average difficulty (approximately 50 atoms per molecule maximum) can be completed in a minimum of four weeks. Certain unforeseen difficulties that may occur during the analysis can increase this time to two or three months. Of course the minimal time is based on the availability of a large computer and an automatic data collection system. Approximately a week for each part of the analysis—preliminary investigation, data collection, structure determination, and refinement (±0.01 Å)—has been assumed.

The cost of such an analysis is largely dependent on the expenditures for computer time and man-hours required. Depending upon the problem this may be between DM 20000 and DM 200000. It clearly follows that routine X-ray structural analyses should be applied only in situations where less expensive methods do not provide sufficient information.

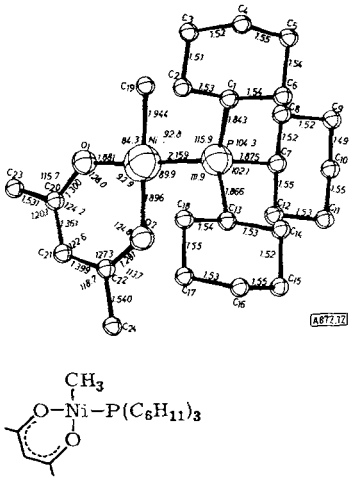
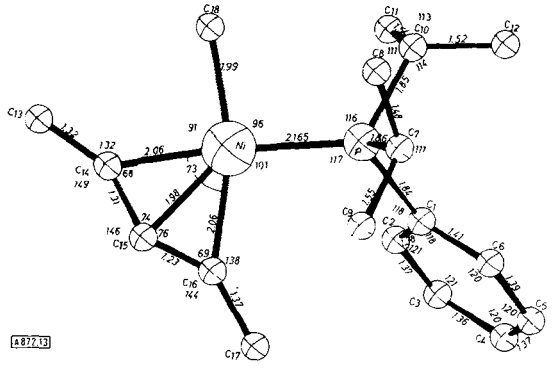


Fig. 12. Structure of 2,4-pentanedionatomethyltricyclohexylphosphanenickel(II) and structural formula.



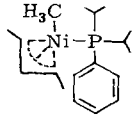


Fig. 13. Structure of methyldiisopropylphenylphosphane-π-pentenylnickel and structural formula.

I would like to thank my co-workers Dr. B. L. Barnett, B. Boleslawsky, K. H. Claus, M. Eckhardt, and Dr. Y.-H. Tsay for their enthusiastic support.

Received: November 18, 1972 [A 872 IE]
German version: Angew. Chem. *84*, 412 (1972)
Translated by Dr. *B. L. Barnett*, Mülheim/Ruhr

[1] *W. Hoppe*, Angew. Chem. *77*, 484 (1965); Angew. Chem. internat. Edit. *4*, 508 (1965); *W. R. Busing* and *H. A. Levy*, ORNL-4054 (1967); *S. C. Abrahams*, Chem. Engng. News *41*, No. 22, p. 108 (1963); *U. W. Arndt* and *B. T. M. Willis*: Single Crystal Diffractometry. Cambridge University Press, London 1966.

[2] *E. Ziegler, D. Henneberg*, and *G. Schomburg*, Angew. Chem. *84*, 371 (1972); Angew. Chem. internat. Edit. *11*, 348 (1972).

[3] *E. A. Mayer*, Z. Anal. Chem. *205*, 153 (1964).

[4] *C. Krüger* and *A. Wilson*, Fall Joint Computer Symposium, Las Vegas 1969.

[5] *G. H. Stout* and *L. H. Jensen*: X-Ray Structure Determination. Macmillan, London 1968; *M. J. Buerger*: Crystal-Structure Analysis. Wiley, New York 1960.

[6] For a detailed description see *W. Hoppe* in the AED Handbook (Siemens, Berlin 1966, p. 10).

[7] *C. Krüger*, Programm DIKAP, unpublished.

[8] A compilation of the present empirical and analytical methods for data reduction can be found in *F. R. Ahmed*: Crystallographic Computing. Munksgaard, Copenhagen 1970.

[9] *W. Hoppe*, Angew. Chem. *78*, 289 (1966); Angew. Chem. internat. Edit. *5*, 267 (1966); *R. Huber*, Acta Cryst. *19*, 353 (1965); *D. van der Helm, ibid. A 25*, S 63 (1969).

[10] *D. Sayre*, Acta Cryst. *5*, 60 (1952); *D. Harker* and *J. S. Kasper, ibid. 1*, 70 (1948); *H. Hauptmann* and *J. Karle*: Solution of the Phase Problem. Monograph No. 3, Polcrystal Book Service; Acta Cryst. *3*, 181 (1950); *J. Karle* in *R. Brill* and *R. Mason*: Advances in Structure Research by Diffraction Methods. Wiley, New York 1964; *J. Karle* and *I. Karle*, Acta Cryst. *21*, 849 (1966); *M. M. Woolfson*: Direct Methods in Crystallography. Oxford University Press, London 1961; *W. Hoppe, J. Gassmann, K. Zechmeister, et al.* in [8].

[11] *R. B. K. Dewar*, Dissertation, University of Chicago 1968.

[12] *J. S. Rollet*, Acta Cryst. *A 21*, A 240 (1967); *H. Koyama* and *K. Okada, ibid. A 25*, S 129 (1969); *H. Koyama* and *K. Okada*, J. Chem. Soc. *B 1969*, 940.

[13] *W. Hoppe* and *J. Gassmann*, Acta Cryst. *B 24*, 97 (1968); *Y.-H. Tsay*, Dissertation, Georgetown University, Washington D. C. 1970.

[14] a) *M. J. Stewart et al.*, X-RAY-67 Program System for X-ray Crystallography. Computer Science Center, University of Maryland, Maryland 20742 (USA), Tech. Report 67—58; b) *F. R. Ahmed, S. R. Hall, M. E. Pippy*, and *C. P. Huber*: NRC Crystallographic Programs for the IBM 360 Systems. National Research Council of Canada, Ottawa 7, 1970.

[15] *C. K. Johnson*, Oak Ridge National Laboratory, Oak Ridge, Tennessee (USA), ORNL-3794.

[16] *H. Dietrich* and *M. Soltwisch*, Angew. Chem. *81*, 785 (1969); Angew. Chem. internat. Edit. *8*, 765 (1969); *C. Krüger*, unpublished; *M. J. Bennett, F. A. Cotton*, and *J. Takats*, J. Amer. Chem. Soc. *90*, 903 (1968).

[17] *P. W. Jolly* and *K. Jonas*, Angew. Chem. *80*, 705 (1968); Angew. Chem. internat. Edit. *7*, 731 (1968); *P. W. Jolly, K. Jonas, C. Krüger*, and *Y.-H. Tsay*, J. Organometal. Chem. *33*, 109 (1971).

[18] *K. Jonas* and *G. Wilke*, Angew. Chem. *82*, 295 (1970); Angew. Chem. internat. Edit. *9*, 312 (1970); *B. L. Barnett, C. Krüger*, and *Y.-H. Tsay*, unpublished.

[19] *C. Krüger*, unpublished.

[20] *G. Wilke et al.*, unpublished; *F. Heydenreich*, Dissertation, Universität Bochum 1971; *K. F. Zinkgräf*, Dissertation, Universität Heidelberg 1968; *B. L. Barnett* and *C. Krüger*, unpublished.

[21] *H. Bönnemann, H. Schenkluhn*, and *G. Wilke*, unpublished.

[22] *J. C. J. Bart*, Angew. Chem. *80*, 697 (1968); Angew. Chem. internat. Edit. *7*, 730 (1968); J. Chem. Soc. *B 1969*, 350.

[23] *J. J. Daly* in *J. D. Dunitz* and *J. A. Ibers*: Perspectives in Structural Chemistry. Wiley, New York 1970, Vol. 3, p. 194.

Application of Computers to MO Theory and Chemical Kinetics

By Günther von Bünau[*]

1. Introduction

The rapid development of electronic computers in recent years has led to the situation where the methods and ideas of theoretical chemistry can be applied in ever-increasing degrees to the problems facing the experimentalist. Whenever it is suspected that observed phenomena may be traced back to molecular properties the question arises of the possibility of a calculation delivering a quantitative statement about the structure, stability, and reactivity of the molecule. There is little doubt today that such a calculation must ultimately return to the quantum mechanical theory of molecules, *i.e.* solution of the Schrödinger equation. Nevertheless, it is not yet clear to many chemists how relatively simple it is to carry out their own quantum mechanical calculations with programs and computers already available. The FORTRAN texts of some standard programs (for example, Hückel[1] and CNDO[2]) have already been published in books. Many other programs of importance to theoretical chemistry can be readily obtained from the Quantum Chemistry Program Exchange Project (QCPE) of the University of Indiana (Chemistry Department, Bloomington, Indiana 47401, USA). (In Germany the QCPE programs are distributed by the Deutsches Rechenzentrum in Darmstadt.) Moreover, most computing centers have program libraries already containing QCPE and other programs of interest to chemists. Comprehensive descriptions and directions with respect to input data exist for all well-tested programs.

The purpose of this article is, therefore, to give the experimental chemist a feeling for the nature of the programs which are available for the solution of his problems and for the input data necessary for molecular calculations. First, we consider programs for the calculation of the coordinates of the atomic nuclei in a molecule. These coordinates represent the most important input data for most quantum mechanical calculations and are also important in calculation of reaction kinetic frequency factors (Section 2). For an understanding of the differences among the numerous quantum mechanical models, it is also necessary to analyze the Schrödinger equation and discuss the various possibilities for its approximate solution (Section 3). A few simple MO theory examples calculated at the Max-Planck-Institut für Kohlenforschung in Mülheim will then be described in detail to illustrate these points (Section 4). Following this, a few special methods from reaction kinetics will be discussed which allow the estimation of activation energies of H atom transfer reactions (BEBO method, Section 5.1) and the calculation of the energy-dependence of unimolecular decompositions (quasi-equilibrium theory, Section 5.2). Finally, the phenomenological treatment of complicated kinetic systems with the aid of a computer will be mentioned (Section 6).

[*] Priv.-Doz. Dr. G. von Bünau
Max-Planck-Institut für Kohlenforschung
Abt. Strahlenchemie
433 Mülheim/Ruhr, Stiftstrasse 34—36 (Germany)

2. Coordinate Calculations

The coordinates of the atoms in a molecule may always be determined by the usual methods of vector calculations since the bond angles and distances are either known or are varied in the calculation. For larger molecules, the accomplishment of this task can be very tedious and is better left to a computer[3,4]. The program KOORD, a variation of QCPE 136, in use at Mülheim not only calculates the atomic coordinates of a molecule in any orientation, but also derives quantities such as: center of mass coordinates, principal moment of inertia, rotational partition function, and spectroscopic rotational constants. In addition, KOORD also calculates the translational partition function from the molecular mass and draws projections of three-dimensional molecular models (Fig. 1).

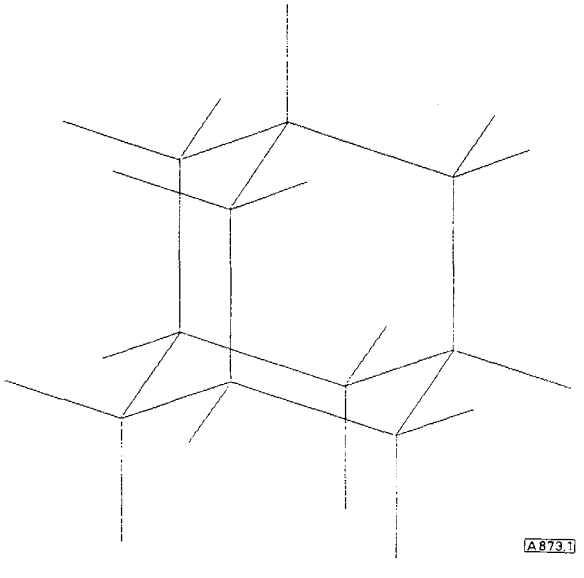


Fig. 1. Plotter drawing of the adamantane molecule (projected stick model).

Program KOORD requires about 12000 core locations. The Mülheim computer requires 0.38 s to determine the 24 coordinates of the ethane molecule; only 0.46 s are necessary for determination of the 78 coordinates of adamantane. Thus, in general, the computational time is small compared to the time required for the output of the computer calculation with a rapid line printer or plotter.

With certain assumptions, the coordinate calculations may also be used to estimate the frequency factors for

reaction rate constants. For instance, in the sense of the Eyring theory, the rate constant k_r of a bimolecular reaction

$$A + B \rightleftharpoons AB^{\ddagger} \rightarrow \quad (1)$$

may be written as

$$k_r = \frac{kT}{h} \times \frac{Q^*}{Q_A \times Q_B} \exp\left(-\frac{\Delta E_A}{RT}\right) \quad (2)$$

where k is the Boltzmann constant, T the absolute temperature, and h Planck's constant. Q_A, Q_B, and $Q^{\ddagger}$ represent the partition functions of the molecules A, B, and $AB^{\ddagger}$ respectively, and can be written as products of the translational, rotational, and vibrational partition functions. At sufficiently low temperatures, the contribution from the vibrational partition function is small so that the total partition function may be taken from the coordinate calculation. Correspondingly, the frequency factor

$$A = \frac{kT}{h} \times \frac{Q^*}{Q_A \times Q_B} \quad (3)$$

of a bimolecular reaction may always be estimated from the coordinate calculation if the vibrational partition functions may be neglected or cancel out of the ratio of the total partition functions of the transition and initial states.

3. Molecule Theory

In the quantum mechanical theory of molecules, each molecule is assigned a function of state Ψ which may be found by solution of a Schrödinger equation set up especially for that molecule. The state function is necessarily quite complex since, according to the axioms of quantum mechanics, all measurable properties of molecules can be extracted from Ψ by subjecting it to some characteristic computational procedure.

The energy of a molecule is of prime interest. Given the approximation that the total energy of the molecule be represented as a sum of energies of translational, rotational, vibrational, and electronic motion, it is possible to solve the separated Schrödinger equations for each type of motion. It is especially significant for quantum chemistry that the separate treatment of the molecular electronic state is in general a very good approximation (Born-Oppenheimer approximation, Section 3.1). The real basis of the MO theory is, however, the orbital approximation (Section 3.2) which is familiar to the chemist from the special case of the electron configurations of atoms (*e.g.* $1s^2 2s^2 2p^2$ for the ground state of the C atom). For the practical calculation of the electronic Ψ function, the complicated molecular orbitals are written as linear combinations of simpler "basis orbitals" (Section 3.3). Sometimes, only the molecular orbitals of the valence electrons are calculated by application of empirical parameters (Section 3.4).

3.1. Born-Oppenheimer Approximation

Every quantum mechanical description of a molecule consisting of N atoms and n electrons presupposes the calculation of the (total) wavefunction Ψ of the molecule. Ψ is a function of the atomic and electronic coordinates and the time t; Ψ^2 is the probability density for finding the system in a given configuration. In principle, Ψ can be determined by solution of the Schrödinger equation

$$H\Psi = -\frac{\hbar}{i} \cdot \frac{\partial}{\partial t} \Psi \quad (4)$$

where $i = \sqrt{-1}$ and the operator H represents

$$H = -\frac{\hbar^2}{2m} \sum_k^n \nabla_k^2 - \sum_k^n \sum_\nu^N \frac{Z_\nu e^2}{r_{k\nu}} + \sum_{k<l} \frac{e^2}{r_{kl}} - \frac{\hbar^2}{2} \sum_\nu^N \frac{1}{M_\nu} \nabla_\nu^2 + \sum_{\nu<\mu} \frac{Z_\mu Z_\nu e^2}{R_{\mu\nu}} \quad (5)$$

Here, ∇_k^2 is the Laplacian operator for the k^{th} electron

$$\nabla_k^2 = \frac{\partial^2}{\partial x_k^2} + \frac{\partial^2}{\partial y_k^2} + \frac{\partial^2}{\partial z_k^2} \quad (6)$$

$\hbar = h/2\pi$, h is Planck's constant, m is the mass and e the charge of the electron, $r_{k\nu}$ the distance between the k^{th} electron and the ν^{th} nucleus, r_{kl} the distance between electrons k and l, $R_{\mu\nu}$ the distance between atomic nucleii μ and ν of charge Z_μ and Z_ν respectively.

Physically, the terms on the right hand side of eq. (5) can be interpreted as follows:

1. The kinetic energy of the electrons
2. The potential energy of the electrons in the field of the atomic nucleii
3. The mutual electrostatic repulsion of the electrons
4. The kinetic energy of the nucleii
5. The mutual electrostatic repulsion of the nucleii

In addition to these terms, the complete Hamiltonian operator H must contain further terms which consider the interactions of the electrons with external fields (*e.g.* in ESR) and nuclear spins (*e.g.* in NMR), and relativistic effects (*e.g.* for high energy molecular beams). A description of the explicit forms of such terms may be found in ref[5]. The calculation of such weak interactions as well as the time dependence of Ψ are accessible only with the help of quantum mechanical perturbation theory. There, we presume a knowledge of the wave functions of the unperturbed system, which may be taken from the Schrödinger equation for the stationary molecular states.

$$H\overset{0}{\Psi} = E\overset{0}{\Psi} \quad (7)$$

E is the total energy of the molecular state under consideration. Apart from the special cases already mentioned, all quantum mechanical methods of calculation are ultimately based on eq. (7). Equation (7) cannot be solved exactly and must be further simplified before an approximate solution can be found for chemically interesting cases. The numerous

approximation techniques employed in the last few decades are based on various physical models, the most important of which is the Born-Oppenheimer approximation[6].

The Born-Oppenheimer approximation is based on the fact that the electrons, owing to their several-thousand-fold smaller masses, move much faster than the nuclei. The electrons thus adjust to any change in position of the nuclei (*e.g.* the vibrations of the nuclei about their equilibrium positions) so rapidly that relaxation effects can be ignored. This approximation corresponds to the possibility of separating the last two terms in eq. (5) and solving separated Schrödinger equations for nuclear and electronic motion.

3.2. Orbital Approximation

In the orbital approximation, the total electronic wave function is represented as a product of one-electron wave functions ψ_i

$$\Psi_{el} = \psi_1(1)\,\psi_2(2)\cdots\psi_n(n) \tag{8}$$

Since the electrons are indistinguishable, Ψ_{el} must be invariant (except for a change of sign) on exchange of electron coordinates (Pauli principle). Equation (8) does not meet this criterion but linear combinations of such products can be found which do fulfil the Pauli principle. For this purpose, the individual electrons are usually assigned a spin function and only products of the same total spin are combined.

In the case of filled shells (*i.e.* each occupied orbital is filled with two electrons of opposite spin), the orbital approximation implies that Ψ_{el} is a solution of the Hartree-Fock equation:

$$\left[-\frac{\hbar^2}{2m}\nabla_k^2 - \sum_{\nu}^{N}\frac{Z_\nu e^2}{r_{k\nu}} + \sum_l (2J_l - K_l)\right]\psi_k = E_k\psi_k \tag{9}$$

where

$$J_l(1) = \int \frac{e^2\psi_l^2(2)}{r_{12}}\,d\tau_2; \quad K_l(1)\psi_k(1) = \left[\int \frac{e^2\psi_k(2)\psi_l(2)}{r_{12}}\,d\tau_2\right]\cdot\psi_l(1)$$

The electron repulsion term of the Schrödinger equation is approximated in the Hartree-Fock treatment by an expression which considers only an average repulsion, *i.e.* the repulsion of an electron appears in the calculation as the interaction of one electron with the average field generated by all other electrons. Since the total distribution of the electrons can only be obtained from the unknown Ψ function or its square, the expression in brackets in eq. (9), *i.e.* the Hartree-Fock operator, assumes the solution in advance. In this case, an iterative procedure must be used in which an electron configuration is assumed, the Hartree-Fock equation solved, and a new electron distribution obtained and so on, until the electron distribution no longer changes, *i.e.* becomes self-consistent.

The orbital approximation is the starting point for almost all quantum mechanical calculations.

In the usual description outlined here, introduction of the spin quantum number merely leads to a certain algebraic form of the linear combination representation of Ψ_{el}. However, the Hartree-Fock equation no longer contains the spin. The assignment of a spin quantum number may be practical in this connection, but from the standpoint of the theory it is both questionable and dispensable[7].

Since only Ψ^2 and not Ψ is an observable quantity, the statistical (Thomas-Fermi) method should be mentioned here for completeness. The statistical treatment is based on the continuous density distribution of an electron gas as opposed to the Schrödinger equation. It is important only for atoms. Application of the theory to molecules is problematical and difficult[8-10].

3.3. Linear Combination Methods

For practical application of the Hartree-Fock equation to molecular systems a more precise specification of the molecular orbitals ψ_k is necessary. Linear combination expressions are the most simple to handle in a calculation.

$$\psi_k = \sum_l c_{kl}\phi_l \tag{10}$$

It is reasonable that the "basis functions" ϕ_l should be so chosen that they approximate as well as possible the form of the molecular orbitals in the neighborhood of the individual centers. Starting with various physical models, this approximation can be carried out in many different ways. Thus, for example, the ϕ_l can be assigned the analytic form of the hydrogen atomic orbitals:

$$\phi_l \sim P_k(r)\exp\left(-\frac{\alpha r}{k}\right) \tag{11}$$

where $P_k(r)$ is a polynomial in r for which r^{k-1} is the highest power of r occurring. Slater orbitals have a simpler form than the hydrogen orbitals

$$\phi_l \sim r^{k-1}\exp\left(-\frac{\alpha r}{k}\right) \tag{12}$$

in that they contain only one power of r. However, both the hydrogen and the Slater functions cause problems in the calculation of integrals of the type

$$\int \phi_k^*(1)\phi_l^*(1)\frac{e^2}{r_{12}}\phi_m(2)\phi_n(2)\,d\tau \tag{13}$$

This difficulty is avoided by application of orbitals having the analytic form of a Gaussian function

$$\phi_l \sim \exp(-\alpha r^2) \tag{14}$$

A disadvantage of the Gaussian-orbital method is, however, that many basis functions are necessary in order to approximate an atomic orbital. Thus, for example, for representation of a p orbital at least two Gaussian functions are needed:



p Function Gaussian group

It is better to combine four or more Gaussian functions for the representation of a p-function.

3.4. Semiempirical Approximations

Further simplifications result if, instead of all of the electrons, only valence electrons are considered; moreover, only certain integrals are calculated at all while the others are neglected. Thus, the neglect of integrals with differential overlap is a characteristic of many semiempirical methods, *e.g.* integrals of the type in eq. (13) are set equal to zero if $n \neq m$ or $l \neq k$. In the remaining integrals, empirically determined values are put in to compensate for the neglected integrals.

In the simplest semiempirical approximations, the Hückel methods, the explicit or simplified form of the Hartree-Fock operator no longer enters into the calculation and all quantities are empirically determined (π electron theory) or are reduced to the calculation of overlap integrals (extended Hückel theory, EHT). The Hückel methods yield molecular orbital functions which are not self-consistent.

In deciding what to neglect and what to calculate, which basis orbitals and empirical quantities to use, one has a broad range of possibilities which correspond to definite physical models. For identification of these models a large number of code names have been adopted in the literature (see Table 1) whereby the basic object of simplifying the Schrödinger equation is threatening to blossom into a black art. Fundamentally, one would naturally prefer a model that implies the most precise solution of the Schrödinger equation. The performance of an "*ab initio*" calculation (*i.e.* a calculation starting with the Hartree-Fock equation and using no empirically obtained quantities) would often demand an immoderately large expenditure of computer time or would often exceed the capacity of a given computer.

For practical application, therefore, the semiempirical methods have instead received increased attention in recent years, in spite of their notorious theoretical in-

Table 1. Code names of quantum chemical approximations [a].

Code	Explanation
AMO	Alternating MO method, accounts for electronic repulsion in particular by assigning electrons with differing spins to different orbitals [14]
AO	Atomic orbital
ASMO	Antisymmetrized molecular orbitals, *i.e.* molecular orbitals which fulfil the Pauli principle. In this case the total wave function changes sign when the coordinates of two electrons are interchanged (the wave function is antisymmetric with respect to interchange)
BO	Bond orbital
CI	Configuration interaction method, uses a generalized product expression for the wave function (see eq. 8) to account for differences between the Hartree-Fock and the Schrödinger equation
CNDO	Semiempirical, SCF method with complete neglect of differential overlap (see [15])
DO	Differential overlap, *i.e.* consideration of products $\psi_i(1)\,\psi_j(1)\,d\tau_i$ (even if $i \neq j$) in the integration of the Hartree-Fock equation
EHM, EHT	Extended Hückel method (theory) [16]. Iterative variation: IEHM [17]
FEM	Free electron model, treats the molecule as a potential well in which the electrons move freely subject to quantum mechanical boundary conditions
GO, GTO	Gaussian orbital (Gauss-type orbital)
GF	Group functions, mostly two-electron functions which are used in place of atomic orbitals as the basis of a linear combination method [18, 19]
HMO	Hückel-MO method
INDO	Semiempirical SCF method, intermediate neglect of differential overlap [20]
KGO	Constellations with Gauss orbitals, special CI method for use with Gauss orbitals [21]
LC	Linear combination method, for example LCAO: Linear combination of atomic orbitals, correspondingly LCBO, LPGO, LCPO, *etc.*
MC	Multi-configuration method (for example, MCSCF [22]), special form of the CI method
MINDO	Modified INDO method [23]
NO, NSO	Natural orbitals, natural spin orbitals, one-electron functions which facilitate an optimum consideration of configuration interaction [24, 25]
NPSO	Non-paired spatial orbital method [26, 27]
PO	Pars orbital, orbital of a group of atoms within a molecule [28]
PPP	Pariser-Parr-Pople method [29, 30], self-consistent, π-electron method which partially considers electron repulsion, also called P^3 method
SCF	Self-consistent field method, carries out the iterative solution of the complete or approximated Hartree-Fock equation
STO	Slater orbital (Slater-type orbital)
VB	Valence bond method, occasionally also called Heitler-London-Slater-Pauling (HLSP) method
ZDO	Zero differential overlap

[a] The list could be extended almost indefinitely.

Table 2. Selected programs from the Mülheim computing center [a].

Program	Quantum-chemical approximation	Number of valence electrons	Memory requirements $k=1000$ core locations	Computing time (s)
HUCKF	Hückel-MO method (π electron theory with ω-variation and forced convergence)			
SCFCON	Pariser-Parr-Pople method with configuration interaction	triplet 30 singlet 80	38 k	naphthalene 131 (10 electrons)
HMOV	Extended Hückel method with Slater orbitals for 1s, 2s, and 2p valence electrons	98	36 k	ethane 12 (14 electrons)
SCCC-MO	Extended Hückel method with arbitrary basis orbitals and consideration of all valence electrons including 4s, 4p, 3d (maximum 30). Iterative calculation of self-consistent partial charges possible	60	38 k	ethane 29
CNINDO	Semiempirical variation of SCF method (similar to QCPE 141) for open and filled shells	80	38 k	ethane 20
CNDO-CI	Variation of CNINDO with configurational interaction	60	38 k	
CNDO-LS	Perturbation theoretical consideration of spin-orbit coupling within the framework of the CNDO approximation	60	38 k	
MOLVAR	CNDO method with automatic minimization with respect to an arbitrary number of parameters	60	38 k	
SCFAT	Hartree-Fock method for atoms with closed shells			

[a] Tested FORTRAN IV versions, available upon request from *F. Mark* (MPI für Kohlenforschung, Abt. Strahlenchemie, Mülheim). Most of the programs listed here have been developed or adapted (from QCPE programs) for use on the PDP 10 computer by *F. Mark* and his group.

adequacies. This is not only due to the fact that the semiempirical methods require less computer time but also that the "quantum chemical interpolation" of calculable molecular properties is often all that the chemist needs if he is more interested in general trends than numerical values. In the scope of this paper it will suffice to illustrate in simple examples a few typical applications of semiempirical calculations.

In Table 2, the semiempirical techniques currently in use at Mülheim are shown. From the given computation times and the core space requirements one can easily see the characteristic dilemma of quantum chemistry: the calculation expense increases with increasing theoretical rigor. The computation time increases greatly with the size of the molecule (approximately with the third power of the number of valence electrons).

The results of MO theory discussed below were obtained with the extended Hückel method. This method is especially easy to interpret and may be easily applied to excited and ionized species[11] whose treatment by more rigorous methods is still difficult.

4. Examples of the Application of MO Theory

MO calculations yield numerical values for the orbital energies E_k (second line in the example shown in Table 3). In the ground state the 14 valence electrons of ethane pair-wise occupy the seven lowest levels (of which some are degenerate, *i.e.* have the same energy), for which a total electronic energy of $E=-243.673$ eV results. For each E_k there is a corresponding set of coefficients of the linear combination of the orbital function, ψ_k (in the column under E_k), the square of which represents the partial charge distribution in the molecular orbital. From Figure 2 and the coefficients of the two a_{1g} orbitals

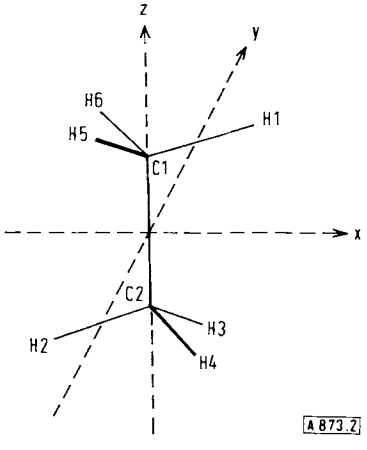


Fig. 2. Coordinate system for ethane and numbering of the atoms (see Table 3).

it can be seen that the a_{1g} orbitals provide the main contribution to the C—C bonding in ethane. In the $2a_{1g}$ MO, for example, the $2p_z$ (C) atomic orbitals con-

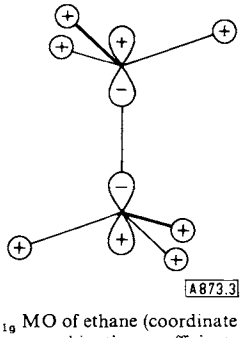


Fig. 3. Schematic representation of the $2a_{1g}$ MO of ethane (coordinate system as in Fig. 2). In this MO the linear combination coefficients (+0.5626 and −0.5626 in Table 3) of the p_z basis orbitals localized on C1 and C2 dominate. These orbitals have the same sign in the space between the C atoms and contribute substantially to the C—C bonding energy (the small contribution of the 2s orbitals on C1 and C2 is neglected in the drawing). Correspondingly it is seen that the $2a_{1g}$ MO is C—H bonding.

structively add in the overlapping region of the bond axis (Fig. 3). Correspondingly it follows from Table 3 that the highest occupied (degenerate) $1e_g$ MO is C—C (π) antibonding and C—H bonding, that also the low-lying a_{2u} orbital is C—C (σ) antibonding, and so on. These antibonding contributions are more than compensated by bonding contributions, so that overall bonding MOs

Table 3. Molecular orbitals ψ_k of ethane: Eigenvalues E_k (orbital energies), linear combination coefficients c_{kl} (see eq. (10)), and MO bonding energies for the occupied and lowest unoccupied (in the ground state) orbitals of ethane (see Fig. 2 and 3).

	$2a_{2u}$	$1e_g$		$2a_{1g}$	$1e_u$		$1a_{2u}$	$1a_{1g}$
				E_k				
	3.213	−13.751	−13.751	−14.104	−15.855	−15.855	−21.856	−26.682
				c_{kl}				
H(1)	−0.2604	−0.0610	−0.3700	0.1165	−0.3128	−0.0115	0.1883	0.0847
H(2)	0.2604	−0.0610	−0.3700	0.1165	0.3128	0.0115	−0.1883	0.0847
H(3)	0.2604	−0.2899	0.2378	0.1165	−0.1664	0.2651	−0.1883	0.0847
H(4)	0.2604	0.3509	0.1322	0.1165	−0.1464	−0.2766	−0.1883	0.0847
H(5)	−0.2604	−0.2899	0.2378	0.1165	0.1664	−0.2651	0.1883	0.0847
H(6)	−0.2604	0.3509	0.1322	0.1165	0.1464	0.2766	0.1883	0.0847
Cs(1)	−0.1230	0	0	−0.0785	0	0	0.4003	0.4596
Cs(2)	0.1230	0	0	−0.0785	0	0	−0.4003	0.4596
Cx(1)	0	−0.0755	−0.4579	0	−0.3994	−0.0147	0	0
Cx(2)	0	0.0755	0.4579	0	−0.3994	−0.0147	0	0
Cy(1)	0	0.4579	−0.0755	0	−0.0147	0.3994	0	0
Cy(2)	0	−0.4579	0.0755	0	−0.0147	0.3994	0	0
Cz(1)	1.0538	0	0	0.5626	0	0	0.1021	−0.0199
Cz(2)	1.0538	0	0	−0.5626	0	0	0.1021	0.0199
	MO bonding energies							
	7.3395	−0.6561	−0.6561	−1.1661	−1.7373	−1.7373	−2.5089	−3.6038

result (MO bonding energy negative; numerical values in eV).

The electronic excitation (raising of an electron from $1e_g$ to the $2a_{2u}$ orbital, unoccupied in the ground state) as well as ionization (removal of an electron from the $1e_g$ MO) leads to a degenerate state which according to the Jahn-Teller principle[12] must assume a conformation of lower symmetry. It is, therefore, pointless to retain the D_{3d} symmetry for calculations on excited or ionized ethane.

As an illustration, let us consider two distorted conformations of the ethane molecule which are distinguished by the 1,1 and 1,2 approach of the H atoms (Fig. 4). Such conformations can be considered as models for the transition states for elimination of molecular H_2 which plays an important part in the vacuum UV photolysis of ethane[13]. The EHT calculation indicates that for both excited and ionized ethanes the transition state for 1,1 elimination is energetically preferred to that for 1,2 elimination. As yet it has been experimentally shown only

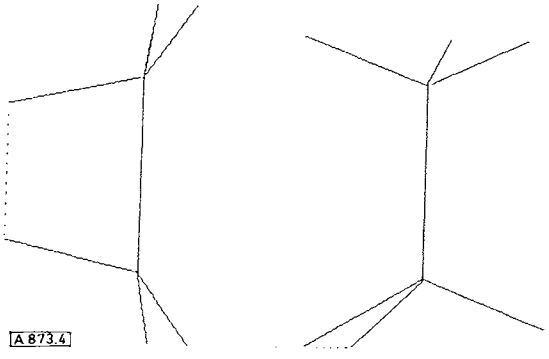


Fig. 4. Plotter drawing of the transition state for the 1,2 (left) and 1,1 (right) elimination of an H_2 molecule from ethane. The dotted lines correspond to an H···H distance of 1.1 Å (compared to *ca.* 1.78 Å in undistorted ethane).

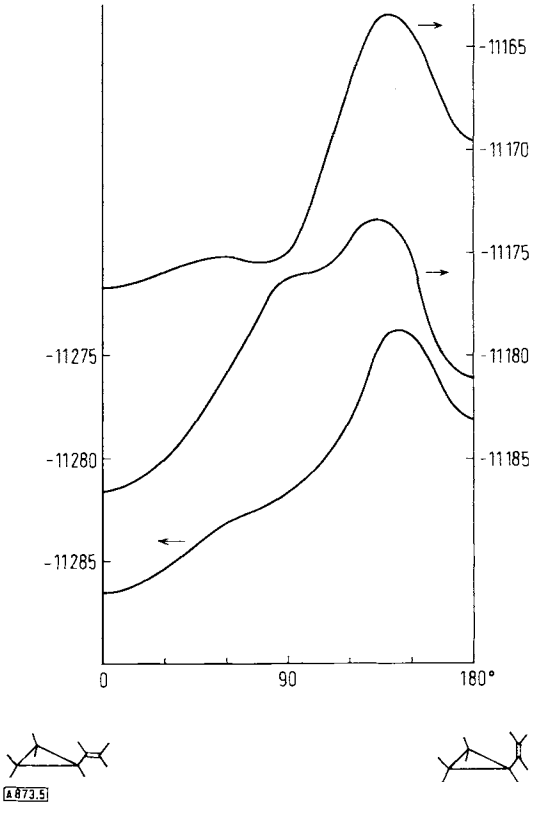


Fig. 5. Total electronic energy (kcal/mol) of vinylcyclopropane (from extended Hückel theory) as a function of the torsional angle about the C—C_2H_3 bond: ground state (lowest curve, left ordinate) first and second excited states (middle and upper curves respectively, right ordinate).

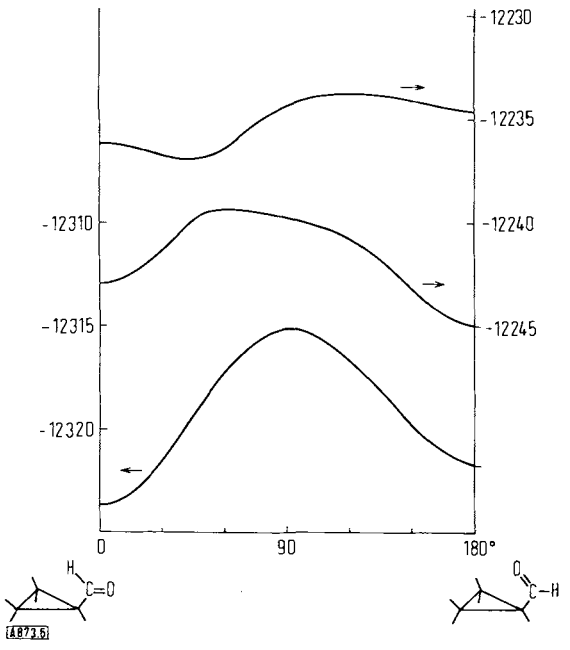


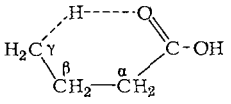
Fig. 6. Total electronic energy (kcal/mol) of cyclopropanecarbaldehyde as a function of the torsional angle about the C—CHO bond for the ground state (lower curve, left ordinate) and the first and second excited states (middle and upper curves, respectively, right ordinate).

in the case of electronic excitation that 1,1 elimination occurs preferentially.

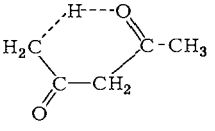
Since EHT calculations (like most other semiempirical methods) do not yield good values for equilibrium bond distances, one can only expect reasonable results from model calculations with given fixed bond distances (*e.g.* in an assumed transition state) if the comparison is limited to sufficiently similar systems. However, this situation frequently occurs in practice.

Calculations of activation energies for conformational changes also number among the applications of MO theory to reaction kinetics. As an example we may consider the rotational barriers of vinylcyclopropane and cyclopropanecarbaldehyde which have been the objects of various spectroscopic and theoretical investigations in recent years[31-34]. Of special interest was the question of the importance of π-electron conjugation between the double bond and the cyclopropane ring. It is possible to answer this question by calculating the total MO energy as a function of the angle of rotation about the C—C_2H_3 and C—CHO bonds respectively for the ground and first excited states. If electron conjugation is important, then an increase in the rotational barrier is expected with electronic excitation (similar to the case of butadiene). The results of such calculations are shown in Figures 5 and 6, in which the torsional angle 0° belongs to the *trans*-conformation. It is apparent that the rotational barrier for vinylcyclopropane is somewhat increased by excitation (analogous to butadiene) whereas for cyclopropanecarbaldehyde the barrier is lowered. Conjugation effects are therefore only important in the former case.

Mass spectrometry of organic molecules offers a broad, hardly touched field of application for MO theory[35,36]. Analysis of conformational changes and charge distributions in the dissociating ions is common in the literature of this field. Thus, for example, it is assumed that in the McLafferty rearrangement of the butyric acid ion a proton migrates from the γ position to the carbonyl group in a six-membered transition state



whereupon the C—C bond between the α and β C-atoms is broken and ethylene is eliminated. It is *a priori* not possible to decide which of these two steps determines the rate of the overall reaction. EHT calculations for several conformations of the transition state show that the proton migration and not the dissociation of the C—C bond determines the activation energy of the rearrangement.



Moreover, the EHT calculation explains why in the analogous case of 2,4-pentadione the McLafferty rearrangement assumes only minor importance. In this case it is calculated that the activation energy for the H transition is substantially greater than for butyric acid and the energy of the C_α-C_β bond in the rearranged ion is even slightly stronger than in the initial state.

5. Calculation of Reaction Rate Constants

Since the Schrödinger equation contains the time as well as the coordinates of all the atomic nuclei of a system, every imaginable reaction kinetic situation must in principle be reducible to this basis. A practical way of doing this is to solve separated Schrödinger equations for the individual states of motion (see Section 3) and to consider the statistical distribution of energy states, *i.e.* to ascertain the partition functions previously mentioned (Section 2). (The explicit time-dependence of the Schrödinger equation is only important in special cases, for example for radiative transitions between electronic states.) For many important (and most thermal) reactions the electronic partition function is equal to one, *i.e.* only *one* electronic state is occupied during the entire reaction (adiabatic reaction). The application of the Schrödinger equation to this state then requires the calculation of the electron energy E as a function of the coordinates of all nuclei of the reacting system. In the simplest case, dissociation of a diatomic molecule, E is dependent on only *one* coordinate, the internuclear distance (which is therefore also the reaction coordinate), and may be graphically portrayed as a potential curve. In general, however, E is a many-dimensional potential energy surface on which the special route of least energy expense is singled out as the reaction coordinate. The activation energy of

the reaction is determined by the saddle point along the reaction coordinate.

Considering the difficulties which arise in an MO theoretical calculation of the electronic energy for only one nuclear configuration of a given molecule it is obvious that the calculation of the activation energy in general represents a formidable computational task. Simplifications are possible in cases where the reaction coordinate is known, for example the rotation about a bond or other elementary isomerizations (Section 4). In other cases plausible theoretical models exist which determine the reaction coordinate. Two important models of this type for which tested programs exist in the Mülheim computing center will be described in the following sections.

5.1. BEBO Method

The BEBO method[*] allows the calculation of activation energies and reaction rate constants in the important special case of H atom transfer reactions[37]:

$$AH + B \rightleftarrows A\cdots H\cdots B \rightarrow A + HB \qquad (15)$$

In this model it is taken that the bond HB is partially formed during the reaction before the A—H bond is completely broken: The reaction coordinate is defined by assuming conservation of bond order, *i.e.* the sum of the bond orders of A ··· H and H ··· B should be equal to one along the reaction coordinate.

Application of this concept assumes further that a well-defined relationship exists between bond order and bond length on the one hand and bond energy and bond order on the other. Such relationships are verified by a great amount of empirical material so that it is possible to express the potential energy V along the reaction coordinate as a function of experimental single bond distances R_i and energies E_i:

$$V = f(E(A—H), E(H—B), R(A—H), R(H—B), R(A—B)) \qquad (16)$$

The maximum of V along the reaction coordinate corresponds then to the potential energy of activation V^*, which must be corrected for the zero point energies of the initial and transition states in order to obtain the theoretical value for the observable activation energy.

In the BEBO approximation, the transition state for the H atom transfer is interpreted as a linear triatomic species; one of the four normal vibrations of the transition state is omitted since it corresponds to the reaction coordinate. The remaining three normal vibrations represent a stretching and two degenerate bending modes for which at small amplitudes a parabolic potential can be assumed. The frequencies of these vibrations are then given directly by the masses of A and B and the force constants (*i.e.* the second derivatives of the potentials with respect to the corresponding normal coordinates).

The BEBO method suggests itself for application in all cases where the necessary data are already available. Starting with experimental single bond lengths determined by various methods[39] and *Pauling*'s single bond energies[38], the calculated activation energies shown in Table 4 are obtained; where available, literature values are shown for comparison. (In Table 4 the value 0 is given for those cases in which the potential V does not show a maximum along the reaction coordinate.) Since zero-point energies are not taken into account in Table 4, these values may be further improved. On the other hand, the BEBO values appear more questionable the smaller they become since the theoretical prerequisites of the normal coordinate

Table 4. Potential energy of activation, V^* in kcal/mole, calculated by the BEBO method. Values in parentheses taken from [40].

	F	O	H	Cl	C	N	Br	S	P	I	Si	Se	As
F—H	3.6		31.8 (35.0)										
O—H	0	3.2											
H—H	1.4 (1.7)	4.4 (5.2)	8.2 (8.0)				18.4 (19.4)			33.7 (33.5)			
Cl—H	0	0.7	4.3 (5.2)	0									
C—H	1.4 (1.2)	3.6 (8.3)	7.8 (7.4)	5.4 (3.9)	12.1 (14.1)		16.4 (18.2)			30.7 (35.0)			
N—H	0		2.8 (2.0)	0	5.0 (5.7)	2.9							
Br—H			1.7 (0.9)	0	5.1		0						
S—H			1.0	0	3.1 (4.1)		1.1	0					
P—H			1.8	0					2.6				
I—H			0.9 (0.7)	0	3.3 (2.3)					0			
Si—H	1.0	0.5	1.7	0	3.6		0	0.8		0	3.1		
Se—H			0									0	
As—H			0	0			0			0			0

[*] Derived from **B**ond **E**nergy and **B**ond **O**rder.

analysis are no longer fulfilled. On the whole, comparison between experimental activation energies and calculated V^* values shows a very satisfactory agreement.

Table 5. Kinetic isotope effects at room temperature for H abstraction by radicals, calculated by the BEBO method.

Reaction 1:	$C_2H_6+C_2H_5$	$C_2H_6+C_2H_3$	$C_2H_6+C_2H$	$C_2H_4+C_2H_3$	$C_2H_4+C_2H$	$C_2H_2+C_2H$
Reaction 2:	$C_2D_6+C_2D_5$	$C_2D_6+C_2D_3$	$C_2D_6+C_2D$	$C_2D_4+C_2D_3$	$C_2D_4+C_2D$	$C_2D_2+C_2D$
k_1/k_2	28.9	23.9	5.5	29.7	10.4	32.1

A special application of the BEBO method is the calculation of kinetic isotope effects which, among others effects, must be considered in mechanistic investigations of reactions in radiation chemistry. As the examples in Table 5 show, the kinetic isotope effect is large and is determined essentially by the quantum mechanical tunnel effect. An experimental confirmation of the calculated values in Table 5 has yet to be provided.

For the application of the BEBO method the computation expense is relatively small. The Mülheim program requires only 8000 storage locations; the computing times are typically of the order of 10 s and are slightly dependent on the temperature of the system considered.

5.2. Quasi-equilibrium Theory of Mass Spectra

At low pressures—for example in a mass spectrometer, and also in gas reactions—the rate constant k of a unimolecular decomposition depends not only on the activation energy E_A of the decomposition reaction but also on the internal energy E of the molecule. The theory of mass spectra formulated by *Rosenstock, Wallenstein, Wahrhaftig,* and *Eyring*[41] assumes that the rate at which energy supplied to the molecule (for example by electron impact or photoionization) is distributed over all the vibrational degrees of freedom is always large compared to the rate of decomposition. There then exists a quasi-equilibrium distribution of states which can be ascertained by the methods of statistical mechanics. For the energy-dependent rate constant *Rosenstock et al.* derived the expression

$$k(E) = \frac{s}{h} \frac{W^*(E-E_A)}{\rho(E)} \qquad (17)$$

where s is a symmetry factor (number of equivalent decomposition paths), $W^*(E-E_A)$ the number of states of the activated complex with energy greater than E_A, and $\rho(E)$ the density of states between E and $E+dE$. W^* and ρ depend in a complicated manner on the normal vibrations of the molecule, which for application of the theory must be known input parameters.

The program available at Mülheim (QET) is essentially an adapted version of the original IBM program written by *Vestal*[42]. It may be applied to molecules with up to 100 degrees of freedom and a total of 25 primary, secondary, and tertiary decomposition modes and delivers information on: breakdown spectra of ions, intensities of metastable ions, kinetic energies of fragments, and temperature dependence of mass spectra. As an illustration, the breakdown graphs of ions from methane are shown in Figure 7.

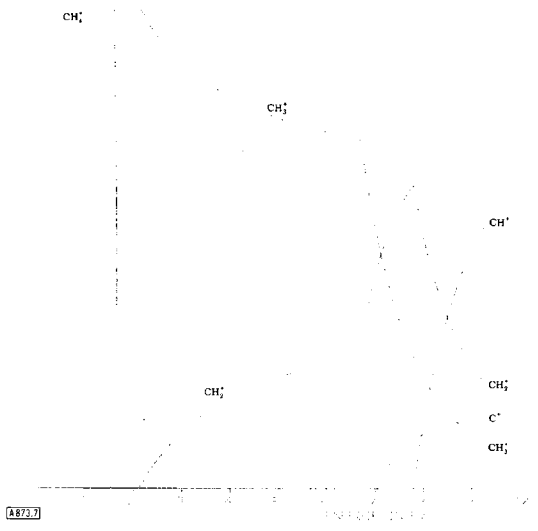


Fig. 7. Breakdown graph for the methane ion (plotter drawing) from the quasi-equilibrium theory (relative ion intensity as a function of the energy content of the molecule in excess of the ionization energy). Each vertical line (E = constant) defines a "mono-energetic mass spectrum" (sum of the intensities = 1).

For each point of the energy scale (corresponding to energy in excess of the ionization energy supplied to the methane molecule) the graph shows an intensity distribution of fragments of the methane ions (the intensities are normalized to unit sum). Thus it may be seen from Figure 7 that CH_4^+ with an energy content higher than 1.7 eV is completely decomposed into CH_3^+. Since CH_4^+ corresponds to the most intense line in the mass spectrum of methane it is clear that, in general, only a small fraction of the usual 70 eV carried by the ionizing electrons is transferred to the methane molecule.

The QET program requires *ca.* 33000 core locations and a relatively large expense in computer time which increases sharply with the size of the molecule and the number of decomposition reactions. About 4 minutes computing time is required to calculate the mass spectrum of ethane (with ten decomposition reactions).

6. Integration of Kinetic Equation Systems

A computing problem *par excellence* is the evaluation of data resulting from pulse radiolysis studies. Pulse radiolytic systems are characterized by a large number of parallel and consecutive reactions all having similar rate constants. Thus it is not possible to neglect several reactions in com-

parison to a rate determining step as is often done in reaction kinetics. Instead, one must solve numerically the total system of coupled, nonlinear differential equations which corresponds to the chemical reaction system. Since the raw data (changes in optical density as a function of time) as a rule do not have the desired exactness, the evaluation can only be carried out through comparison with model calculations and not by computational search for an unknown reaction scheme involving the measured values.

For adapting a given reaction scheme to the measured data, programs are generally used which achieve an optimum determination (in the sense of the least squares method) of the rate constants and activation energies from concentration *vs.* time measurements. Starting with estimated values of the rate constants the system of differential equations is solved iteratively; after each iteration an improvement of the estimated values is made. The technique was applied in the elucidation of thermal isomerization in the cyclodecatriene series[43].

I thank Dr. F. Mark for several important suggestions and Dr. P. Potzinger for critically reading the manuscript.

Received: November 18, 1971 [A 873IE]
German version: Angew. Chem. *84*, 418 (1972)
Translated by Dr. *L. C. Glasgow*, Mülheim/Ruhr

[1] *K. B. Wiberg:* Physical Organic Chemistry. Wiley, New York 1964.

[2] *J. A. Pople* and *D. L. Beveridge:* Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970.

[3] *P. M. Kuznesof*, QCPE 94.

[4] *M. J. S. Dewar*, QCPE 136.

[5] *J. O. Hirschfelder, C. F. Curtiss,* and *R. B. Bird:* Molecular Theory of Gases and Liquids. Wiley, New York 1954, p. 1044.

[6] *M. Born* and *R. Oppenheimer*, Ann. Physik *84*, 74 (1927).

[7] *F. A. Matsen*, J. Amer. Chem. Soc. *92*, 3525 (1970).

[8] *V. Fock*, Z. Physik *61*, 126 (1930).

[9] *P. Gombas:* Die statistische Theorie des Atoms und ihre Anwendungen. Springer, Vienna 1949.

[10] *G. S. Handler* and *S. Golden*, J. Chem. Phys. *44*, 1812 (1966).

[11] Cf. *G. von Bünau*, Habilitationsschrift, Technische Universität Braunschweig 1971.

[12] *H. A. Jahn* and *E. Teller*, Proc. Roy. Soc. *A 161*, 220 (1937).

[13] *J. R. McNesby*, Actions chim. et biol. radiations *9*, 37 (1966).

[14] *R. Pauncz, J. de Heer,* and *P. O. Löwdin*, J. Chem. Phys. *36*, 2247, 2257 (1962).

[15] *J. A. Pople, D. P. Santry,* and *G. A. Segal*, J. Chem. Phys. *43*, 129 (1965).

[16] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); see also QCPE 30, 64, and 95.

[17] *B. J. Duke*, Theoret. Chim. Acta *9*, 260 (1968).

[18] *M. Klessinger* and *R. McWeeny*, J. Chem. Phys. *42*, 3343 (1965).

[19] *M. Klessinger*, J. Chem. Phys. *43*, 117 (1965).

[20] *J. A. Pople, D. L. Beveridge,* and *P. A. Dobosh*, J. Chem. Phys. *47*, 2026 (1967); see also QCPE 141, 142, and 144.

[21] *H. Preuss*, Mol. Phys. *8*, 157 (1964).

[22] *M. L. Benston* and *D. P. Chong*, Mol. Phys. *14*, 449 (1968).

[23] *N. Baird* and *M. J. S. Dewar*, J. Chem. Phys. *50*, 1262 (1969); see also QCPE 137.

[24] *W. Kutzelnigg*, Theoret. Chim. Acta *1*, 327 (1963).

[25] *P. O. Löwdin*, Phys. Rev. *97*, 1474 (1955).

[26] *J. W. Linnett*, J. Amer. Chem. Soc. *83*, 2643 (1961).

[27] *D. M. Hirst* and *J. W. Linnett*, J. Chem. Soc. *1962*, 1035, 3844.

[28] *O. E. Polansky* and *G. Derflinger*, Int. J. Quantum Chem. *1*, 379 (1967).

[29] *R. Pariser* and *R. G. Parr*, J. Chem. Phys. *21*, 466, 767 (1953).

[30] *J. A. Pople*, Trans. Faraday Soc. *49*, 1375 (1953).

[31] *L. S. Bartell* and *J. P. Guillory*, J. Chem. Phys. *43*, 647 (1965).

[32] *H. Günther* and *D. Wendisch*, Angew. Chem. *78*, 266 (1966); Angew. Chem. internat. Edit. *5*, 251 (1966).

[33] *W. Lüttke* and *A. de Meijere*, Angew. Chem. *78*, 544 (1966); Angew. Chem. internat. Edit. *5*, 512 (1966).

[34] *G. R. DeMare* and *J. S. Martin*, J. Amer. Chem. Soc. *88*, 5033 (1966).

[35] *J. C. Lorquet*, Mol. Phys. *9*, 101 (1965).

[36] *K. Hirota* and *Y. Niwa*, J. Phys. Chem. *72*, 5 (1968).

[37] *H. S. Johnston:* Gas Phase Reaction Rate Theory. Ronald Press, New York 1966.

[38] *L. Pauling:* The Nature of the Chemical Bond. Cornell University Press, Ithaca 1960, 3rd. Edit.

[39] Chemical Society, Spec. Publ. No. 11: Tables of Interatomic Distances and Configuration in Molecules and Ions. London 1958 and 1965 (Suppl.).

[40] *A. F. Trotman-Dickenson* and *G. S. Milne:* Tables of Bimolecular Gas Reactions. NSRDS-NBS 9, Washington 1967.

[41] *H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig,* and *H. Eyring*, Proc. Nat. Acad. Sci. U.S. *38*, 667 (1952).

[42] *M. Vestal* and *G. Lerner*, ARL 67-0114 (1967).

[43] *B. Weimann*, to be published.

Glossary of Some Computer Terms

A/D converter (Analog-to-Digital converter)—a device for converting an analog value (usually an electrical voltage) into a numerical representation.

Batch operation—programs are processed sequentially, possibly in parallel running "batch streams" ("multiprogramming batch"). No interactive work.

Bit—a digit position in the binary number system; derived from "*b*inary dig*it*".

Byte—a group of binary positions (bits) treated as a unit. Most byte-oriented computers work with 8-bit bytes. One character (letter or number) is stored in a byte. Word-oriented computers (for example, the PDP10) sometimes offer instructions which permit working with variable-length bytes.

Byte instructions—computer instructions which manipulate bytes.

Channel status—the current state of the parameters characteristic for data acquisition, for example, "active", "inactive", data rate, run-time.

Closed-loop operation—experimental parameters are controlled by the computer during an experiment by analyzing measured values.

Core image—the momentary state of a program in memory during program execution.

Contact scanner—a device which enables the computer to determine the state of on-line instruments and register related signals (for example, start and stop signals).

Conversational time-sharing operation—a time-sharing system (see definition) which permits a programmed dialog between the user and the computer.

Data buffer—temporary storage for accumulating data. The use of data buffers allows a more rational handling of data.

Data rate—transfer rate of data, expressed in words, bits, bytes, data points, *etc.*, per unit time.

Data reduction—decreasing the extent of information of measured data to an amount or form essential to a problem.

D/A converter (Digital-to-Analog converter)—see A/D converter.

Dedicated system—a system in which a computer is used strictly for the data acquisition and processing for one single instrument (or a group of instruments of the same type, for example several chromatographs).

Disk—a magnetic data storage medium. Several magnetic disks can be grouped in a stack on a rotating axis. One distinguishes between a fixed-head disk (one read/write head per concentric path) and a movable-head disk (one head per surface).

Enable—a condition which exists when several switching signals yield a "true" value in an AND function.

Failsafe system—a computer system which is safeguarded against failures of hardware and software components.

Floating-point instructions—instructions for processing data coded in floating-point format, that is, data expressed as an exponent and a mantissa.

Hardware—the material part of a computer system.

High-level programming language—allows the user to express algorithms in a computer independent form; a problem oriented as opposed to computer oriented form of expression. FORTRAN and BASIC are two such languages.

"Integrated" instrument—an instrument with a "built-in" computer; sometimes also called an "instrument computer".

Interactive time-sharing operation—see conversational time-sharing operation.

Interface—an electronic adapting unit between instrument and computer.

Interrupt system—an arrangement whereby brief interruptions of the running program are permitted if a data word (or byte) is to be transferred to or from a peripheral unit.

Job—a sequence of tasks for the computer which are initiated by a user at a terminal (or by submission of a deck of cards).

K—abbreviation for $2^{10}=1024$. For example, a core memory capacity of 32 K words corresponds to $32 \times 1024 = 32768$ words.

Line-driver—a unit which allows the program-controlled opening and closing of circuits, and therefore the control of on-line instruments.

Monitor—see operating system.

Multi-mini system—a computer system which is made up of several small computers. One of them can function as the central processor and all of the others are connected to it. The small computers can also be organized in a network fashion.

Multiplexer—a device used if a data path is to be switched among several instruments; in on-line systems a multiplexer is used with an A/D converter common to several instruments.

Off-line operation—the computer processes jobs which, in contrast to on-line operation, have no real-time requirements.

On-line operation—the computer is directly coupled to analytical instruments.

Operating system, monitor—an executive or controlling program which regulates the progress of computer operation, that is, the distribution of computing time, the allocation of core storage, and the use of peripheral units for the different jobs.

Periphery—the "exterior" devices of the computer such as card readers, magnetic tapes, and line printers.

Priority levels—a graduated hardware interrupt system allows not only program interruption, but permits a data

transfer between the computer and its periphery according to speed requirements and real-time demands; data transfers in progress on lower priority levels are interrupted if an interrupt signal is received for a level of higher priority. Besides such hardware priority levels, there are also software priority levels in the form of different queues, in which the programs to be run are placed, depending on their instantaneous status, requirements, size, *etc.*

Process-control computer—a computer which is used for supervision and control of experiments, manufacturing processes, and so on.

Random access—a programmed reading or writing of data on a storage medium independent of where the data is actually stored. Possible with magnetic disks, drums, and core storage, but not with magnetic tapes, paper tapes, *etc.*, that have to be read or written serially.

Real-time data acquisition—the computer takes data from an analytical instrument in real-time, that is (with a delay of a few microseconds) during the measurement.

Satellite computer—a subordinate (small) computer for handling tasks given to it by a central computer.

Software—computer programs; one distinguishes between "system software" (necessary for operation or the support of the operation) and "application software" (problem-oriented programs).

Swapping operation—movement of programs (in the form of their core images) between disk or drum units and core storage, should total core capacity be insufficient to hold all currently active programs.

Teletype—a company product designation which has become a common term to mean any input/output typewriter-like device used as a computer terminal.

Terminal—data station (for example, teletype, display device) which allows the user to communicate with the computer.

Text editor—a program for the creation and correction of programs and data sets by type-in from a terminal.

TI correction—correction of intensity distortions caused by pressure changes during the running of a mass spectrum.

Time-sharing system—a system which allows several users to work with the computer simultaneously.

TTY—an abbreviation for teletype (see definition).

[A 875 IE]
German version: Angew. Chem. *84*, 429 (1972)

An Alternative Approach to the Nomenclature of Cyclic Conjugated Polyolefins, together with some Observations on the Use of the Term "Aromatic"

By Douglas Lloyd and D. R. Marshall[*]

So much ambiguity and disagreement has arisen concerning the usage of the word 'aromatic' that it might be better to discontinue the use of this term.

1. Introduction

The term 'aromatic' is remarkable in organic chemistry for the variety of meanings and interpretations which have been ascribed to it in more than a century of use. Perhaps even more remarkable is the fact that although this word is one of the commonest used by chemists, it has no firmly defined meaning and different individuals may mean very different things by the term. This indeterminacy stems to a large extent from its checkered history with ever-changing meaning.

In recent years a number of definitions, some more satisfactory and explicit than others, have been made but on the whole each individual tends to use the term to suit his own preconceived ideas. Furthermore, the avidity with which contemporary chemists use this magic term was commented on by a speaker at a recent symposium on "Aromaticity, Pseudoaromaticity, Antiaromaticity"[1] who described it as the modern chemists' equivalent of being possessed by devils.

2. Original Meaning and Changes in Meaning of the Term "Aromaticity"

The term 'aromatic' was first applied by chemists in the early part of the nineteenth centry to describe compounds which had an aromatic odour and which had been isolated

[*] Dr. D. Lloyd
Department of Chemistry, Purdie Building
University of St. Andrews
St. Andrews Fife (Scotland)
Dr. D. R. Marshall
Department of Chemistry, University College of North Wales
Bangor Caernarvonshire (Wales)

from many volatile vegetable oils. Its meaning was thus the same as the everyday non-scientific meaning.

It was soon noticed that many of these 'aromatic' compounds contained relatively more carbon than the so-called 'aliphatic' organic compounds which had been obtained from fats, and they were described by *Kekulé* in the 1860's as "Kohlenstoffreichere Verbindungen"[2]. When it was recognized that these carbon-rich compounds were derivatives of benzene, the term 'aromatic' was appropriated to convey a structural meaning instead of its hitherto purely descriptive meaning, namely a derivative of benzene.

When *Kekulé* first proposed the cyclohexatriene structure for benzene[2], he commented on the particular stability of this ring-system and in effect defined aromatic compounds as benzene derivatives.

Kekulé's use of the word 'aromatic' was thus based on *structural features*, but almost at once the suggestion was made by *Erlenmeyer*[3] that the concept of aromaticity should be based on *properties* of compounds and encompass substances of similar behavior rather than those with a common structural feature. Thus the seeds of mid-twentieth century confusion about the meaning of the term were sown over a hundred years ago and almost as soon as the structure of benzene was elucidated. The possibility of these two alternative interpretations has subsequently bedeviled organic chemistry.

When *Armit* and *Robinson*[4] formulated the concept of the 'aromatic sextet' in 1925 they also made the observation that aromatic compounds were characterized by "reduced unsaturation and the tendency to retain the type", as shown, for example, by their tendency to undergo substitution rather than addition reactions. Here aromaticity is clearly being considered in terms of the properties of compounds rather than in structural terms.

Hückel's rule, propounded in the 1930's[5], which states that "amongst fully conjugated, planar, monocyclic polyolefins only those possessing $(4n+2)$ π-electrons, where n is an integer, will have special electronic stability", also implies a relationship between aromatic character and properties, in particular the stability of compounds. Both *Armit* and *Robinson*, and *Hückel*, introduced another factor by associating aromaticity with particular electronic structures.

Aromaticity had thus been correlated with structural features, with chemical reactivity (or lack of it), with electronic structures or with stability, the latter term being capable of further sub-divisions of interpretation.

3. Some Modifications in Nomenclature

Until more recent times this ambiguity of definition was not of great import, for the compounds which had aromatic properties or stability were benzene derivatives and whatever fundamental definition was used, the same set of compounds was being described. In fact 'aromatic compound' was in effect a synonym for 'benzene derivative'. The only difficulty encountered was with certain five-membered ring heterocyclic compounds, which in some, but not all, respects resembled benzene derivatives in their properties, and of course, did not have a benzene-like structure.

Following the stimulus supplied by the appreciation of the significance of Hückel's rule, a plethora of so-called 'non-benzenoid aromatic compounds' has been described[6]. These compounds resemble benzene in having closed cyclic conjugated systems of electrons but they do not have the particular structural feature of benzene derivatives, namely the six-membered ring. Nor do they necessarily have the properties which until recent decades were considered as characteristic of aromatic systems, for example the ability to undergo electrophilic substitution reactions, or a resistance towards oxidizing agents.

Not surprisingly the tropylium cation, accepted as an example of a non-benzenoid aromatic structure in the terms of Hückel's rule, does not react with electrophiles. For example no exchange of deuterium for hydrogen is observed either on prolonged treatment with concentrated deuteriosulfuric acid or with a solution of aluminum bromide in deuteriobromic acid, conditions under which benzene undergoes hydrogen/deuterium exchange almost instantaneously[7]. At the other end of the scale, [18]annulene, an example of a non-benzenoid aromatic hydrocarbon, decomposes in a short time on standing[8], and only undergoes electrophilic substitution under carefully defined conditions[8, 9]. Indeed not even all benzene derivatives are typically 'aromatic' in their chemical behavior.

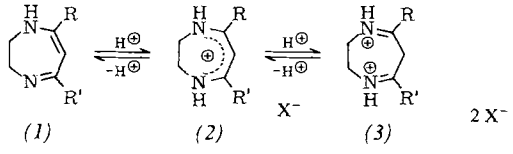
Confusion has been made worse by the introduction of further terms indicating modified aromaticity such as 'pseudo-aromatic'[10] and 'anti-aromatic'[11, 12]. An anti-aromatic system has been defined as one in which electron delocalization considerably raises the energy of the molecule[11, 12], and has been applied to cyclic peripherally conjugated polyolefins. The results of kinetic measurements on hydrogen-deuterium exchange in a number of cyclopropene derivatives have been interpreted on this basis[12, 13]. A typical property of anti-aromatic compounds is the paramagnetic ring-current observed in annulenes and dehydroannulenes having $4n$ π-electrons[14].

Pseudo-aromatic molecules have been defined[15] as those with non-totally symmetric ground states, a symmetry criterion which, for molecules with only peripheral conjugation, also applies to those having $4n$ π-electrons. It had been frequent practice to describe all non-aromatic cyclic conjugated systems as pseudo-aromatic but this term does not draw attention to the destabilization which may be observed in $4n$ π-electron systems.

We have contributed to this list of terms denoting modified aromaticity by attempting to make a definition[16] of the term 'quasi-aromatic'[17] as follows: "We propose that molecules should be called quasi-aromatic only if they contain an acyclic conjugated π-electron system and show chemical properties typical of aromatic compounds, especially reaction by substitution with retention of type. A significant mesomeric stability is implied"[16]. This definition was rightly criticized by *Marchand*[18] who said that there was a need to resolve the meaning of aromaticity in some suitable physical terms before introducing such extra terms as quasi-aromatic.

3.1. The Example of 2,3-Dihydro-1,4-diazepinium Salts

We had used the term "quasi-aromatic" to describe the behavior of 2,3-dihydro-1,4-diazepinium salts *(2)*. These compounds have proved to be excellent substrates for the



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

examination of 'quasi-aromatic' character. The ring structure serves to fix the conjugated system in a favorably stable conformation. On the other hand it is clear that the ring cannot be 'aromatic' in the classic structural sense because the conjugation does not extend all round the ring, part of which is formed of sp^3-hybridized carbon atoms. Since these dihydrodiazepinium salts have been the subject of an intensive chemical investigation by us[19], we have used this system specifically to provide examples to support our arguments. Other complementary examples might be taken, for example, from the chemistry of the corrins[20], which contain the same kind of conjugated system included within a larger ring structure, or of open-chain analogs, namely the salts of α,ω-diazapolymethines[20a], or of the transition-metal chelates of β-diketones[21, 22, 23a]. (It had been argued that the latter compounds might have complete cyclic conjugated systems involving the metal atom[22] but later workers are not in agreement with this interpretation[23]. An excellent review of the position concerning these chelates has recently been given by *H. Musso et al.*[23a].)

2,3-Dihydro-1,4-diazepinium salts possess an extremely stable electronic system which resists breakdown and are characterized by a great "tendency to retain the type"[4]. Their stability constants (with respect to the diamines and dicarbonyl compounds formally derived from them by hydrolysis) are high, mostly $\sim 10^6$—10^9[24]. The monocation *(2)* is the predominant species over a very wide pH range, for the pK_a values for the equilibrium with the related bases *(1)* are usually ~13—14[25, 26], while only in >70% sulfuric acid do the dications *(3)* predominate over the monocations[27]; this suggests an effective resonance energy of 20—30 kcal/mol.

The chemical similarity of the dihydrodiazepinium salts to benzenoid compounds is demonstrated by the ease with which they undergo typical 'aromatic' substitution reactions. Thus they are readily halogenated[28], and nitrated[29, 30], and, although they are cations, couple with diazonium ions[31]. The resultant 6-nitrodihydrodiazepinium salts can be reduced to typically 'aromatic' amines[30, 32]—for example with nitrous acid they form diazonium salts[30, 32].

All of these chemical properties and reactions are just those which have always been firmly associated with what have been called aromatic compounds, yet, as stated previously, in no classical structural sense can dihydrodiazepinium salts be considered to be aromatic compounds. This illustrates nicely the pitfalls of trying to use chemical reactivity as an index of 'aromaticity'.

Other definitions of aromaticity in terms of some particular properties appear commonly to include some subjective judgment to decide where the boundary between 'aromatic' and 'non-aromatic' shall be drawn. In fact in many cases hitherto, compounds have been described as aromatic without any real definition.

A structural definition, restricting its usage to that prevalent in most text-books of general organic chemistry, namely as a synonym for 'benzenoid' would be unambiguous but it is questionable if such a tautological exercise has any value.

The present attitude towards 'aromaticity' is coming to resemble a medieval theological disputation and the time has come when a reformation (or a counter-reformation) is needed.

4. New Suggestions and Definitions

We suggest that because of this confusion and lack of common consent as to its meaning[33], it would be better if the use of the term 'aromatic' were discontinued, save perhaps with its general and original connotation of 'perfumed', and that it should pass with other technical terms which have outlived their precision and usefulness, into the realm of the historian of chemistry.

The term "arenes", presently defined as "the generic name of monocyclic and polycyclic hydrocarbons"[34] should be specifically restricted to benzenoid hydrocarbons; "aryl" derivatives should be similarly defined. We also repeat our suggestion[35] that it is preferable to denote derivatives of benzene as "benzenoid" rather than "aromatic". This word is unambiguous. Alternatively "aryl" could be used as long as its meaning is rigorously defined as suggested[*].

We would also suggest that cyclic conjugated systems in general should be termed simply as either *Hückel* or *anti-Hückel* (or for the larger annulenes *non-Hückel*) systems[**], these terms replacing, respectively, what is probably the most general present-day usage of "aromatic" and "anti-aromatic", namely the energetic criterion, as defined, for example, by *Breslow*[12] and *Dewar*[36]. This replacement is however necessary just because of the lack of a universally recognized usage or meaning of the troublesome term "aromatic".

The terms benzenoid or aryl would thus refer to structural features and the terms Hückel or anti-Hückel (or counter-Hückel) to ground-state stability.

---

[*] Professor *M. Cais* (private communication) has suggested that the continued use of terms such as "benzene-like" or "benzenoid-like" might be helpful in discussing and comparing properties of non-benzene derivatives with those of benzene; for example it might be useful to talk about the benzene-like properties of ferrocene.

[**] There may be semantic, and indeed more than semantic, objections to the use of the term 'anti-Hückel', since Hückel theory did not embrace any concept of conjugative destabilization of $(4n)$-π-electron systems. However, since the name of Hückel is so firmly associated with the stability of $(4n+2)$-π-electron systems, it seems worthwhile to maintain this association. If $(4n)$-π-electron systems show opposite properties, it would then seem reasonable to denote this by "opposite to Hückel", *i. e.* anti-Hückel. An alternative and probably preferable term would be "counter-Hückel".

Since for more than a century "aromatic" also embraced a characteristic sort of reactivity, namely the tendency to undergo substitution rather than addition reactions, we consider that it would be useful to have a specific term to mean "the tendency to retain the type"[4]. We suggest as possible words to describe such behavior either *regenerative* or *meneidic*. The former word is descriptive of the process which takes place—the original electronic system is regenerated after being temporarily lost in the transition state; the latter word is of Greek origin (from *menein*, to stay, persist, remain; and *eidos*, type, form)[37]. Thus benzene normally behaves as a regenerative or meneidic system; ethylene does not.

The terms regenerative or meneidic need not necessarily be confined to electrophilic substitution reactions. Pyridines and nitrobenzenes show their regenerative or meneidic character equally well in their substitution reactions with nucleophiles. Similarly the various carboxyl derivatives, acids, esters, amides, *etc.* show regenerative or meneidic character in their reactions. The terms might also be considered to embrace substitution at sp^3-hybridized as well as at sp^2-hybridized atoms, but it is intended that they should be restricted to the latter and to what have been described as S_A (for substitution through association) reactions[38], wherein a new bond is formed before the old bond breaks. Any loosening of this restriction would destroy the convenience of the term by making it less specific in its meaning.

We thus propose this change in nomenclature, wherein we differentiate between structural features, ground-state properties, and chemical reactivity. These three factors had all at different periods been regarded as criteria for aromaticity. Unfortunately these criteria are not always compatible and compounds may not satisfy them all equally well, and it becomes a matter of opinion whether or not a compound is "aromatic". For this reason and the consequent wide diversion in the interpretation of the term we suggest that its use should be discontinued.

We propose that the terms *arenes*, *aryl*, and *benzenoid* be used to denote a *structural* feature, namely the presence of a benzene ring, *Hückel* and *anti-Hückel* (or *counter-Hückel*) to refer to *ground-state properties*, and either *regenerative* or *meneidic* to refer to *chemical reactivity*, namely the tendency of an unsaturated molecule to react by substitution rather than addition[*].

In keeping with these suggestions we would, for example, describe 2,3-dihydro-1,4-diazepinium salts as compounds which, although they are not Hückel compounds, are none the less examples of molecules having regenerative or meneidic character.

We wish to acknowledge the contribution which discussions with friends, especially Dr. A. R. Butler of the University of St. Andrews and Professor J. R. Nunn of Rhodes University, Grahamstown, made to the form of this paper. Some of the material presented in the paper formed part of a lecture delivered by Douglas Lloyd at a symposium which has been published (1971) by the Israel Academy of Sciences and Humanities[39].

Received: February 22, 1971 [A 874 IE]
revised: September 20, 1971
German version: Angew. Chem. *84*, 447 (1972)

[*] It has also been suggested [40] that molecules showing diamagnetic, paramagnetic and no ring-currents be called, respectively, *diatropic*, *paratropic*, *atropic*. Although, in general, diatropic and paratropic molecules would be the same ones that we call *Hückel* and *Counter-Hückel*, this nomenclature refers specifically to magnetic properties, whereas Hückel and Counter-Hückel refer fundamentally to energetic properties.

[1] International Symposium on "Aromaticity, Pseudoaromaticity and Antiaromaticity", Jerusalem, March—April, 1970.

[2] *F. A. Kekulé*, Bull. Soc. Chim. France [2], *3*, 98 (1865); Liebigs Ann. Chem. *137*, 129 (1866); Ber. dtsch. chem. Ges. *2*, 362 (1869).

[3] *E. Erlenmeyer*, Liebigs Ann. Chem. *137*, 327 (1866).

[4] *J. W. Armit* and *R. Robinson*, J. Chem. Soc. *127*, 1604 (1925).

[5] *E. Hückel*, Z. Physik *70*, 204 (1931); *72*, 310 (1931); Grundzüge der Theorie ungesättigter und aromatischer Verbindungen. Verlag Chemie, Berlin 1938.

[6] See *D. Lloyd*, Carbocyclic Non-benzenoid Aromatic Compounds, Elsevier, Amsterdam 1966.

[7] *K. I. Zhdanova, L. N. Vinogradov*, and *V. R. Kalinachenko*, Doklady Akad. Nauk SSSR *102*, 779 (1955).

[8] *F. Sondheimer, R. Wolovsky*, and *Y. Amiel*, J. Amer. Chem. Soc. *84*, 274 (1962).

[9] *F. Sondheimer*, Pure Appl. Chem. *7*, 363 (1963); *I. C. Calder, P. J. Garratt, H. C. Longuet-Higgins, F. Sondheimer*, and *R. Wolovsky*, J. Chem. Soc. *C 1967*, 1041.

[10] See, *e.g. D. P. Craig* in *D. Ginsburg*: Non-benzenoid Aromatic Compounds. Interscience, New York 1959, Chapter 1.

[11] See, *e.g. R. Breslow*, Chem. Engng. News *43*, No. 26, p. 90 (1965); Angew. Chem. *80*, 573 (1968); Angew. Chem. internat. Edit. *7*, 565 (1968).

[12] *R. Breslow, J. Brown*, and *J. Gajewski*, J. Amer. Chem. Soc. *89*, 4383 (1967).

[13] *R. Breslow* and *M. Douek*, J. Amer. Chem. Soc. *90*, 2698 (1968).

[14] *J. A. Pople* and *K. G. Untch*, J. Amer. Chem. Soc. *88*, 4811 (1966); *F. Sondheimer, I. C. Calder, J. A. Elix, Y. Gaoni, P. J. Garratt, K. Grohmann, G. Di Maio, J. Mayer, M. V. Sargent*, and *R. Wolovsky*, Chem. Soc. (London) Spec. Publ. No. 21, 75 (1967); *H. C. Longuet-Higgins, ibid.* No. 21, 109 (1967); *F. Baer, H. Kuhn*, and *W. Regel*, Z. Naturforsch. *22a*, 103 (1967); *H. J. Dauben, J. D. Wilson*, and *J. L. Laity*, J. Amer. Chem. Soc. *90*, 811 (1968).

[15] *D. P. Craig*, J. Chem. Soc. *1951*, 3175.

[16] *D. Lloyd* and *D. R. Marshall*, Chem. Ind. (London) *1964*, 1760.

[17] The term 'quasi-aromatic' was probably first used specifically by *L. Mester*, J. Amer. Chem. Soc. *77*, 4301 (1955).

[18] *A. P. Marchand*, Chem. Ind. (London) *1965*, 161.

[19] See the series of papers (I—XV) on diazepines by *D. Lloyd, D. R. Marshall et al.*; Part XV, J. Chem. Soc. *B 1971*, 1615.

[20] *R. Grigg, A. W. Johnson*, and *K. Richardson*, Chem. Commun. *1968*, 896; *A. Hamilton* and *A. W. Johnson*, J. Chem. Soc. *C 1971*, 3879.

[20a] *J. Kucera* and *Z. Arnold*, Coll. Czech. Chem. Commun. *32*, 1704 (1967).

[21] See *e.g.*: *H. Reihlen, R. Illig*, and *R. Wittig*, Ber. dtsch. chem. Ges. *58*, 12 (1925); *C. Djordjevic, J. Lewis*, and *R. S. Nyholm*, Chem. Ind. (London) *1959*, 122; *J. P. Collman, R. A. Moss*, and *W. S. Trahanovsky, ibid. 1960*, 1213; *J. P. Collman, R. A. Moss, H. Maltz*, and *C. C. Heindel*, J. Amer. Chem. Soc. *83*, 531 (1961); *R. W. Kluiber, ibid. 82*, 4839 (1960); *83*, 3030 (1961).

[22] *M. Calvin* and *K. M. Wilson*, J. Amer. Chem. Soc. *67*, 2003 (1945); *J. P. Collman, R. L. Marshall*, and *W. L. Young*, Chem. Ind. (London) *1962*, 1380; *R. E. Hester*, Chem. Ind. (London) *1963*, 1397; *J. P. Collman* in: Reactions of Co-ordinated Ligands, Amer. Chem. Soc. *1963*, p. 78.

[23] *R. H. Holm* and *F. A. Cotton*, J. Amer. Chem. Soc. *80*, 5658 (1958); *J. A. S. Smith* and *E. J. Wilkins*, J. Chem. Soc. *A 1966*, 1749; *R. C. Fay* and *N. Serpone*, J. Amer. Chem. Soc. *90*, 5701 (1968); *A. Trestianu, H. Niculescu-Majewska, I. Bally, A. Barabás*, and *A. T. Balaban*, Tetrahedron *24*, 2499 (1968); *M. Kuhr* and *H. Musso*, Angew. Chem. *81*, 150 (1969); Angew. Chem. internat. Edit. *8*, 147 (1969).

[23a] *B. Bock, K. Flatau, H. Junge, M. Kuhr*, and *H. Musso*, Angew. Chem. *83*, 239 (1971); Angew. Chem. internat. Edit. *10*, 225 (1971).

[24] *C. Barnett, D. R. Marshall*, and *D. Lloyd*, J. Chem. Soc. *B 1968*, 1536.

[25] *G. Schwarzenbach* and *K. Lütz*, Helv. Chim. Acta *23*, 1162 (1940).

[26] *D. Lloyd, R. H. McDougall*, and *D. R. Marshall*, J. Chem. Soc. *C 1966*, 780.

[27] *A. M. Gorringe*, Ph. D. Thesis, University of St. Andrews, 1968.

[28] *D. Lloyd* and *D. R. Marshall*, J. Chem. Soc. *1958*, 118; *R. P. Bell* and *D. R. Marshall, ibid. 1964*, 2195; *C. Barnett, H. P. Cleghorn, G. E. Cross, D. Lloyd*, and *D. R. Marshall, ibid. C 1966*, 93; *A. M. Gorringe, D. Lloyd, F. I. Wasson, D. R. Marshall*, and *P. A. Duffield, ibid. C 1969*, 1449; *D. Lloyd* and *D. R. Marshall*, Paper presented a meeting of the Heterocyclic Group of the Chemical Society, London 1970.

[29] *C. Barnett*, Chem. Commun. *1967*, 637; J. Chem. Soc. *B 1967*, 2436; *A. M. Gorringe, D. Lloyd, D. R. Marshall*, and *L. A. Mulligan*, Chem. Ind. (London) *1968*, 130.

[30] *A. M. Gorringe, D. Lloyd*, and *D. R. Marshall*, J. Chem. Soc. *C 1970*, 617.

[31] *E. M. Grant, D. Lloyd*, and *D. R. Marshall*, Chem. Commun. *1970*, 1320.

[32] *A. M. Gorringe, D. Lloyd*, and *D. R. Marshall*, Chem. Ind. (London) *1968*, 1160.

[33] As evidenced by every speaker at the Jerusalem symposium [1].

[34] IUPAC. Rule for the Nomenclature of Organic Chemistry A-12, 4.

[35] *D. Lloyd*: Alicyclic Compounds. Arnold, London and American Elsevier, New York 1963, p. 103; *D. Lloyd*: The Chemistry of Simple Organic Compounds. University of London Press, London 1964.

[36] *M. J. S. Dewar*, Chem. Soc. Spec. Publ. No. 21, 177 (1967).

[37] This term is based on a suggestion kindly made by Professor *K. J. Dover*, Department of Greek, University of St. Andrews.

[38] *E. M. Kosower*, An Introduction to Physical Organic Chemistry, Wiley, New York 1968, pp. 63ff.

[39] *D. Lloyd* and *D. R. Marshall* in: "Aromaticity, Pseudo-aromaticity, Anti-aromaticity". The Israel Academy of Sciences and Humanities, Jerusalem 1971, p. 85.

[40] *P. J. Garratt, N. E. Rowland*, and *F. Sondheimer*, Tetrahedron *27*, 3157 (1971).

Metal Ion Function in Carbonic Anhydrase

By R. H. Prince and P. R. Woolley[*]

The purpose of this review is to present an up-to-date account of the chemistry of the metal ion in the enzyme carbonic anhydrase. The interest lies in how the study of the metal may lead to deductions concerning the chemistry of the enzyme's action and in the way that metalloenzyme chemistry seems to demand a new appraisal of some aspects of the established chemistry of metal complexes.

1. Preliminary Consideration: The Properties of Metal Complexes

1.1. The Free Metal Ion

The gross features of coordination chemistry can be rationalized in terms of the quantum-mechanical picture of the metal ion built up by placing electrons in hydrogen-like orbitals. The electrons of a free ion in the ground state possess characteristic energy and charge distribution. These lead to a conception of ionic radius, net charge, and, in conjunction with excited states, polarizability. These three attributes are manifested in the metal ion's coordination chemistry as maximum coordination number, polarizing power, Lewis acid strength, stereochemical behavior, reactivity, *etc* (cf. for example ref. [1a]).

1.2. The Complexed Metal

Consider a metal ion M chelated by a ligand of fixed geometry L_c which leaves at least one open coordination site. This can be occupied by a ligand L'.

$$M + L_c \rightarrow ML_c$$

$$ML_c + L' \rightarrow L'ML_c$$

The complexation of M by L_c will modify the properties of M as compared either with the free ion or with the solvated ion. In addition, the properties of L_c and L' will be modified by coordination. The first, obvious change in the metal ion will be a reduction in the remaining number of vacant or solvated inner-sphere coordination sites when L_c is bound. Complexation of L_c will also result in a change of charge; overall, if L_c bears a net charge, and in the charge localized on the metal ion. This will be substantially reduced compared with the charge on the free ion, and will result in a rearrangement of electronic energies. If the complexation takes place in solution, the effect on charge localized upon the metal ion will correspond to the difference between complexation by L_c and by solvent molecules.

A change in local charge and in electronic energy in the metal ion will result in other changes; in polarizing power, which decreases as local charge decreases; in polarizability and redox potential[*]; and consequently in Lewis acid strength and hardness/softness of the metal towards L', and the inertness and stability of the M—L' bond.

1.3. The Complexed Ligands

There are three relevant comparisons: i) complexed L_c with free or solvated L_c; ii) complexed L' with free or solvated L'; and iii) the complex $L'ML_c$ with the complex L'M·solvent (*i.e.*, the effect of L_c upon the interaction between M and L').

[*] Dr. R. H. Prince and Dr. P. R. Woolley
University Chemical Laboratory
Lensfield Road
Cambridge CB2 1EW (England)

[*] Generally the former increases and the latter becomes more negative as the ligand's donor power increases.

i) Complexation of L_c will often induce a modification of its chemical reactivity; it will probably result in restrictions upon the stereochemical flexibility of L_c; and if L_c bears a negative charge then neutralization will occur—this will be most effective if the centers of negative charge are the donor atoms themselves, as in the case of carboxyl groups.

ii) The effect of complexation on L′ will be basically similar to the effect on L_c, although as L′ is monodentate it will, other things being equal, be more labile than L_c. The kind of modifications of reactivity which the metal ion might bring about are well known. They include the enhancement of almost any process which would bring more negative charge towards the metal ion, such as ligand deprotonation, or susceptibility to nucleophiles or to reducing agents.

iii) In what ways could $L'ML_c$ differ from L′M·solvent? One is the nature of the microenvironment of the M—L′ interaction; for example in a polar situation the chelating ligand could exclude polar molecules from the region of the M—L′ bond, thus intensifying electrostatic interactions; or, in a nonpolar solvent, the reverse could occur. Another way in which L_c could significantly affect the properties of the M—L′ bond is by changing the properties of M described above: hardness, acid strength, *etc.* The M—L′ bond would be sensitive to this, and also to the geometry of the arrangement of donor atoms of L_c around M.

2. Carbonic Anhydrase: Structure and Catalytic Reactivity

Carbonic anhydrase (CA) is a hydrolytic enzyme which catalyzes the hydration and hydrolysis of many carbonyl and related systems: various slightly different forms occur in different organisms. The simplest reaction catalyzed is the hydration of carbon dioxide[1]

$$CO_2 + OH^- \rightleftharpoons HCO_3^-$$

Other reactions are catalyzed less effectively, *e.g.* the hydration of many aldehydes[2]

$$CH_3CHO + H_2O \rightleftharpoons CH_3CH(OH)_2$$

the hydrolysis of esters[3]

$$CH_3COOAr + OH^- \rightarrow CH_3COO^- + HOAr$$

of certain sultones[4], and of 2,4-dinitrofluorobenzene[5]. Each of these reactions involves bond cleavage, and most of their nonenzymatic pathways involve a transition complex in which the coordination number at an electrophilic center has increased by one oxygen atom.

The catalytic power of carbonic anhydrase is very high: its turnover number (*i.e.* under saturation conditions) for CO_2 hydration is around 10^6 s^{-1}[6]; the spontaneous hydration rate is 7.0×10^{-4} s^{-1} so that carbonic anhydrase enhances the rate by a factor of 10^9. The hydroxide-catalyzed rate constant is 8×10^3 l mol^{-1} s^{-1}[6, 7]. For other substrates the acceleration is less dramatic but still considerable. Detailed tabulations of the extensive biochemical and chemical literature on carbonic anhydrase already exist[8] and will not be repeated: results will be summarized here which are concerned with the metal ion's function, and only the most recent work is cited.

2.1. Catalytic Effects and Inhibition

Carbonic anhydrase kinetics follow the Michaelis-Menten pattern in most cases, and some typical K_m and k_2 values are shown in Table 1.

It will be observed from the Michaelis and inhibition constants (Table 2) that with the exception of CO_2 the strongest binding at the active site is associated with large, conjugated molecules. This probably reflects a high degree of hydrophobic character around the active site, though this is by no means conclusive as there is evidence for the preferential association of aromatic molecules with the polar surface, rather than with the interior, of certain micelles[9]. The extremely strong binding of sulfonamides has not yet been explained, and the requirement for an aryl (rather than, say, benzyl) sulfonamide with unsubstituted nitrogen must be due to a need for very accurate matching of enzyme's and inhibitor's stereoelectronic topography, consistent with the

Table 1. Kinetic parameters of some CA-catalyzed reactions (data from refs. [2, 3, 6, 8] and literature cited therein). The kinetic regime followed is the Michaelis-Menten scheme:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

(E = enzyme, S = substrate, P = product). The experimental constants are k_2 and $K_m = \frac{k_2 + k_{-1}}{k_1} \approx \frac{k_{-1}}{k_1}$ (K_m in mol/l $\times 10^{-3}$, k_2 in s^{-1}).

CA Form	CO_2 Hydration			HCO_3^- Dehydration			CH_3CHO Hydration			pNPA [b] Hydrolysis		
[a]	pH	K_m	k_2	pH	K_m	k_2	pH	K_m	k_2	pH	K_m	k_2
HCAB	6.30	6.3	5.2×10^3							7.0	5.2	0.8
	7.55	1.0	2.2×10^4	7.05	32	2.3×10^4				9.0	5.8	2.1
HCAC	6.30	18.0	2.8×10^5							7.0	22.0	37
	7.55	9.3	6.3×10^5	7.05	68	3.7×10^5				9.0	24.0	55
BCA	6.30	12.5	1.8×10^5				7.08	650	700	7.44	1.4	0.13
	7.55	12.5	7.1×10^5	7.05	[c]		7.64	610	880	8.22	8.6	1.1

[a] HCAB and HCAC are human carbonic anhydrase, forms B and C respectively. BCA is bovine carbonic anhydrase.
[b] pNPA = *p*-nitrophenyl acetate.
[c] $k_{enz} = k_2/K_m = 8.9 \times 10^6$ (l mol^{-1} s^{-1}).

Table 2. Inhibition constants of some sulfonamide inhibitors $R—SO_2NH_2$ [55]. $K=([E][I])/[EI]$; E = enzyme, I = inhibitor.

R		K (mol/l)
C_6H_5		4.6×10^{-7}
p-$CH_3—C_6H_4$		1.0×10^{-7}
p-$H_2N—C_6H_4$		9.0×10^{-7}
α-Naphthyl		1.6×10^{-7}
β-Naphthyl		1.0×10^{-7}
o-$HOOC—C_6H_4$		5.3×10^{-7}
$NC—CH_2—CH_2$		380×10^{-7}
$C_6H_5—CH_2$		150×10^{-7}
highly conjugated, aromatic	typically	0.08×10^{-7}
$R—SO_2—NHR'$	typically	6000×10^{-7}

suggestion[10] that an enzyme should bind certain substrate-analogs more strongly than substrates. There is considerable evidence that sulfonamide and other ionizable inhibitors bind as anions[22], and the Hammett relationship has been used to show that sulfonamide binding involves an *increase* of residual negative charge on the donor nitrogen[11]. While the anionic inhibitors could bind to zinc, in fact the order of inhibitor binding strength does not follow the order of binding to free Zn^{2+} in aqueous solution, but does follow quite well the lyotropic series (see Table 2a)[43].

Table 2a. Inhibition of CA [43] and complexation of Zn^{2+} (aq) [54] by small anions.

Anion	$K=[E][I]/[EI]$ (mol/l)	Anion	$K=[Zn^{2+}][I]/[ZnI^+]$ (mol/l)
F^-	0.4	ClO_4^-	very large
Cl^-	0.05	NO_3^-	10^7
CH_3COO^-	0.03	I^-	10
Br^-	0.02	Br^-	1
NO_3^-	0.01	Cl^-	1
I^-	0.002	SCN^-	0.07
ClO_4^-	0.001	F^-	0.05
SCN^-	0.0007	CH_3COO^-	0.03

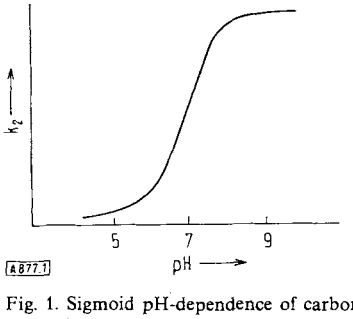


Fig. 1. Sigmoid pH-dependence of carbonic anhydrase. (The scale of the ordinate depends on the substrate.)

The turnover number of carbonic anhydrase plotted against pH invariably yields a sigmoid curve, corresponding to an increase in activity in increasingly alkaline solutions. These curves all contain a point of inflection between pH 6.9 and 8.0, showing that carbonic anhydrase has a group ionizing in this region. On the basis of the established ionization behavior of proteins, this pK_a might be attributed to the terminal NH_2 group of the polypeptide chain, or to an imidazole nitrogen in a histidine residue; another possible origin of this pK_a is the ionization of a zinc-bound water molecule. The ionizing group is clearly intimately linked with the active site.

2.2. Constitution and Structure of Carbonic Anhydrase

Recent chemical analysis[12] has shown unambiguously that carbonic anhydrase consists of protein and one zinc ion only. X-ray structural work is in progress, but for practical reasons has been very slow[13]. A study at 5.5 Å resolution has shown that:

i) The molecule is roughly ellipsoidal, $40\times45\times55$ Å.

ii) The zinc is near the center of the molecule, and its coordination site communicates with the surrounding medium *via* a "cleft" in the molecule.

iii) The one SH group is 14 Å from the zinc, implying by default that the zinc ligating groups must bind through N and O.

iv) Sulfonamide inhibitors bind by projecting into the cleft, and binding onto or close to the zinc ion.

A further study at higher resolution which when complete should yield the atomic coordinates of human carbonic anhydrase, form C (HCAC), has given the following preliminary results[14]:

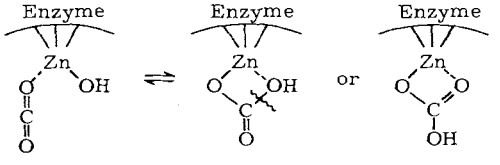
v) In the region of the active site all the peptide N—H and C=O groups are paired off, so that the protein in this region must be relatively hydrophobic.

vi) The zinc ion appears to be ligated by *three* protein groups, imidazole nitrogen, in an approximately tetrahedral arrangement, with the fourth coordination site open to the surrounding medium.

vii) In the cleft near the zinc atom, the surrounding water molecules appear to be ordered.

3. Metal-Centered Investigations

In 1949 *Smith* put forward a general theory of action of hydrolytic enzymes[15], as it had been recognized that many of these enzymes contained a metal ion which seemed to be essential for catalytic function. According to his hypothesis "... the M—S complex is bound to protein in such a manner as to produce an electronic deformation at the sensitive bond. The real catalysis is then acidic or basic by the Brønsted mechanism". *Smith* cites carbonic anhydrase as the simplest example of his theory, the "sensitive bond" being the C—OH bond in bicarbonate.



By implication, *Smith* allows the protein part of the enzyme no role except perhaps that of a template to ensure that only the correct substrate is attacked. This is a weakness in his theory, since the sheer size of the enzyme suggests that it is more than simply a molecule which can bring Zn, CO_2, and OH^- together. However, the theory did emphasize the

role of the metal and its coordination sphere, and this at least can be put to experimental test. In the following discussion evidence will be adduced to criticize the hypothesis that the enzyme's activity depends upon the existence of a zinc-bound hydroxyl group.

3.1. Apocarbonic Anhydrase

The means to investigate the role of zinc in carbonic anhydrase came when *Lindskog*[16] first succeeded in removing reversibly the very tightly-bound zinc ion under conditions mild enough to avoid denaturation. The equilibrium

$$E - Zn + n\,o\text{-phen} + H^+ \rightleftharpoons EH + Zn(o\text{-phen})_n^{2+}$$

was set up and driven to the right using dialysis to remove the $Zn(o\text{-phen})^{2+}$. The apoenzyme was catalytically almost inactive, and most of the activity was restored by adding zinc ions in the molar ratio 1:1. The slight residual activity of apoCA is not significant, as the polar groups on the enzyme's exterior should promote slight general acid/base catalysis. Its gross structure, as revealed by sedimentation[16] and ORD[17], is the same as that of ZnCA, although it denatures more rapidly. This implies that the zinc's function is probably not merely to organize the protein's tertiary structure, so that it must be concerned directly with the active site.

3.2. Displacement of Zinc by Other Metals

The preparation of new derivatives of carbonic anhydrase has been attempted by adding equimolar or excess quantities of Co^{2+}, Ni^{2+}, Fe^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+}, Be^{2+}, Mg^{2+}, Ca^{2+}, Ba^{2+}, and Fe^{3+}[16, 17]. The replacement of one metal by another in compounds of unknown structure provides a valuable probe into the nature of the metal coordination subject to the guarded assumption that the coordination site is the same for the different metals. This assumption is tentatively supported in the case of carbonic anhydrase by *Coleman*'s observation[17] that the various metallo-CA's do not incorporate radioactive zinc.

A metalloenzyme can be studied by varying the metal ion only, and if the thermodynamic, magnetic, kinetic, and spectral properties of the different metalloenzymes thus obtained are compared with the properties of simple coordination compounds of the metal ions concerned, it is frequently possible to extract information[19] about the coordination in the enzyme.

3.2.1. Activity of Metallocarbonic Anhydrases

Typical results[20] show the following trend of activities, corrected for any remaining zinc and for the residual activity of apoCA: native CA, 100%; Zn^{2+} + apoCA, 94%; Co^{2+} + apoCA, 50%; other metal ions + apoCA, 0%. Only Zn^{2+}CA and Co^{2+}CA are significantly active.

3.2.2. Inhibitor Binding

This shows a clear correlation with activities (Figure 2). The apoenzyme and the inactive MCA's bind acetazolamide[*] weakly, in contrast to the active enzymes ZnCA and CoCA which bind acetazolamide 10^2 to 10^3 times more strongly and are inhibited by it. This suggests very strongly that the sulfonamide group and the metal ion interact. The X-ray data, the fact that sulfonamides bind as anions, the fact that other inhibiting anions cannot bind unless their concentration is great enough to displace the more strongly bound sulfonamide, and the UV spectral evidence (see Section 3.2.3) all support the notion of a metal-inhibitor bond. Therefore when an inhibitor binds to carbonic anhydrase it alters the coordination of the zinc or cobalt, possibly displacing a group already bound, in such a way that reaction can no longer take place. The sigmoid (as opposed to hyperboloid) binding curves of acetazolamide do show that the inhibitor is displacing something, rather than simply adding to the enzyme.

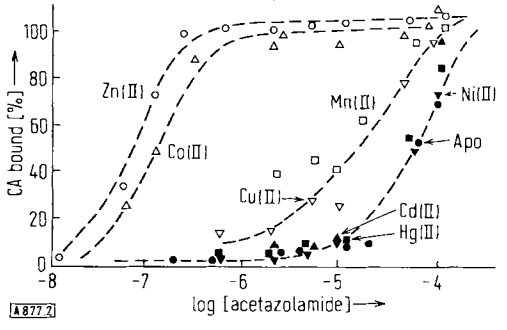


Fig. 2. Acetazolamide binding to metal-substituted carbonic anhydrase. (From ref. [18].)

3.2.3. Stoichiometry, Kinetics, and Thermodynamics of Metal Ion Binding

A commonplace feature of coordination chemistry is the neutralization of basic ligand groups upon complexation, with liberation of protons if complexation occurs at pH values below the pK of these groups. However *Lindskog*[21] showed that in carbonic anhydrase the reverse took place, *viz.*, at pH 6:

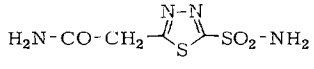
$$Zn^{2+} + \text{apoCA} \rightarrow \text{ZnCA} + (1.3 \pm 0.15)\,H^+$$

at pH 9:

$$Zn^{2+} + \text{apoCA} \rightarrow \text{ZnCA} + (2.2 \pm 0.1)\,H^+$$

The zinc is therefore inducing a further ionization upon binding and the proximity of the ionizing group to the zinc ion in ZnCAl will be reflected in the perturbation of the

[*] 5-Sulfamoyl-1,3,4-thiadiazol-2-acetamide. The trivial name is derived from 5-acetamido-1,3,4-thiadiazole-2-sulfonamide.



ligand field at zinc as the pH passes from 6 to 9. This cannot be examined with ZnCA, but it should be reflected in the d-d electronic spectrum of CoCA. In fact the visible spectrum of CoCA has an acid and an alkaline form[21], and well-defined isosbestic points show that the pH-dependent equilibrium is between two forms only. These are related by an ionization with a pK_a around 7.1, and the spectra show that in both forms the coordination is irregular (Figure 3).

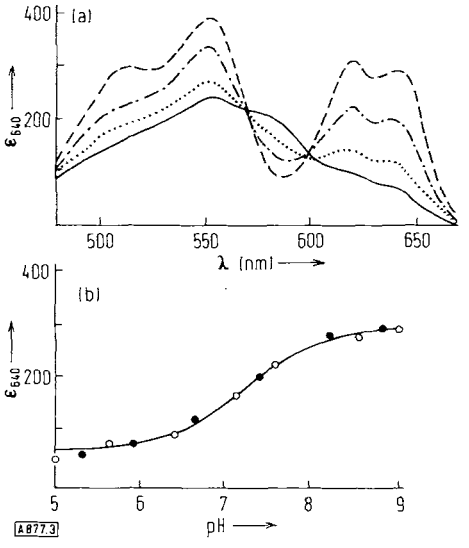


Fig. 3. Visible spectra of cobalt-carbonic anhydrase a) in acidic (——) and increasingly alkaline solution (· · · · ·, – · – · –, – – – –); b) extinction at various pH values (from ref. [21]).

This ionization pK_a is destroyed not only by removal of zinc but also by inhibitors, as shown by *Coleman*[22]. The binding of anionic inhibitors is accompanied at low pH by the release of protons and at high pH by release of hydroxide ions; if E^- and EH are the two forms of the holoenzyme and I^- the inhibiting anion, then in acid:

$$HI + EH \rightarrow EH{\cdot}I + H^+$$

and in alkali:

$$I^- + E^- \xrightarrow{+H_2O} EH{\cdot}I + OH^-$$

The amounts of H^+ or OH^- liberated as a function of pH were successfully related to the pK_a values of the inhibitor and the enzyme. It will be noted that the pK_a values associated with activity, inhibition, and metal-dependent ionization are roughly the same, suggesting that the same group may be involved.

The kinetics and thermodynamics of the binding of zinc by carbonic anhydrase have been investigated[23,24] and Table 3 shows the second-order rate constants, activation parameters, and thermodynamic constants of binding. These are compared with those for smaller ligands of various coordination numbers. Both rate process and equilibrium are entropy-dominated, in spite of a smaller opposing enthalpy. The entropy terms are substantial, and the only ligand comparable in this respect is CDTA (cyclohexenediamine tetraacetate), a formally hexadentate ligand. While it is most unlikely that apocarbonic anhydrase is hexadentate (which illustrates the danger of overinterpreting an observed behavioral similarity between an enzyme and a proposed model), the similarity between carbonic anhydrase and CDTA is very probably a consequence of the same cause: the expulsion of a large number of water molecules. The effect in the case of CDTA is due to charge neutralization, and in carbonic anhydrase the binding of the metal may also result in charge neutralization in the active site region.

Further evidence for this may be cited (see literature quoted in ref. [24]): the difference UV spectrum of ZnCA minus apoCA is similar to the difference spectra produced when a tyrosine or a tryptophan derivative is transferred from water to a less polar solvent. This similarity suggests that one or more tyrosine and/or tryptophan groups are in a more polar environment in the apoenzyme than in the holoenzyme. Other workers concluded on the basis of studies with fluorescent sulfonamides that the active site of the native enzyme is nonpolar. It is interesting to note that recent structural work on a number of enzyme systems shows the active site to be located in a nonpolar environment[24a].

The positive binding enthalpy supports a small coordination number, so that during the reaction more M—L bonds are broken than formed, as expected if the zinc is three or four coordinate (aquated zinc is hexacoordinate). The metals whose binding results in an active enzyme are those with

Table 3. Rate and equilibrium parameters for the reaction M + apoCA → MCA (data from refs. [23, 24, 53, 54]).

M	Ligand	k (l mol^{-1} s^{-1})	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (e.u.)	ΔH (kcal/mol)	ΔS (e.u.)
Zn	typical small unidentate	10^{7-8}				
Zn	typical small bidentate (bipyridyl)	10^6	+6	−9	−10	+8
Zn	typical small tridentate (terpyridyl)	10^6	+8	−4		
Zn	apoCA, pH 5.5	$<10^4$	+21	+28	+3.9	+61
Zn	apoCA, pH 7.0	10^4	+21	+30	+9.8	+88
Co	apoCA, pH 7.0				+9.4	
Ni	apoCA, pH 7.0				+3.2	
Cu	apoCA, pH 7.0				+3.4	
Cd	apoCA, pH 7.0				+4.4	
Zn	CDTA (cyclohexene-diamine tetraacetate)				+4.7	+82

the most endothermic binding to carbonic anhydrase. This is consistent with the Irving-Williams sequence of stabilities ($Co < Ni < Cu > Zn$) and *if* the five metals Zn, Co, Cd, Cu, and Ni all bind at the same site it may be responsible for the activity pattern. *Dennard* and *Williams*[19] have pointed out that a catalytically active metal must not bind too strongly to its apoenzyme or it will lose coordination flexibility.

3.3. Spectroscopic and Magnetic Studies

The d-d transition in CoCA has been extensively studied. Basically three kinds of spectrum are obtained from CoCA: One each in acid and in alkaline solution and one for inhibited forms (Fig. 4). Their interpretation is difficult; they show that the coordination cannot be simple. The spectrum of $CoCA \cdot CN^-$ is similar to that of $[CoCl_4]^{2-}$, suggesting tetrahedral coordination, although this is not conclusive; irregular six-coordinate Co^{2+} complexes are known which give very similar spectra[25].

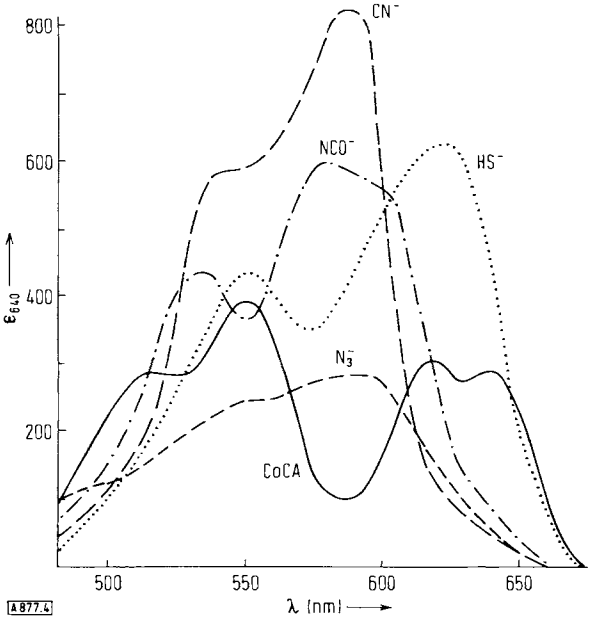


Fig. 4. Visible spectra of cobalt-carbonic anhydrase in alkaline solution in the presence of inhibiting anions (from ref. [21]).

Optical rotatory dispersion (ORD) studies have been carried out by *Coleman* on HCAB[17]. Zn-, Co-, and apoCA have similar ORD spectra in the UV, implying that they have the same gross protein conformation. The visible region of the CoCA ORD is featureless, in spite of the d-d transition, which means that the Co site in HCAB is optically inert. *Coleman* postulated a square-planar binding of cobalt, with the additional coordination of H_2O or OH^-, which are not strong enough ligands to destroy the approximate symmetry. In fact the tetrahedral coordination of cobalt with two equivalent donors would be an equally good explanation, and in the light of X-ray data seems preferable. Inhibitors give rise to a visible-ORD spectrum in CoCA, explicable as resulting from the displacement of H_2O or OH^- by a ligand higher in the spectrochemical series. Furthermore, CuCA binds cyanide less tightly than CoCA, which may reflect the greater destabilization of trigonal or tetragonal Cu^{2+} by the addition of an axial ligand.

A ^{35}Cl-NMR study of ZnCA in chloride solutions showed that the zinc in bovine carbonic anhydrase (BCA) has at least one, and probably only one, open coordination site. *Ward*[26] showed by line-broadening that the chloride ions in the $CA—Cl^-$ complex are bound directly to zinc, the consequent high electric field gradient resulting in rapid quadrupole relaxation. Titration by cyanide, which displaces chloride, gave the number of chlorides bound. Chloride binding was pH-dependent, and the pK of carbonic anhydrase measured thereby was in turn sensitive to the concentration of chloride, being 6.2 at $[Cl^-]=0$ and 9.3 at $[Cl^-]=0.5$ mol/l. Extension of this work to human and horse carbonic anhydrases shows that the more active forms have a lower zero-chloride pK_a and a higher molar relaxivity than the less active forms. If the pK_a is that of ionizing zinc-bound water, then it is not surprising that the stronger polarization of ligand water (higher field) is accompanied by a greater molar relaxivity (higher field gradient), both of which could result from an increased positive charge on the zinc ion. It would however be more surprising if the more highly polarized hydroxide ion were the better nucleophile, and this may hint that if the hydroxide mechanism is correct then the activity of carbonic anhydrase is due to other factors as well.

An investigation[27] of solvent proton relaxation by the paramagnetic Co^{2+} ion in CoCA reveals a strong, pH-dependent, inhibitable relaxivity associated with the active site. The relaxivity was less at low pH, and the acid form of the enzyme possessed the same molar relaxivity as the inhibited form. It was concluded that a rapidly-exchanging, cobalt-bound hydroxide could be displaced by inhibitors, or prevented from exchanging by protonation (p$K_a \approx 7$). For the rapidly-exchanging form several parameters were calculated: r_{Co-H} (if OH^-) = 2.5 Å; r_{Co-H} (if OH_2) = 2.8 Å; proton residence time $\approx 10^{-5}$ s. The interatomic distances calculated are too small for anything except Co—O—H, and although better agreement with the expected distance ($r_{Co-H} = 2.85$ Å) is obtained assuming $Co—OH_2$ rather than $Co—OH^-$, the difference thus obtained from a technique giving $\left\langle \frac{1}{r^6} \right\rangle$ is probably insignificant.

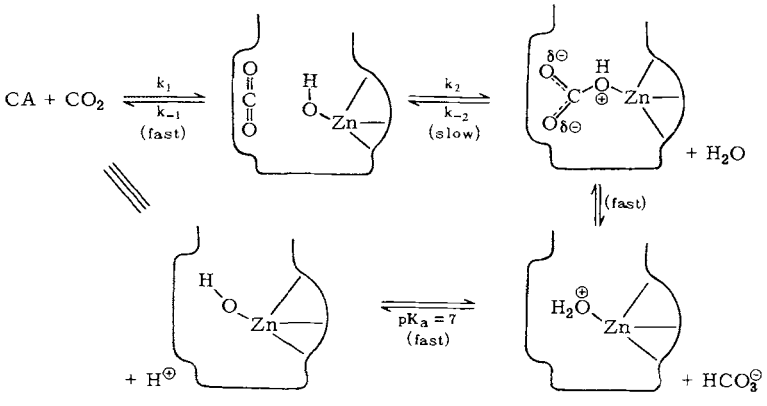
Further evidence for the zinc-hydroxide/zinc-water species is found in the kinetic pattern of sulfonamide substitution[28], which upon analysis resembles the pattern of ligand substitutions of 3d metal-ion inner-sphere complexes; after an outer-sphere pre-equilibrium the rate constant of inner-sphere complex formation is independent of the nature of the substituent, depending only upon the rate at which inner-sphere sites are vacated by water molecules.

Some work carried out by *Riepe* and *Wang*[29] should be mentioned, because although not directly related to the zinc ion it provides key evidence in the problem of substrate binding. Based on delicate difference infrared spectroscopy, their work indicated that while CO_2 is *not* bound directly to zinc, its isoelectronic analog N_3^- is so bound. However, the binding of N_3^- and of CO_2 are mutually exclusive,

which suggests that CO_2 is bound in a position very close to the zinc ion, where it is accessible to bound ligands. In addition, *Riepe* and *Wang* showed that the binding constant of azide ion decreased with increasing pH and did not level off, implying that the azide ion is displaced specifically by OH^- rather than by another deprotonated group.

4. The Mechanistic Role of Zinc

The results presented above provide extremely good evidence that the zinc ion in all forms of carbonic anhydrase is coordinated by protein and water. While none shows beyond all doubt that the pK_a around 7 recurrent in carbonic anhydrase chemistry is due to the ionization of one zinc-bound water molecule, it is hard to offer an alternative explanation, particularly of the UV-spectral and relaxation data. The existence of this zinc-aquo complex seems a necessary condition for the activity of carbonic anhydrase. In view of the evidence that CO_2 is bound close to but not onto zinc, a mechanistic scheme of the kind shown is very plausible[30].



Does this stand up to quantitative examination? From CO_2 hydration data for alkaline BCA, $k_2 = 8 \times 10^5\ s^{-1}$, while $K_m = (k_{-1} + k_2)/k_1 = 0.0124\ l\ mol^{-1}$[6]. Since k_2 is pH-dependent while K_m is not, probably $k_{-1} \gg k_2$. Assuming a lower limit of $k_{-1} = 10\ k_2$, the lower limit for k_1 is $6 \times 10^8\ l\ mol^{-1}\ s^{-1}$. This is close to the diffusion-controlled limit, and therefore requires a fairly open active site, which is consistent with the observed binding of larger, aromatic substrates and inhibitors.

Table 4. Comparison of k_2 for CA (rate of breakdown of the enzyme-substrate complex) with $50\ k_{OH^-}$ (hypothetical rate of breakdown of the substrate when surrounded by hydroxide ions).

Substrate	$k_2\ (s^{-1})$	$50\ k_{OH^-}\ (s^{-1})$
CO_2	10^6	0.4×10^6
CH_3CHO	10^3	200×10^3
Pyridinecarbaldehydes	10^2	2500×10^2
p-Nitrophenyl acetate	10	50×10

If the reaction step with rate k_2 corresponds to attack by a hydroxide ion, then it can be compared with the rate of attack by free hydroxide (Table 4). Only in the case of CO_2 is k_2 unreasonably high, which implies that the catalytic action of carbonic anhydrase is not due solely to the provision at the active site of "free" hydroxide at relatively low pH.

The dehydration of bicarbonate shows a similar kinetic pattern, although in the case of BCA[6] the enzyme cannot be saturated, so that the $E—HCO_3^-$ complex must be very unstable. *Caplow*[31] studied the catalysis by hypobromous acid of the dehydration reaction, and concluded that a concerted electrophilic displacement must be occurring:

$$HO—Br + HO—CO_2^- \rightarrow HO^- + Br—OH + CO_2$$

The bromine atom acts as a Lewis acid. This is consistent with the kinetic scheme above for dehydration: displacement of zinc-bound water would result in the formation and immediate breakdown of a zinc-bicarbonato complex.

This proposed reaction course leads to a number of questions.

i) Can the very low pK_a of $Zn—OH_2$ in carbonic anhydrase be accounted for?

ii) Can the rapid proton transfer be incorporated into the scheme?

iii) Can the unusual order of inhibitor binding be explained?

iv) Why is carbonic anhydrase so specific in its requirement for Zn^{2+} or Co^{2+}?

Before discussing these problems, it would be germane to introduce some of the concepts useful in enzyme chemistry. The basic assumption is of course that the groups in the enzyme molecule obey the chemical principles governing the behavior of small molecules in aqueous solution. Catalysis by enzymes is remarkable on two accounts: the very large accelerations observed, and the high, sometimes absolute, substrate specificity. Many ideas have been put forward to explain these, some differing only in detail[32]. The basic lines of explanation usually involve appeal to one or more of the following concepts.

i) The lock-and-key picture, according to which substrates are specifically bound as their stereoelectronic topography complements that of the enzyme's substrate-binding site. Specific binding by metal-ion centers in enzymes applies, as one would expect, largely to electron-donating substrates such as anions, O_2, and CO. There are many instances of this[33]. In such cases the influence of the protein on the

metal cannot be very important, as long as the metal has enough coordination sites to bind the substrate, and a sufficiently high ligand exchange rate in the vacant sites. The latter is a function of donor power as well as geometry of the protein[34].

ii) The bringing together (approximation) of reacting groups so as to increase the collision frequency and/or raise the steric probability factor. Approximation of reacting groups is, at its simplest, an effective increase in their concentration at the active site and hence of collision number, but in many cases[35] it is an inadequate explanation of reactivity bestowed upon normally very inert substrates. In the case of carbonic anhydrase, as discussed above, it is barely adequate; it requires an unreasonably high effective concentration of OH^- at the active site. It is also inadequate to explain the greatly reduced activation energy of the catalyzed reaction[36]. Furthermore the attribution of the nucleophilicity of free OH^- to zinc-bound OH^- is implausible.

For many reactions the electronic activation energy is a sensitive function of angle of attack, and the Arrhenius plot gives "averaged" values; it has recently been suggested that enzymes could act by constraining the substrates to meet in a fixed orientation corresponding to an activation energy much lower than that observed in free solution. This procedure is called "orbital steering"[37]. In the case of carbonic anhydrase such an explanation cannot be ruled out.

iii) The strained-molecule hypothesis. Essentially, the enzyme-to-substrate binding distorts the substrate in the direction of reaction, resulting in a lower activation energy with respect to the ground-state enzyme-substrate complex. Involvement of metal in the formation of an enzyme-substrate complex in which the substrate is strained is very plausible, because of the ability of metals to form labile bonds to donors in which the donor atoms or groups are electronically and/or geometrically strained. The postulated ionizing water molecule in carbonic anhydrase is such a donor. The polarizing power of $[(H_2O)_5Zn]^{2+}$ is illustrated by comparing the pK_a of H_2O, $(H_2O)_5ZnOH_2^{2+}$, and H_3O^+; they are 15.7, 10.5[*], and -1.7. Thus the polarizing power of the pentacoordinate zinc ion is less than that of a proton, as would be expected. In carbonic anhydrase the same pK_a drops to about 7.1, which is a substantial change.

iv) The "unusual medium" theory pictures the enzyme as providing an unusual medium, distinct from the aqueous environment, in which the catalyzed reaction takes place. There is considerable evidence that the interior of an enzyme is much less polar than its exterior. It was predicted[39] that this would stabilize the conformation of the enzyme molecule, and this has been borne out by X-ray structure-determination. In the now classic example of lysozyme[40] the enzyme contains a "groove" on its surface. The substrate binds to this groove and the catalyzed reaction then occurs in the nonpolar interior of the enzyme. Such a theory would account for the very large size of many enzyme molecules compared with their substrates.

[*] This figure is derived from the tabulated pK of 9.7 [38, 43, 54] by applying a statistical correction, effectively to reduce the number of ionizable protons from twelve to two.

The idea of an unusual environment at the active site of metalloenzymes has been pursued by *Vallee* and *Williams*[41], who point out that many enzymes containing metal ions possess unusual properties, notably in their UV and ESR spectra and redox potentials. Such anomalies are not observed in biological molecules where the metal is inactive, and are frequently destroyed when the enzyme is inhibited or denatured. The unusual features of metalloenzymes are attributed to the metal's possessing a coordination geometry of a kind not found with simpler ligands; such a geometry is imposed upon the metal by the protein, whose conformation is already fixed. This would modify the properties of the metal ion with regard to coordination by further ligands, as discussed in Section 1. In carbonic anhydrase the environment of the zinc/cobalt may be "unusual" in three respects: in the conformation imposed by it upon the ion; in its apolarity; and in the ordering of water molecules around it. (It is, of course, not unexpected that water molecules should be relatively ordered around an apolar surface in an aqueous solution[42].)

In what way is the coordination of zinc abnormal? If the total coordination number is four (3 protein, 1 water) then the residual charge on the zinc could be greater than if the zinc were hexacoordinate, although since the donor atoms are nitrogens of imidazole rather than oxygens of water this is not conclusive. A higher residual charge on zinc would decrease the pK_a of coordinated water. However, a shift of 3.5 units is large, and further enhancement could be due to the nonpolar nature of the environment around the zinc: ionization would be encouraged if it resulted in better attainment of overall charge-neutrality.

One supposed difficulty in all mechanistic schemes so far proposed for carbonic anhydrase is that the zinc hydroxo complex loses hydroxide to the substrate and regains water, which then ionizes. In the CO_2 hydration (turnover $10^6\ s^{-1}$) the zinc-bound water must therefore ionize at least at this rate. However, if the pK_a of the water is 7.0 and the maximum diffusion-controlled protonation rate is 10^{10} $l\ mol^{-1}\ s^{-1}$, then the predicted maximum deprotonation rate is $10^{10}/10^7 = 10^3\ s^{-1}$.

The suggestion that a nearby histidine residue might assist in deprotonation is not plausible, chiefly because chemical methods designed to detect such a group have only succeeded in one of the less active forms of carbonic anhydrase. However, if the nonpolar active site is surrounded by a region of ordered water molecules then two possibilities arise:

i) The true pK_a of $ZnOH_2$ is even less than 7, which increases the maximum deprotonation rate (the difference between the true and observed pK_a would then have to be explained as due to an equilibrium constant between protons solvated in the ordered region and in bulk phase).

ii) The diffusion-controlled limit for proton transfer is greatly increased, as in ice[42a], with a simultaneous increase in the maximum rate of deprotonation.

The idea of ordered water at the active site may also explain the observed inhibitor binding order[43], which follows the lyotropic series[44] (see Table 2a). The binding of anions and the associated spectral changes in $Co^{II}CA$ show that the

inhibitors do bind to the metal; but the order of binding constants is more easily explicable if the thermodynamic drive for binding comes from the easy assimilation of the anions into an ordered water structure. Such a stabilization of anions bound at the active site could also assist in lowering the pK_a of the zinc-bound water.

From the inorganic point of view, the most remarkable feature of the catalytic power of carbonic anhydrase is the absolutely specific need for Zn^{2+} or Co^{2+}. No other metal imparts significant activity to apoCA, so it is likely that Zn^{2+} and Co^{2+} have more than one property crucial for the hydrolytic mechanism.

Table 5. Selected properties of metal ions (see text).

Metal	Ionic radius (Å) [a]	Water exchange rate $\log_{10}k$ (s^{-1}) [53]	Imidazole assocn. const. $\log_{10}K$ ($l\ mol^{-1}$) [54]
Mn^{2+}	0.80	7.6	1.65
Fe^{2+}	0.76	6.5	—
Co^{2+}	0.71	6.4	2.23
Ni^{2+}	0.69	4.4	3.27
Cu^{2+}	0.92	9.9	4.26
Zn^{2+}	0.72	7.5	2.57
Cd^{2+}	0.95	—	2.80

[a] Cf. ref. [45], p. 45.

One can compare the properties of zinc and cobalt ions with those of other ions, and ionic size, inner-sphere water exchange rate, and strength of binding to imidazole are shown in Table 5. None of these points to any special behavior on the part of zinc and cobalt ions, though they are clearly very similar.

The best explanation seems to lie in the metal's *coordination flexibility*, and in this respect Zn^{2+} and Co^{2+} do indeed stand out[45]. This is illustrated in Table 6, which compares the stability constants for various metals binding to two chelating ligands, one of which gives, with two waters, an octahedral complex, while the other can only do this with some strain.

Table 6. Stability constants of chelates (see text).
$L^1 = H_2N(CH_2CH_2NH)_3H$,
$L^2 = N(CH_2CH_2NH_2)_3$, $K_i = \frac{[ML_i]}{[M][L_i]}$ (data from ref. [54]).

M	$\log_{10}K_1$	$\log_{10}K_2$	$\log_{10}\frac{K_2}{K_1}$
Mn^{2+}	5.0	5.7	0.7
Fe^{2+}	8.0	8.7	0.7
Co^{2+}	11.0	12.7	1.7
Ni^{2+}	14.1	14.8	0.7
Cu^{2+}	20.5	18.7	−1.8
Zn^{2+}	11.9	14.5	2.6
Cd^{2+}	10.8	12.3	1.5
Hg^{2+}	25.3	26	0.7

It would thus seem possible that the essential property of zinc and cobalt ions is that they can bind to imidazole in a nonoctahedral disposition. Other metals, binding more strongly to imidazole, could impose an octahedral geometry upon the donor atoms and seriously distort the active site. It is of interest in this connection that imidazole has recently been shown[46] to give, under similar conditions, both octahedral (hexakis) and tetrahedral (tetrakis) complexes with Co^{2+}. On the simple basis of coordination flexibility one would also expect Cd^{2+} and Mn^{2+} to activate apoCA. Neither should manifest coordination-selective ligand-field stabilization energy (LFSE), and Cd^{2+} is a recognized analog of Zn^{2+}[45]. In fact neither is active in carbonic anhydrase, which shows that some factor as yet unexplained operates in carbonic anhydrase, particularly as cobalt/zinc enzymes such as carboxypeptidase[47] and alkaline phosphatase[48] are partly activated by Cd^{2+} and Mn^{2+}.

The study of carbonic anhydrase has therefore raised the issue of the properties of metals in systems where the coordination environment is fixed by the ligand rather than by the metal. The postulated mechanism based on an active coordinated water molecule requires (i) that the acid-dissociation of this molecule should be thermodynamically and kinetically very much easier than the corresponding dissociation in the free aquated zinc ion, and (ii) that the hydroxo complex should be a very strong nucleophile. This certainly requires quantitative investigation since to satisfy both (i) and (ii) requires a metal ion whose polarizing power is large but not too large.

The sensitivity of the rate of complexation of L′ to the nature of L_c has been shown to depend on the metal ion[49]; the rate of the reaction

$$ML_c + L' \xrightarrow[-H_2O]{k_{assoc.}} L_cML'$$

does not depend upon L_c if $M = Mg^{2+}$, but does depend upon L_c if M is the more polarizable Mn^{2+}, Cu^{2+}, or Zn^{2+}. Interestingly, in one instance the patterns of variation of $k_{assoc.}$ (as L_c was changed) were found[50] to be the same for Zn^{2+} and Co^{2+} but different for Ni^{2+}.

Very little is known about the nucleophilicity of metal-bound water or hydroxide, although there have been some recent indications that Cr^{III}—OH and Co^{III}—OH are good nucleophiles; *Buckingham et al.*[51] showed that the complex

$$N_4Co^{III}(OH)\cdot NH_2—CH_2—CONR_2$$

undergoes very rapid intramolecular hydrolysis of the amide group, while *Earley et al.*[52] showed that the reaction

$$[N_5Cr^{III}OH]^{2+} + CO_2 \rightarrow [N_5Cr^{III}OCO_2]^+ + H^+$$

is at least 10^4 times as fast as the reaction[*]

$$H_2O + CO_2 \rightarrow HCO_3^- + H^+$$

We are very grateful to Drs. K. K. Kannan and A. Liljas for providing pre-publication results on the X-ray structure of CA.—P. R. W. acknowledges with thanks the award of a Research Studentship by the Science Research Council of the U. K.

Received: May 24, 1971 [A 877 IE]
German version: Angew. Chem. *84*, 461 (1972)

[*] *Note added in proof* (April 24, 1972): The kinetics of the hydration of CO_2 have been reinvestigated by *Khalifah* [56]. and he reports that the Michaelis constants for CO_2 hydration by human carbonic anhydrases band C are pH-independent, in contrast to the earlier work (Table 1). This brings human carbonic anhydrase into line with bovine carbonic anhydrase (Table 1).
A nitroxide spin-labeled sulfonamide has been used [57] to examine the active site of bovine CA. Analysis of the ESR signal of the nitroxide radical suggested that the part of the cavity at a distance of 11 Å from the zinc ion is not non-polar but is in fact highly polar. Any conclusion based on the assumption that the amino acid residues around the cavity are entirely nonpolar must therefore be called into question, pending the complete mapping of the molecule by X-ray crystallography.
Using model systems involving zinc, we have investigated two problems raised by the chemistry of CA—the extent to which simpler organic systems can cooperate with zinc ions to catalyze the reactions of carbonyl compounds [58], and the question of the pK_a of zinc-bound water.

[1] *N. U. Meldrum* and *F. J. W. Roughton*, J. Physiol. *75*, 15 P (1932).

[1a] *D. P. Craig* and *R. S. Nyholm* in *F. P. Dwyer* and *D. P. Mellor*: Chelating Agents and Metal Chelates. Academic Press, New York 1964.

[2] *Y. Pocker* and *J. E. Meany*, J. Amer. Chem. Soc. *87*, 1809 (1967); *Y. Pocker* and *J. E. Meany*, Biochemistry *6*, 239 (1967).

[3] *Y. Pocker* and *J. T. Stone*, Biochemistry 7, 4139 (1968), and earlier papers.

[4] *K. Lo* and *E. T. Kaiser*, J. Amer. Chem. Soc. *91*, 4912 (1969).

[5] *P. Henkart, G. Guidotti*, and *J. T. Edsall*, J. Biol. Chem. *243*, 2447 (1968).

[6] *J. C. Kernohan*, Biochim. Biophys. Acta *96*, 304 (1965).

[7] *D. M. Kern*, J. Chem. Educ. *37*, 14 (1960).

[8] *J. T. Edsall*, Ann. New York Acad. Sci. *151*, 41 (1968).

[9] *J. C. Erikson* and *G. Gillberg*, Acta Chem. Scand. *20*, 2019 (1966).

[10] *R. Wolfenden*, Nature *223*, 704 (1969).

[11] *N. Kakeya, M. Aoki, A. Kamada*, and *N. Yata*, Chem. Pharm. Bull. *17*, 1010 (1969).

[12] *E. g. P. O. Nyman* and *S. Lindskog*, Biochim. Biophys. Acta *85*, 141 (1964).

[13] *K. Fridborg, K. K. Kannan, A. Liljas, J. Lundin, B. Strandberg, R. Strandberg, B. Tilander*, and *G. Wiren*, J. Mol. Biol. *25*, 505 (1967).

[14] *A. Liljas*, Seminar at Cambridge, June 1970; *J. Kannan*, personal communication.

[15] *E. Smith*, Proc. Nat. Acad. Sci. U. S. *35*, 80 (1949).

[16] *S. Lindskog* and *B. G. Malmstrøm*, J. Biol. Chem. *237*, 1129 (1962).

[17] *J. E. Coleman*, Biochemistry *4*, 2644 (1965).

[18] *J. E. Coleman*, Nature *214*, 193 (1967).

[19] See, *e. g., A. E. Dennard* and *R. J. P. Williams* in *R. L. Carlin*: Transition Metal Chemistry, Vol. 2, p. 116.

[20] Based on *Coleman* [18] and corrected for residual zinc and apoCA activity.

[21] *S. Lindskog*, J. Biol. Chem. *238*, 945 (1963).

[22] *J. E. Coleman*, J. Biol. Chem. *242*, 5212 (1967).

[23] *R. W. Henkens* and *J. M. Sturtevant*, J. Amer. Chem. Soc. *90*, 2669 (1968).

[24] *R. W. Henkens, G. D. Watt*, and *J. M. Sturtevant*, Biochemistry *8*, 1874 (1969).

[24a] *M. F. Perutz*, Phil. Trans. Roy. Soc. (London) *B 257*, 265 (1970); *D. M. Blow* and *T. A. Steitz*, Annu. Rev. Biochem. *39*, 64 (1970).

[25] *F. A. Cotton* and *R. H. Soderberg*, J. Amer. Chem. Soc. *85*, 2402 (1963).

[26] *R. L. Ward*, Biochemistry *8*, 1879 (1969); *R. L. Ward*, Biochemistry *9*, 2447 (1970).

[27] *M. E. Fabry (Riepe), S. H. Koenig*, and *W. E. Schillinger*, J. Biol. Chem. *245*, 4256 (1970).

[28] *J. Olander* and *E. T. Kaiser*, J. Amer. Chem. Soc. *92*, 5758 (1970).

[29] *M. E. Riepe* and *J. H. Wang*, J. Biol. Chem. *243*, 2779 (1968).

[30] First suggested by *R. P. Davis*. See *Boyer et al.*: The Enzymes. Vol. V, p. 545.

[31] *M. Caplow*, J. Amer. Chem. Soc. *93*, 230 (1971).

[32] For a full discussion, see *W. P. Jencks*: Catalysis in Chemistry and Enzymology. McGraw-Hill, New York 1969.

[33] *E.g. J.O. Alben, L. Yen*, and *N. J. Farrier*, J. Amer. Chem. Soc. *92*, 4475 (1970); *K. Garbett, D. W. Darnall, I. Klotz*, and *R. J. P. Williams*, Arch. Biochem. Biophys. *135*, 419 (1969); *J. Naylor* and *R. J. P. Williams*: The Chemistry of Alkaline Phosphatase Catalysis. Conference of the Chem. Soc., Canterbury, July 1970.

[34] *J. P. Jones, E. J. Billo*, and *D. W. Margerum*, J. Amer. Chem. Soc. *92*, 1875 (1970).

[35] Discussion in ref. [32], chapter 1.

[36] Ref. [30], p. 556.

[37] *D. R. Storm* and *D. E. Koshland*, Proc. Nat. Acad. Sci. U. S. *66*, 445 (1970).

[38] *T. M. Hunt*: Metal Ions in Aqueous Solution, Benjamin, London 1963, p. 50.

[39] *H. F. Fischer*, Proc. Nat. Acad. Sci. U. S. *51*, 1285 (1960); see also ref. [24a].

[40] *D. C. Phillips*, Proc. Nat. Acad. Sci. U. S. *57*, 484 (1967).

[41] *B. L. Vallee* and *R. J. P. Williams*, Proc. Nat. Acad. Sci. U. S. *59*, 498 (1968); Chem. Brit. *1968*, 399.

[42] *E. g.* ref. [32], chapter 8.

[42a] *M. Eigen* in *S. Claesson*: Proceedings of 5th Nobel Symposium. Interscience, New York 1967, p. 246.

[43] *J. A. Verpoorte, S. Mehta*, and *J. T. Edsall*, J. Biol. Chem. *242*, 4221 (1967).

[44] *M. J. Blandamer*, Quart. Rev. Chem. Soc. *24*, 169 (1970); *I. Fridovitch*, J. Biol. Chem. *238*, 592 (1963).

[45] *E. g. F. A. Cotton* and *G. Wilkinson*: Advanced Inorganic Chemistry. Wiley, New York 1966, 2nd Edit., pp. 610, 865.

[46] *W. J. Davis* and *J. Smith*, J. Chem. Soc. *A 1971*, 317.

[47] *D. S. Auld* and *B. L. Vallee*, Biochemistry *9*, 4353 (1970).

[48] *M. L. Applebury, B. P. Johnson*, and *J. E. Coleman*, J. Biol. Chem. *245*, 4968 (1970).

[49] *M. A. Cobb* and *D. N. Hague*, Chem. Commun. *1971*, 20; *T. J. Cayler, M. A. Cobb, D. N. Hague, A. M. John*, and *D. J. Zetter*: The Role of Metals in Enzymic Reactions. Conference of the Chem. Soc., Canterbury, 1970.

[50] *M. A. Cobb* and *D. N. Hague*, Chem. Commun. *1971*, 20.

[51] *D. A. Buckingham, D. M. Foster*, and *A. M. Sargeson*, J. Amer. Chem. Soc. *92*, 6151 (1970).

[52] *J. E. Earley* and *W. Alexander*, J. Amer. Chem. Soc. *92*, 2294 (1970).

[53] *D. J. Hewkin* and *R. H. Prince*, Coord. Chem. Revs. *5*, 61 (1970).

[54] *L. G. Sillen* and *A. E. Martell*: Stability Constants. Spec. Publ. No. 17 of the Chem. Soc., London 1964.

[55] *H. A. Krebs*, Biochem. J. *43*, 525 (1948).

[56] *R. G. Khalifah*, J. Biol. Chem. *246*, 2561 (1971).

[57] *J. F. Hower, R. W. Henkens*, and *D. B. Chesnut*, J. Amer. Chem. Soc., *93*, 6665 (1971).

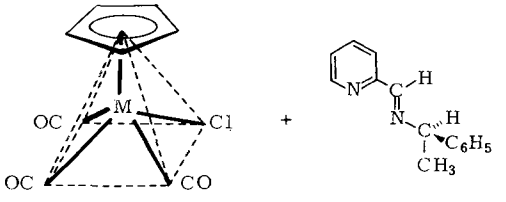
[58] *R. H. Prince* and *P. R. Woolley*, J. Chem. Soc. (Dalton), in press.

Optically Active Molybdenum and Tungsten Complexes with Tetragonal-pyramidal Configuration[1]

By *Henri Brunner* and *Wolfgang A. Herrmann*[*]

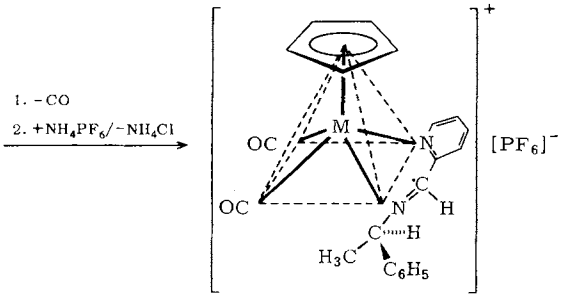
Compounds of the type $C_5H_5M(CO)_2LX$ (M = Mo or W) have square-pyramidal structures with the C_5H_5 ligand at the apex of the pyramid[2-4]. Interconversion of *cis-trans*-isomers can be followed by NMR spectroscopy[5-7]. Bidentate ligands LL, replacing the two substituents L and X, necessarily occupy *cis*-positions and *cis-trans*-isomerizations are excluded. With asymmetric chelate ligands LL' compounds of the type $C_5H_5M(CO)_2LL'$ should occur in enantiomeric forms; however, since derivatives with coordination number 5 generally isomerize readily, only a few compounds of five-ligated phosphorus have as yet been isolated in optically active form[8,9]. Whereas these compounds usually undergo rapid pseudorotation, we now report optically active molybdenum and tungsten complexes with surprisingly stable tetragonal-pyramidal configuration.

When tricarbonylchloro(π-cyclopentadienyl) complexes of molybdenum *(1)* or tungsten *(2)* are treated with the Schiff base of pyridin-2-aldehyde and (−)-α-phenylethylamine *(3)*, one CO group is replaced and the Cl ligand is displaced into the outer coordination sphere. Thus are formed the cationic complexes *(4a, b)* and *(5a, b)*, respectively, as chlorides that contain asymmetric Mo or W atoms.



(1), M = Mo
(2), M = W

(3)



(4a, b)
(5a, b)

In this reaction the bidentate Schiff base *(3)* functions on the one hand as a ligand lowering the symmetry and on the other as an optically active agent for resolution of the racemate. After conversion of the chlorides into hexa-

[*] Prof. Dr. H. Brunner and Dipl.-Chem. W. A. Herrmann
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

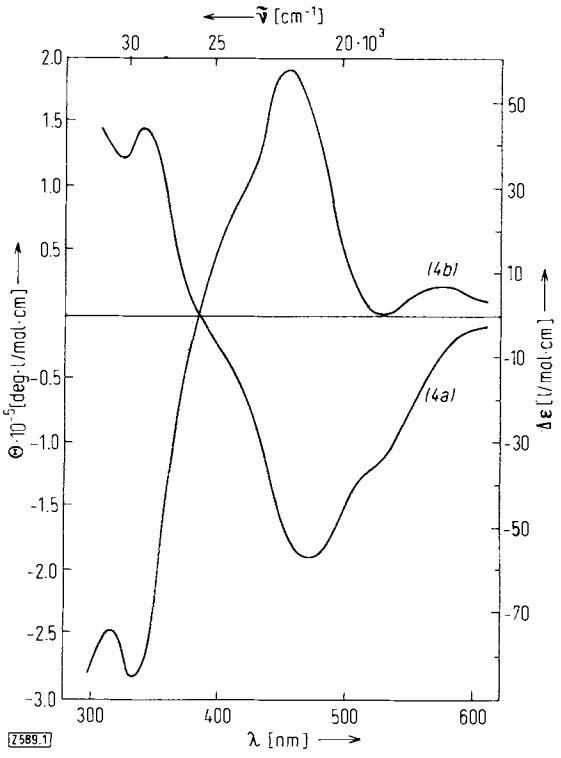


Fig. 1. CD spectra of the diastereoisomeric molybdenum complexes *(4a)* and *(4b)* in acetone.

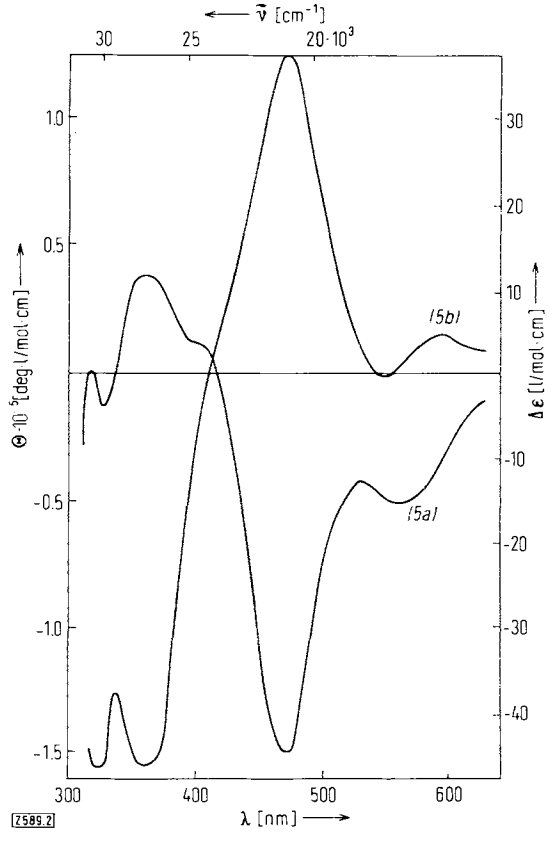


Fig. 2. CD spectra of the diastereoisomeric tungsten complexes *(5a)* and *(5b)* in acetone.

fluorophosphates the diastereoisomers can be separated on the basis of their differing solubilities by repeated fractional crystallization from an acetone/methylene chloride/ethanol mixture (20:3:1). It is remarkable that of the diastereoisomeric pair *(4a, b)* it is the levorotatory (at 436 nm) isomer *(4b)*, but of *(5a, b)* the dextrorotatory isomer *(5a)*, that is preferentially enriched in the sparingly soluble fraction. The absolute configurations are not known.

In the solid state and in solution the diamagnetic salt-like complexes *(4a)*, *(4b)*, *(5a)*, and *(5b)* are configurationally stable at room temperature. However, the complexes decompose slowly under the action of atmospheric oxygen and of light, with slight increase in the specific conductivity. Two strong CO bands appear in the carbonyl region of the IR spectra of these compounds. The ^{1}H-NMR spectra show, besides the signals of the chelate ligand, a sharp singlet due to the protons of the cyclopentadienyl ring. The complexes are deep red with a metallic sheen and dissolve readily in acetone or dimethyl sulfoxide, but very slightly in water or apolar solvents.

Figures 1 and 2 show the CD spectra of the complexes *(4a)*, *(4b)* and *(5a)*, *(5b)*, respectively. The diastereoisomeric pairs give approximate mirror images over parts of their CD curves.

Received: December 22, 1971 [Z 589 IE]
German version: Angew. Chem. *84*, 442 (1972)

[1] Part 11 of Optically Active Transition-metal Complexes.—Part 10: *H. Brunner* and *W. A. Herrmann*, Chem. Ber. *105*, 770 (1972).

[2] *S. Chaiwasie* and *R. H. Fenn*, Acta Crystallogr. *24 B*, 525 (1968).

[3] *J. H. Cross* and *R. H. Fenn*, J. Chem. Soc. *A 1970*, 3019.

[4] *M. A. Bush*, *A. D. U. Hardy*, *Lj. Manojlovic-Muir*, and *G. A. Sim*, J. Chem. Soc. *A 1971*, 1003.

[5] *J. W. Faller* and *A. S. Anderson*, J. Amer. Chem. Soc. *92*, 5852 (1970).

[6] *G. Wright* and *R. J. Mawby*, J. Organometal. Chem. *29*, C 29 (1971).

[7] *J. W. Faller*, *A. S. Anderson*, and *A. Jakubowski*, J. Organometal. Chem. *27*, C 47 (1971).

[8] *D. Hellwinkel*, Chem. Ber. *99*, 3642 (1966).

[9] *J. Ferekh*, *J. F. Brazier*, *A. Munoz*, and *R. Wolf*, C. R. Acad. Sci. Paris *270 C*, 865 (1970).

A Simple Synthesis of [2.2]Paracyclophanes

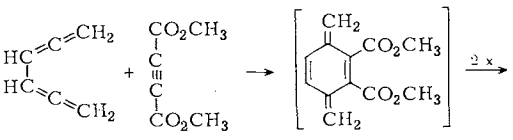
By *Henning Hopf*[*]

Dedicated to Professor R. Criegee on the occasion of his 70th birthday

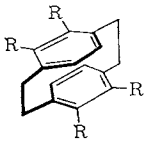
Addition reactions to 1,2,4,5-hexatetraene (biallenyl) *(1)*[1] are of interest because this acyclic C_6H_6 hydrocarbon contains one conjugated and two cumulated diene systems. To find out whether [2+2]-cycloaddition to the allene groups or [2+4]-cycloaddition to the "inner" double bonds is favored[2], we have treated *(1)* with dienophiles; we report here the reaction of biallenyl *(1)* with dimethyl acetylenedicarboxylate *(2)*.

Warming a solution of equimolar amounts of *(1)* and *(2)* in benzene for 9 hours at 65 °C, followed by removal of the solvent and recrystallization from benzene affords very shiny crystalline scales (m.p. 213—215 °C, uncorr.; yield 32%), to which structure *(4a)* may be assigned on the basis of the following data.

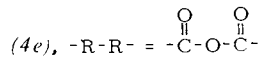
[*] Dr. H. Hopf
Institut für Organische Chemie der Universität
75 Karlsruhe, Richard-Willstätter-Allee 2 (Germany)



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



(4a), R = CO_2CH_3
(4b), R = H
(4c), R = CH_2OH
(4d), R = CO_2H



(4e), -R-R- =

According to the mass spectrum *(4a)* is a dimer of the 1:1 adduct of *(1)* and *(2)*[3]. The IR spectrum (KBr) shows intense bands at 1724, 1264, 1127, and 1107 cm^{-1} ($COOCH_3$) accompanied by weaker absorption maxima at 3000, 1577, 1553, 869, 788, and 725 cm^{-1} [Ar—H; the aromatic bands of the parent hydrocarbon *(4b)* appear at 3030, 1575, 930, 893, and 725 cm^{-1} [4, 5]]. The NMR spectrum [($CDCl_3$/TMS), $\tau = 3.10$ (4H/s), 6.15 (12H/s), and 6.78 ppm (8H/AA'BB'—M)] shows the shift of the aromatic protons to higher field characteristic of [2.2]paracyclophane systems [*(4b)*: $\tau = 3.63$ (s) and 6.95 (s)[6]]. The unstructured UV spectrum (ethanol) with bands at $\lambda_{max} = 302$ ($\varepsilon = 2080$) and 213 nm (42000) also indicates the [2.2]paracyclophane structure of *(4a)* [*(4b)*: $\lambda_{max} = 302$ (160), 284 (250), and 224 nm (25000)[4, 7]].

(4a) withstands several hours' heating at 250 °C without change and thus presumably exists in the *anti*-conformation shown. The *syn*-isomer should, by analogy to results of *Reich* and *Cram*[8], be less stable and rearrange to *(4a)* at high temperatures.

Formation of the tetraester *(4a)* from *(1)* and *(2)* can be most simply explained as occurring through the intermediate quinodimethane derivative *(3)*. Such intermediates are formed in several other syntheses of [2.2]paracyclophanes[5, 9a, 9b] but from cyclic precursors. This is evidently the first case of formation of a quinodimethane from acyclic precursors by 1,4-cycloaddition.

Pure biallenyl is not necessary for preparation of *(4a)*: the C_6H_6 hydrocarbon mixture obtained by dimerization of propargyl bromide[10], which contains about 40% of *(1)*, can be treated directly with *(2)* since the other C_6H_6 isomers—mainly 1,2-hexadien-5-yne (propargylallene)—do not react with *(2)* under the conditions stated. Thus this

[1] *H. Hopf*, Angew. Chem. *82*, 703 (1970); Angew. Chem. internat. Edit. *9*, 732 (1970).

[2] Cf. papers by *Bertrand et al.* on cycloadditions to vinylallene, *e.g. M. Bertrand*, *J. Grimaldi*, and *B. Waegell*, Bull. Soc. Chim. France *1971*, 962.

[3] Calculated and experimental elemental analyses are in agreement.

[4] *D. J. Cram* and *H. Steinberg*, J. Amer. Chem. Soc. *73*, 5691 (1951).

[5] *D. T. Longone* and *C. L. Warren*, J. Amer. Chem. Soc. *84*, 1507 (1962).

[6] *D. J. Cram* and *R. C. Helgeson*, J. Amer. Chem. Soc. *88*, 3515 (1966).

[7] *D. J. Cram*, *R. H. Bauer*, *N. L. Allinger*, *R. A. Reeves*, *W. J. Wechter*, and *E. Heilbronner*, J. Amer. Chem. Soc. *81*, 5977 (1959).

[8] *H. J. Reich* and *D. J. Cram*, J. Amer. Chem. Soc. *91*, 3517 (1969).

[9] a) *B. H. Smith*: Bridged Aromatic Compounds. Academic Press, New York 1964; b) *G. W. Brown* and *F. Sondheimer*, J. Amer. Chem. Soc. *89*, 7116 (1967).

[10] *H. Hopf*, Chem. Ber. *104*, 1499 (1971).

[11] Proof of the structures rests on IR, NMR, UV, and mass spectra, as well as on elemental analyses.

addition becomes an attractive method of preparing [2.2]paracyclophanes.

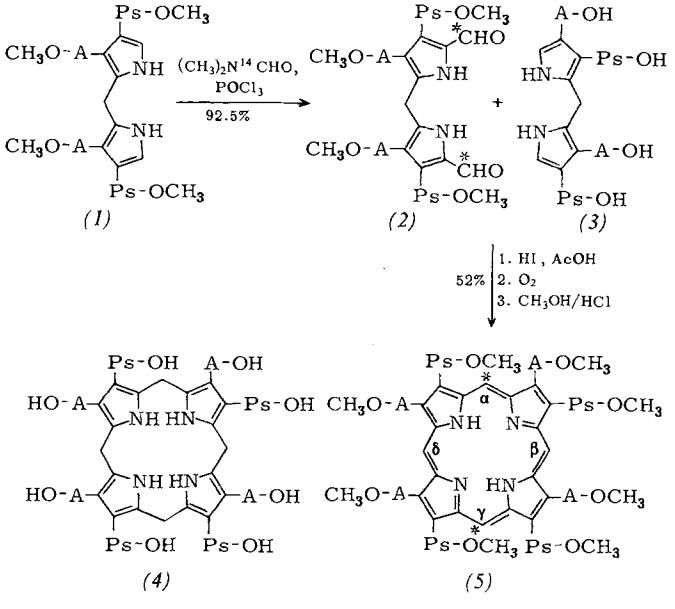
Reduction of the ester *(4a)* with $LiAlH_4$/THF leads to the tetraol *(4c)*[11], and its hydrolysis (KOH/CH_3OH) to the tetracarboxylic acid *(4d)*[11]. This acid cyclizes to the anhydride *(4e)*[11] when boiled with glacial acetic acid, and decarboxylates to the parent compound *(4b)* on heating with copper powder in quinoline[11].

Received: December 13, 1971 [Z 598 IE]
German version: Angew. Chem. *84*, 471 (1972)
Publication delayed at the author's request

Total Synthesis of [α,γ-$^{14}C_2$]Uroporphyrin III

By *Burchard Franck, Dietrich Gantz,* and *Fritz Hüper*[*]

Uroporphyrin III *(6)* and its hexahydro derivative, uroporphyrinogen III *(4)*, have been discussed as biosynthetic precursors of the biologically important tetrapyrroles heme, chlorophyll, and vitamin B_{12}[1]. Specifically ^{14}C-labeled uroporphyrin III and uroporphyrinogen III have not previously been available for testing of these proposals by feeding experiments[2]. We report here a procedure for the total synthesis of [α,γ-$^{14}C_2$]uroporphyrin III as its octa-



A = —CH_2—CO—
Ps = —CH_2—CH_2—CO— *(6)*, A—OH, Ps—OH instead of A—OCH_3, Ps—OCH_3

methyl ester *(5)* which is stable and is the appropriate depot compound for feeding experiments. This compound readily yields uroporphyrinogen III by hydrolysis and reduction.

The α- and γ-methine groups were selected for specific ^{14}C-labeling. First, the radioactivity can then be introduced during the last stage of a *convergent synthesis*[4] which is superior to linear approaches in the number of steps and yield; and, secondly, the corresponding C atoms of important products biosynthesized from *(4)* can be selectively isolated for localization of radioactivity[5, 6].

The dipyrrylmethanes *(1)* and *(3)* were obtained by, respectively, 13- and 11-stage syntheses modelled on work by *MacDonald*[7] and by *Treibs*[8]. Only the Vilsmeier reaction with [^{14}CO]dimethylformamide/$POCl_3$ came into consideration for converting *(1)* into the radioactive dialdehyde *(2)* for subsequent acid-catalyzed ring closure to a porphyrin. In other syntheses of aldehydes the requisite large excess of radioactive formylating agent reduces the radioactive yield considerably. Even in the Vilsmeier reaction of *(1)* the radioactive dimethylformamide must be used in, admittedly smaller, excess (in contrast to the procedure usual in isotope labeling) in order to allow the dipyrrylmethane, which is valuable because of its tedious preparation, to react in optimal yield. This being done, the ^{14}C-labeled dialdehyde *(2)* is obtained from *(1)* in a weight yield of 92.5% and a radioactive yield of 17%. Condensation of the radioactive dialdehyde *(2)* with the dipyrrylmethane *(3)* in glacial acetic acid in presence of hydriodic acid, and subsequent oxidation by air and methylation by methanol/HCl, afforded radioactive crystalline uroporphyrin III octamethyl ester *(5)*, m. p. 258—261 °C (258 to 260 °C[7]) in 52% yield based on *(2)*.

[(^{14}CHO)^2]Dipyrrylmethanedicarbaldehyde (2)

[^{14}CO]Dimethylformamide[9] (140 mg, 1.9 mmol, 2.5 mCi) in anhydrous CH_2Cl_2 (0.2 ml) was treated successively, with ice-cooling, with $POCl_3$ (0.18 ml, 2.0 mmol), and dropwise with a solution of the dipyrrylmethane *(1)* (100 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (1 ml) and $POCl_3$ (0.05 ml, 0.54 mmol). This reaction mixture was kept for 1 h at 20 °C, then warmed for 1 h at 50 °C whereupon the CH_2Cl_2 distilled off; the mixture was then cooled again to 0 °C, dissolved in ice-water (100 ml) and treated with sodium acetate until its reaction was weakly alkaline. After three days the precipitated product was filtered off, washed with water, and recrystallized from 60% ethanol, yielding the dialdehyde *(2)* (103 mg, 92.5%; 0.43 mCi, 17%).

[α,γ-$^{14}C_2$]Uroporphyrin III octamethyl ester (5)

A solution of *(2)* (99 mg, 0.19 mmol, 0.15 mCi) and *(3)* (77.6 mg, 0.19 mmol) in glacial acetic acid (120 ml) was treated with 56% HI (0.6 ml) in glacial acetic acid (28 ml)[7]. After 20 min sodium acetate (1.9 g) in glacial acetic acid (28 ml) was added to the deep red reaction mixture, air was bubbled through and after 24 h the dark brown precipitate was collected. This was dissolved in 5% methanolic HCl and kept for 24 h at 20 °C, ice-water was added, and the mixture was extracted with $CHCl_3$. The dried residue from the $CHCl_3$ extract was purified by layer chromatography ($CHCl_3$ + 1% of CH_3OH; silica gel, E. Merck) and recrystallization from $CHCl_3$/acetone, affording *(5)* (92.5 mg, 52%; 0.079 mCi).

Received: January 14, 1972 [Z 599a IE]
German version: Angew. Chem. *84*, 432 (1972)

[*] Prof. Dr. B. Franck and Dr. D. Gantz
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)
Dr. F. Hüper, present address:
Farbenfabriken Bayer AG
56 Wuppertal-Elberfeld (Germany)

[1] *J. Lascelles:* Tetrapyrrole Biosynthesis and its Regulation. Benjamin, New York 1964; *L. Bogorad* and *R. F. Troxler* in *P. Bernfeld:* Biogenesis of Natural Compounds. 2nd Edit., Pergamon Press, Oxford 1967, p. 247.

[2] Uniformly labeled uroporphyrin III and uroporphyrinogen III, previously obtained by biosynthesis [3], are not suitable for demonstration of possible rearrangement into isomers during biosynthetic experiments.

[3] *L. Bogorad* and *G. S. Marks*, Biochim. Biophys. Acta *41*, 356 (1960); *K. Salomon, J. E. Richmond*, and *K. I. Altmann*, J. Biol. Chem. *196*, 462 (1952).

[4] *L. Velluz, J. Ralls*, and *G. Nominé*, Angew. Chem. *77*, 185 (1965); Angew. Chem. internat. Edit. *4*, 181 (1965); *R. E. Ireland*: Organic Synthesis. Prentice-Hall, Englewood Cliffs, N. J. 1969.

[5] *F. Schmidtchen*, Diplomarbeit, Universität Münster 1970.

[6] *B. Franck, D. Gantz, F.-P. Montforts*, and *F. Schmidtchen*, Angew. Chem. *84*. 433 (1972); Angew. Chem. internat. Edit. *11*, 421 (1972).

[7] *E. J. Tarlton, S. F. MacDonald*, and *E. Baltazzi*, J. Amer. Chem. Soc. *82*, 4389 (1960).

[8] *A. Treibs* and *W. Ott*, Liebigs Ann. Chem. *615*, 137 (1958).

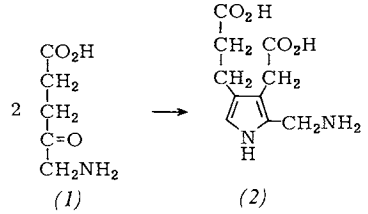
[9] [^{14}CO]Dimethylformamide was prepared by distillation from a 200 °C melt of dimethylammonium chloride and sodium [^{14}C]formate in a special microapparatus [10] and subsequent removal of product water by distillation in CH_2Cl_2 vapor.

[10] *D. Gantz*, Dissertation, Universität Münster 1971.

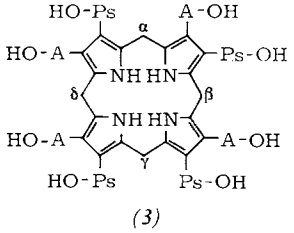
On the Biosynthesis of Heme and Vitamin B_{12} from [α,γ-$^{14}C_2$]Uroporphyrinogen III

By *Burchard Franck, Dietrich Gantz, Franz-Peter Montforts*, and *Franz Schmidtchen*[*]

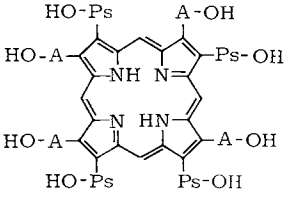
According to mechanistic considerations[1] and some experimental findings[2], uroporphyrinogen III *(3)* and its dehydrogenation product, uroporphyrin III *(4)*, come into consideration as biosynthetic precursors of the biologically important tetrapyrroles heme *(6)* and vitamin B_{12} *(8)*. Uroporphyrinogen III itself arises from eight molecules of 5-aminolevulic acid *(1)* by way of the monopyrrole, porphobilinogen *(2)*[3]. The biosynthesis of heme *(6)* and vitamin B_{12} *(8)* is substantially confirmed up to the porphobilinogen *(2)* stage by isotope experiments.



(1) *(2)*

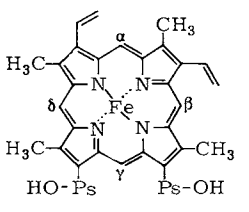


(3)



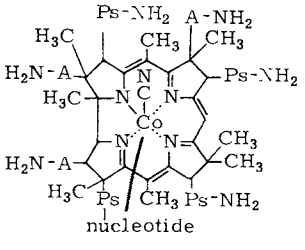
(4)

(5), OCH_3 instead of OH



(6)

(7), Fe instead of Fe(Cl)



(8)

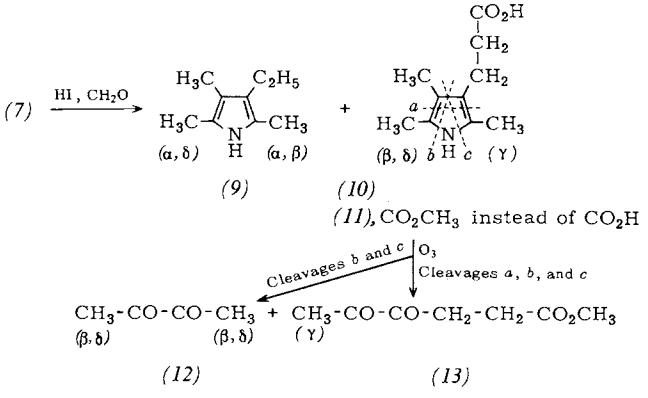
A = $-CH_2-CO-$

Ps = $-CH_2-CH_2-CO-$

There has not hitherto been any proof, by feeding experiments with radioactively labeled precursors, of the biosynthetic intermediates assumed for the conversion of porphobilinogen *(2)* into the above tetrapyrroles *(6)* and *(8)*. By using specifically ^{14}C-labeled [α,γ-$^{14}C_2$]uroporphyrinogen III *(3)*, which has now become available[4], we have been able to show that this biosynthetic unit is converted with high incorporation and without isomerization into the blood pigment heme *(6)*, but not into vitamin B_{12} *(8)*.

Eight batches (each 20 ml) of duck's blood, hemolyzed by freeze-thawing[5], were incubated for 48 h at 32 °C with various amounts (0.22—1.19 mmol) of [α,γ-$^{14}C_2$]uroporphyrinogen III *(3)*[6] having a specific radioactivity amounting to 0.79 mCi/mmol. These batches were worked up separately. When freed quantitatively from porphyrins without metal atom and purified to constant radioactivity, the hemin *(7)* obtained had a mean radioactivity of 1.65 μCi/mmol, corresponding to 0.21% specific incorporation[7]. The absolute incorporations[8] lay between 33 and 61%.

A specific degradation was carried out to show that the ^{14}C radioactivity of the isolated hemin *(7)* resided only in the α- and γ-methine groups and that the biosynthesis of *(7)* from [α,γ-$^{14}C_2$]uroporphyrinogen III was thus direct and unaccompanied by isomerization[9]. Methylating fission of *(7)* by 67% hydriodic acid and paraformaldehyde in glacial acetic acid/H_3PO_2[10] afforded radioactive phyllopyrrole *(9)* and radioactive phyllopyrrolecarboxylic acid *(10)* which contained the α-, β-, and δ- or β-, γ-, and δ-methine-C atoms, respectively, in their α-methyl groups as indicated in the formula. Ozonolysis of the methyl phyllopyrrolecarboxylate *(11)* in $CHCl_3$, which occurs with participation of resonance structures[11] at *a*, *b*, and *c*, yielded inactive biacetyl *(12)*[12] and radioactive methyl 4,5-dioxohexanoate *(13)*[12] with the β- and δ-, or



(9) *(10)*

(11), CO_2CH_3 instead of CO_2H

(12) *(13)*

Table. Radioactivities of hemin *(7)* and its degradation products.

Substance	Radioact. (μCi/mmol)	Labeled C atoms per molecule	
		Calc.	Found [13]
(7)	1.37	2	2.0
(9)	0.334	0.5	0.49
(11)	0.335	0.5	0.49
(12)	0.0002	0	0.00
(13)	0.0448	max. 0.5	0.066 [13]

[*] Prof. Dr. B. Franck, Dr. D. Gantz, Dipl.-Chem. F.-P. Montforts, and Dipl.-Chem. F. Schmidtchen
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

γ-methine-C atoms, respectively, in the methyl groups. The relative amounts of labeled C atoms (see Table), calculated from the specific radioactivities found for the degradation products *(9)* and *(11)*—*(13)*, show that only the α- and γ-methine groups of heme were radioactive. The inactivity of the biacetyl *(12)*, which contains only the β- and δ-methine-C atoms, excludes labeling at these positions.

For investigation of vitamin B_{12} biosynthesis a 1-l liquid culture (cornsteep/glucose[14]) of *Propionibacterium shermanii* (ATCC 9617) was used which was kept anaerobically (N_2) for the first three days and then aerobically (100 ml of O_2 per min) for four days. To this were added, in two equal portions on the first and the second day, 4.29 μmol of [α,γ-$^{14}C_2$]uroporphyrinogen III of specific radioactivity 0.79 mCi/mmol. Later the vitamin B_{12} (6.6 mg) formed was determined microbiologically[15] and, after addition of inactive vitamin B_{12} and isolation the specific radioactivity was measured. For the undiluted vitamin this amounted to 0.017 μCi/mmol, corresponding to a specific incorporation of $<0.0025\%$, which is no longer significant[16].

Received: January 14, 1972 [Z 599b IE]
German version: Angew. Chem. *84*, 433 (1972)

[1] *D. Shemin*, Naturwissenschaften *57*, 185 (1970); *J. H. Mathewson* and *A. H. Corwin*, J. Amer. Chem. Soc. *83*, 135 (1961); *L. Bogorad* and *R. F. Troxler* in *P. Bernfeld*: Biogenesis of Natural Compounds. 2nd Edit., Pergamon Press, Oxford 1967, p. 247.

[2] *R. A. Neve*, *R. F. Labbe*, and *R. A. Aldrich*, J. Amer. Chem. Soc. *78*, 691 (1956); *D. Mauzerall* and *S. Granick*, J. Biol. Chem. *232*, 1141 (1958); *B. F. Burnham* and *R. A. Plane*, Biochem. J. *98*, 13c (1966).

[3] *D. Shemin* and *C. S. Russell*, J. Amer. Chem. Soc. *75*, 4873 (1953); *S. Schwartz*, *K. Ikeda*, *I. M. Miller*, and *C. J. Watson*, Science *129*, 40 (1959); *C. Bray* and *D. Shemin*, J. Biol. Chem. *238*, 1501 (1963).

[4] *B. Franck*, *D. Gantz*, and *F. Hüper*, Angew. Chem. *84*, 432 (1972); Angew. Chem. internat. Edit. *11*, 420 (1972).

[5] *S. Granick*, J. Biol. Chem. *232*, 1101 (1958).

[6] Qbtained from [α,γ-$^{14}C_2$]uroporphyrin III octamethyl ester *(5)* [4] by hydrolysis of the ester groups by 20% aqueous HCl at 20 °C and subsequent reduction by 2.5% sodium amalgam in aqueous solution.

[7] Spec. radioactivity of the isolated radioactive hemin divided by that of the [α,γ-$^{14}C_2$]uroporphyrinogen III fed and multiplied by 100.

[8] Total radioactivity of the isolated radioactive hemin divided by that of the [α,γ-$^{14}C_2$]uroporphyrinogen III fed and multiplied by 100.

[9] *E. g.* uroporphyrinogens isomerize easily in acid solution: *L. Bogorad* and *G. S. Marks*, J. Biol. Chem. *235*, 2127 (1960); *D. Mauzerall*, J. Amer. Chem. Soc. *82*, 2602 (1960).

[10] *M. W. Roomi* and *S. F. MacDonald*, Canad. J. Chem. *48*, 139 (1970); *R. A. Chapman*, *M. W. Roomi*, *T. C. Morton*, *D. T. Krajcarski*, and *S. F. MacDonald*, *ibid. 49*, 3544 (1971).

[11] *J. Wibaut*, J. Chim. Physique *53*, 143 (1956).

[12] Isolated as 2,4-dinitrophenylosazone.

[13] The observed spec. radioactivities of the degradation products were referred to that of the isolated radioactive hemin *(7)* with two ^{14}C atoms. Since in the degradation of the hemin the radioactivity of the α- and γ-methine groups is divided between two molecules each of the phyllopyrrole *(9)* and the methyl phyllopyrrolecarboxylate *(11)*, these degradation products should each contain 25% of the radioactivity of the hemin. The methyl 4,5-dioxohexanoate *(13)* can contain only a fraction of the radioactivity of the γ-methine group of *(7)* since in the ozonolysis of *(11)* it is formed mainly by fission according to *a* and only to a slight extent according to *b* and *c*.

[14] *J. D. Speedie* and *G. W. Hull*, US-Pat. 2951107 (1960); Chem. Abstr. *54*, 15852i (1960).

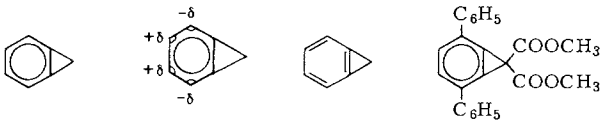
[15] United States Pharmacopeia *15*, 885 (1955); Internal report Difco Laboratories: Microbiological Assay of Vitamins and Amino Acids. Difco Company, Detroit 1964, p. 17.

[16] After conclusion of our feeding experiments *G. Müller* and *W. Dieterle*, Hoppe-Seylers Z. physiol. Chem. *352*, 143 (1971), announced that, using a biosynthetically obtained mixture of uniformly ^{14}C-labeled uroporphyinogens I and III and cell suspensions of *Propionibacterium shermanii*, they too observed no incorporation into the corrin ring of vitamin B_{12}.

X-Ray Structure Analysis of a Benzocyclopropene Derivative

By *Ernst Carstensen-Oeser*, *Berthold Müller*, and *Heinz Dürr*[*]

A benzene ring is appreciably deformed when annelated to a strained small ring. Previous NMR spectroscopic studies and calculations[1–3] for benzocyclopropene *(1)* indicated angular deformation of the kind shown in *(2)*[3] and changes in bond lengths in the six-membered ring that suggested a preference for the mesomeric limiting structure *(3)*[1,2].



(1) *(2)* *(3)* *(4)*

To determine these effects quantitatively we have carried out an X-ray structure analysis of a benzocyclopropene. Dimethyl 2,5-diphenylbenzocyclopropene-1,1-dicarboxylate *(4)*[4] is particularly suitable for this purpose: it crystallizes in well formed colorless needles of m. p. ≥ 175 °C.

The crystals are monoclinic, space group $P2_1/a$; $a=22.15\pm0.01$, $b=7.91\pm0.01$, $c=10.92\pm0.01$, $\beta=99.2\pm0.1°$; $Z=4$. The intensities of 3542 reflections were measured on an automatic diffractometer. We determined the sign of 297 reflections with the largest E values by triple product methods[5].

The structural model obtained by E-Fourier synthesis was refined to an R value of 7.7%.

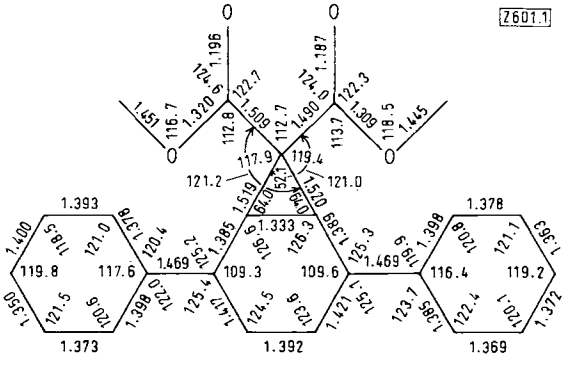


Fig. 1. Bond lengths and angles of *(4)*. The maximal values of all standard deviations amounted to 0.008 Å or 0.5°.

The result of the investigations (Fig. 1) confirmed the angular deformation shown in *(2)*. These changes in bond lengths and angles caused by the annelated strained ring must be viewed in comparison with those in *p*-terphenyl, for which a very accurate X-ray structure analysis has been carried out[6]. The bond lengths give *no* evidence for the Kekulé structure *(3)*. The unsaturated three-membered

[*] Dr. E. Carstensen-Oeser and Dipl.-Ing. B. Müller
Eduard-Zintl-Institut der Technischen Hochschule
Lehrstuhl für Strukturforschung
61 Darmstadt, Hochschulstrasse 4 (Germany)
Prof. Dr. H. Dürr
Institut für Organische Chemie der Universität
66 Saarbrücken 15 (Germany)

ring has the same interatomic distances as in cyclopropene[7].

The benzocyclopropene system is not quite planar; the three-membered and the six-membered ring form an angle of $1.5 \pm 0.5°$. The planes of the two phenyl substituents in the crystal are twisted by 3.1° and 8.2° from the plane of the benzene ring in the benzocyclopropene system.

Received: November 18, 1971 [Z 601 IE]
German version: Angew. Chem. *84*, 434 (1972)

[1] *E. Vogel, S. Korte, W. Grimme*, and *H. Günther*, Angew. Chem. *80*, 279 (1968); Angew. Chem. internat. Edit. *7*, 289 (1968).

[2] *M. Cooper* and *S. L. Manatt*, J. Amer. Chem. Soc. *92*, 1605 (1970).

[3] *J. B. Pawlizek* and *H. Günther*, J. Amer. Chem. Soc. *93*, 2050 (1971); *H. Günther* and *J. B. Pawlizek*, Org. Magn. Res. *3*, 267 (1971).

[4] *H. Dürr* and *L. Schrader*, Angew. Chem. *81*, 426 (1969); Angew. Chem. internat. Edit. *8*, 446 (1969).

[5] *D. Sayre*, Acta Cryst. *5*, 60 (1952); *J. Karle* and *I. L. Karle*, *ibid. 21*, 849 (1966); *R. E. Long*, Dissertation, University of California at Los Angeles 1965.

[6] *H. M. Rietveld, E. N. Maslen*, and *C. J. B. Clews*, Acta Cryst. *B 26*, 693 (1970).

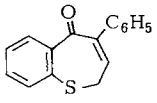
[7] *J. D. Dunitz* and *V. J. Schomaker*, J. Chem. Phys. *20*, 1708 (1952); *R. H. Kasai, R. J. Myers, D. F. Eggers*, and *K. B. Wiberg*, *ibid. 30*, 512 (1959).

Synthesis of Stable 1-Benzothiepins[1]

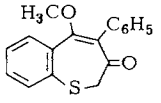
By *Hans Hofmann, Bernd Meyer*, and *Peter Hofmann*[*]

Stable 3-benzothiepins have been known for some time[4]. Attempts to prepare similar stable 1-benzothiepins have so far been successful only in one case [compound *(6)*][5]; in all other experiments only products of further reaction were isolated[6]. This is difficult to explain when it is remembered that 1-benzoxepin and 3-benzoxepin, for instance, are about equally stable and have approximately the same resonance energy[7]. We have therefore worked out methods of preparing 1-benzothiepins and have carried out an HMO analysis of the ring system.

In the 1-benzoxepin series the synthetic route through the enol derivatives of seven-membered ring 1,3-diketones permits use of extremely mild reaction conditions[5, 8]. Analogously, we have prepared the substituted 4-phenyl-1-benzothiepins *(3)*—*(5)* from the ketones *(1)*[8] and *(2)*[9].

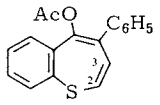


(1)

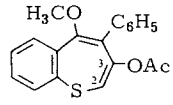


(2)

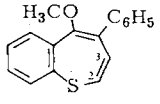
Acetylation of *(1)* with acetic anhydride in triethylamine in presence of 4-dimethylaminopyridine[10] at −15 °C afforded 5-acetoxy-4-phenyl-1-benzothiepin *(3)*. Analogous acetylation of *(2)* gave 3-acetoxy-5-methoxy-4-phenyl-1-benzothiepin *(4)*. Methylation of *(1)* with dimethyl sulfate and potassium *tert*-butoxide in tetrahydrofuran at 0 °C, followed by chromatography of a benzene solution on silica gel and rubbing with a little methanol, led to 5-methoxy-4-phenyl-1-benzothiepin *(5)*[11] (see Table).



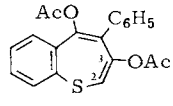
(3)



(4)



(5)



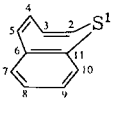
(6)

Table. Comparison of *(3)*, *(4)*, and *(5)* with 3,5-diacetoxy-4-phenyl-1-benzothiepin *(6)* [5].

	(3)	*(4)*	*(5)*	*(6)* [5]
M.p. (°C)	98.5–100.5	87–88	77–79	86–87
Yield (%)	61	70	45	75
(cryst. from)	(Methanol)	(Methanol)		(Methanol)
Color	Pale yellow	Almost colorless	Pale yellow	Almost colorless
UV (*n*-heptane)				
λ_{max} (nm)	264	267	270	261
log ε (at λ_{max})	4.27	4.24	4.24	4.35
log ε (at 370 nm)	2.47	2.29	2.60	2.39
IR (KBr) (cm^{-1})				
$\nu_{C=O}$ (acetate)	1755	1759		1770
^{1}H-NMR ($CDCl_3$) (τ, ppm)				
H-2	3.92/d	4.10/s	3.96/d	4.0/s
H-3	3.57/d		3.60/d	
	(J_{AB} = 9 Hz)		(J_{AB} = 9 Hz)	
CH_3CO	8.14/s	8.43/s		8.35/s
				8.15/s
CH_3O		6.80/s	6.67/s	

In the UV spectra the striking feature is the characteristic extensions of the long-wave absorption maxima which, as for the corresponding 1-benzoxepins, extend into the visible region[1]. The chemical shifts of H-2 and H-3 accord very well with the values calculated from the shielding constants[12]. In the ^{1}H-NMR spectra of analogous 1-benzoxepins H-3 appears upfield from H-2! This is in agreement with the calculated π-electron densities, which in 1-benzothiepins are larger in position 2 but smaller in position 3 than for 1-benzoxepins.

The starting point for our HMO calculations was the following finding: our HMO calculation[14] carried out on a non-planar model of 1-benzoxepin and the SCF—MO data published by *Dewar et al.*[7] gave results in good agreement for the bonding and the π-electron densities. Also, the values given by *Dewar et al.*[15] for 3-benzothiepin accord acceptably with the result of our calculation for a non-planar model of 3-benzothiepin. We have therefore carried out a HMO calculation on the same basis for 1-benzothiepin. We assumed a flat boat as the favored conformation of the hetero ring[16]; the following torsion angles φ between the p_z orbitals of the centers of the model[18] can then be estimated from a Dreiding model[17]:

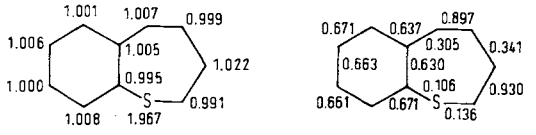


[*] Prof. Dr. H. Hofmann, Dipl.-Chem. B. Meyer [2], and Dipl.-Chem. P. Hofmann [3]
Institut für Organische Chemie der
Universität Erlangen-Nürnberg
852 Erlangen, Henkestrasse 42 (Germany)

bonds 1-2 and 1-11, $\varphi = 60°$; bonds 3-4 and 5-6, $\varphi = 45°$. In the calculations for these bonds the angle-corrected β values were taken from the relation[19]

$$\beta_{ik}(\varphi_{ik}) = \cos\varphi_{ik}\beta_{ik}(\varphi = 0)$$

The parameters for the hetero atom, h_{-S-} (0.5) and k_{C-S} (0.43), are taken from data of *Häfelinger*[20]; only 3p participation is assumed for sulfur. In this way we obtained the results shown in Fig. 1:



Z602.1

Fig. 1. π-Electron densities (left) and π-bond orders for 1-benzothiepin.

The total π-electron energy amounts to $12\alpha + 13.514\beta$, with ΔE between HOMO and LUMO (Highest Occupied; Lowest Unoccupied MO) $= 0.987\beta$[21].

1-Benzothiepin therefore contains an almost unperturbed benzene portion with approximately equal π-bond orders, and a heterocyclic seven-membered ring with localized, slightly conjugated double bonds, definite single bonds and a lone pair located almost exclusively on the sulfur. The lengths of the two C—S bonds amount to 1.742 and 1.763 Å[22]. Thus the C—S single bonds are as long as usual; together with the low π-electron energy and the irreversible elimination of sulfur, they cause the appreciably lower thermal stability of 1-benzothiepins compared to analogous 1-benzoxepins. The 1-benzothiepins prepared so far appear not to differ significantly in stability from the 3-benzothiepins.

Received: January 20, 1972 [Z 602 IE]
German version: Angew. Chem. *84*, 477 (1972)

[1] Heterocyclic seven-membered ring compounds, Part 7.—Part 6: *H. Hofmann* and *P. Hofmann*, Tetrahedron Lett. *1971*, 4055.

[2] The preparative work is taken from the Dissertation in preparation by *B. Meyer*, Universität Erlangen-Nürnberg.

[3] The HMO calculations are taken from the Dissertation in preparation by *P. Hofmann*, Universität Erlangen-Nürnberg.

[4] *G. P. Scott*, J. Amer. Chem. Soc. *75*, 6332 (1953); *K. Dimroth* and *G. Lenke*, Chem. Ber. *89*, 2608 (1956); *R. H. Schlessinger* and *G. S. Ponticello*, J. Amer. Chem. Soc. *89*, 7138 (1967); Tetrahedron Lett. *1968*, 3017.

[5] *H. Hofmann* and *H. Westernacher*, Chem. Ber. *102*, 205 (1969).

[6] *W. E. Parham* and *D. G. Weetman*, J. Org. Chem. *34*, 56 (1969), where previous work is cited.

[7] *M. J. S. Dewar* and *N. Trinajstić*, Tetrahedron *26*, 4269 (1970).

[8] *H.-J. Haberstroh*, Dissertation, Universität Erlangen-Nürnberg 1971.

[9] *B. Appler*, Dissertation, Universität Erlangen-Nürnberg 1972.

[10] *W. Steglich* and *G. Höfle*, Angew. Chem. *81*, 1001 (1969); Angew. Chem. Internat. Edit. *8*, 981 (1969).

[11] Correct C,H analyses are available for all the compounds; molecular weights are taken from mass spectra.

[12] *L. M. Jackman* and *S. Sternhell*: Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. 2nd Edit. Pergamon Press, Oxford 1969, p. 185.

[13] *F. Sondheimer* and *A. Shani*, J. Amer. Chem. Soc. *86*, 3168 (1964).

[14] *P. Hofmann*, Diploma thesis, Universität Erlangen-Nürnberg, 1971.

[15] *M. J. S. Dewar* and *N. Trinajstic*, J. Amer. Chem. Soc. *92*, 1453 (1970).

[16] *A. Mannschreck*, *G. Rissmann*, *F. Vögtle*, and *D. Wild*, Chem. Ber. *100*, 335 (1967).

[17] From Büchi, Flawil (Switzerland).

[18] The numbering of the centers does not correspond to IUPAC rules.

[19] *E. Heilbronner* and *H. Bock*: Das HMO-Modell und seine Anwendung. Verlag Chemie, Weinheim 1968.

[20] *G. Häfelinger*, Tetrahedron *27*, 1635 (1971).

[21] The total π-electron energy for 1-benzoxepin was calculated to be $12\alpha + 16.949\beta$; ΔE between HOMO and LUMO 0.974β.

[22] The bond lengths were calculated from the bond orders of a planar model.

Oxa[17]annulenes[1][**]

By *Gerhard Schröder*, *Günter Plinke* and *Jean F. M. Oth*[*]

Dedicated to Professor R. Criegee on the occasion of his 70th birthday

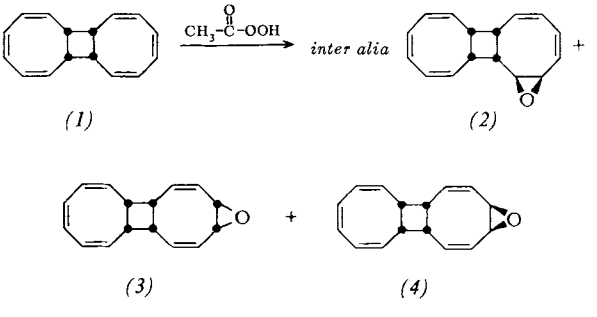
If we replace a —CH=CH— group in an annulene by a hetero atom with a lone pair we arrive at a heteroannulene[2]. Viewed thus, furan and pyrrole are, respectively, oxa- and aza-[5]annulenes, and oxonines[3] and azonines[4] are, respectively, oxa- and aza-[9]annulenes.

Oxa[17]annulenes are isoelectronic with aromatic [18]-annulenes[5]. Two questions interested us particularly about these higher-membered heteroannulenes, namely:

1. What is their π-electron structure?

2. Can configurational isomers be isolated or does a rapid mutual interconversion of configurational isomers occur such as has been observed with many higher-membered carbocyclic annulenes[6]?

Dimeric cyclooctatetraene *(1)* of m. p. 53 °C[7] is a suitable starting material for preparation of oxa[17]annulenes. On epoxidation of *(1)* in chloroform by peracetic acid at 30 °C there are formed, besides bisepoxides, an asymmetric epoxide *(2)* and two symmetrical epoxides *(3)* and *(4)*. Separation and purification of *(2)*—*(4)* is accomplished by column chromatography (SiO_2; pentane/ether 30:1) (see Table 1).



The position of the epoxide ring relative to the cyclobutyl protons in *(2)*—*(4)* was determined from the paramagnetic shift of individual proton resonance signals as observed

[*] Prof. Dr. G. Schröder and Dipl.-Chem. G. Plinke
Institut für Organische Chemie der Universität
75 Karlsruhe, Richard-Willstätter-Allee (Germany)
Prof. Dr. J. F. M. Oth
Organisch-chemisches Institut der ETH
Zürich (Switzerland)

[**] This work was supported by the Badische Anilin- & Soda-Fabrik AG and the Deutsche Forschungsgemeinschaft.

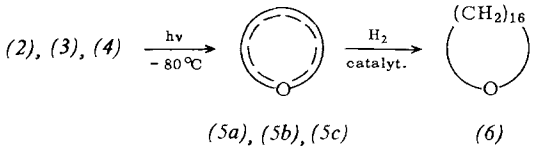
Table 1. Data for compounds *(2)*—*(4)*.

Cpd. [9]	Yield (%) [a]	M.p.(°C)	^{1}H-NMR, τ in ppm [b]	UV, λ in nm (ε) [c]
(2)	≈45	43–44	4.25 (10 H/m) 6.6 (5 H/m) 7.75 (1 H/m)	λ_{sh}224 (7050) λ_{sh}250 (2050)
(3)	≈3	88	4.3 (10 H/sharp m) 6.6 (6 H/sharp m)	λ_{sh}249 (1800)
(4)	≈1	86–89	4.5 (10 H/m) 6.5 (2 H/m) 7.0 (4 H/m)	λ_{max}250 (1600)

[a] Referred to the amount of *(1)* used.
[b] 60-MHz spectrum, in CCl_4, with TMS as internal standard.
[c] In ether.

in the presence of tris(tetramethylheptanedionato)europium[8].

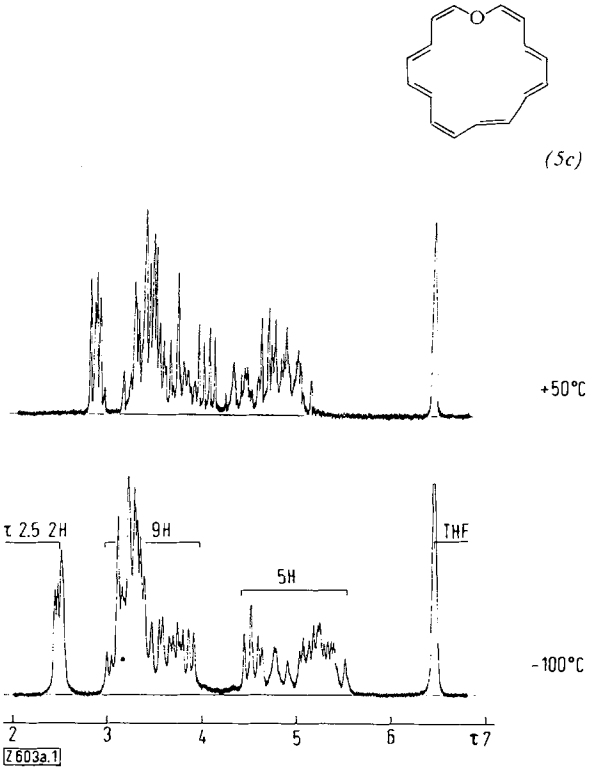
Photolysis of the epoxides *(2)*—*(4)* by a low-pressure UV lamp at −80°C in ether opened a route to the oxa[17]-annulenes *(5a)*—*(5c)*. These three products differ only in the sequence and individual number of *cis*- and *trans*-



double bonds. On catalytic hydrogenation they give the same colorless crystalline monocyclic ether *(6)* (see Table 2).

(5a) is formed almost exclusively from *(2)*, and practically pure *(5c)* from *(4)*. *(3)* affords, besides a little *(5c)*, a mixture that is inseparable by column chromatography and recrystallization and whose NMR spectrum contains all the signals of *(5a)* plus absorption bands that we ascribe to *(5b)*. *(5a)*, *(5a)*/*(5b)*, and *(5c)* are crystalline red compounds that can be purified by column chromatography (SiO_2; pentane/ether 30:1) and recrystallization; they are thermally stable (unchanged when warmed at 60°C) but very sensitive to oxygen.

The NMR spectra of *(5a)*, *(5a)*/*(5b)*, and *(5c)* are very complicated. They are slightly temperature-dependent, which mirrors a certain amount of conformational mobility in the ring. We find no convincing evidence for marked π-electron delocalization in the NMR spectra[10]. The available spectroscopic data do not permit any firm statement about the configurations of the oxa[17]annulenes. Provisionally we suggest the *cis,trans,trans,trans,cis,trans,-cis*-configuration for *(5c)*.



We return now to our original questions:

1. The oxa[17]annulenes with $(4n+2)$ π-electrons are best described as polyolefins.

Table 2. Data for compounds *(5a)*, *(5c)*, and *(6)*.

Cpd. [9]	Yield	M.p.(°C)	^{1}H-NMR, τ in ppm	UV, λ in nm (ε) [c]
(5a)	≈33% from *(2)* ≈ 2% from *(4)*	162 (dec.)	2.5 (1 H/d; J = 12.5 Hz) 3.1–4.1 (10 H/m) 4.1–5.8 (5 H/m) [a]	λ_{max} 304 (34000) λ_{max} 403 (6500)
(5c)	≈ 1.5% from *(2)* ≈ 2% from *(3)* ≈40% from *(4)*	160 (dec.)	2.5 (2 H/two d; J = 6 and 7 Hz) 3.0–4.0 (9 H/m) 4.4–5.5 (5 H/m) [a]	λ_{max} 315 (58000) λ_{max} 407 (7100)
(6)	≈80% from *(5)*	20	6.7 (4 H/pseudo-t; J = 5 Hz) 8.7 (28 H/m) [b]	—

[a] 100-MHz spectrum, in CS_2/[D_8]-THF, at −100°C, with TMS as internal standard.
[b] 60-MHz spectrum in CCl_4, at 40°C, with TMS as internal standard.
[c] In ether.

2. In contrast to higher-membered carbocyclic annulenes[6], configurational isomers can be isolated that are not thermally interconvertible. At +10°C light from a low-pressure UV lamp isomerizes *(5a)*, partially to *(5c)*, but *(5c)* is almost unaltered by irradiation at −80 to +10°C.

Received: January 4, 1972 [Z 603a IE]
German version: Angew. Chem. *84*, 472 (1972)

[1] Annulenes, Part 16.—Part 15: *G. Schröder, U. Prange,* and *J. F. M. Oth*, Chem. Ber., in press.

[2] Correlation of the concept heteroannulenes/annulenes corresponds to that of heteroaromatic/aromatic.

[3] See, *e.g., A. G. Anastassiou* and *R. P. Cellura*, Chem. Commun. *1969*, 903; *J. M. Holovka, R. R. Grabbe, P. D. Gardner, C. B. Strow, M. L. Hill*, and *T. V. van Auken, ibid. 1969*, 1522; *S. Masamune, S. Takada*, and *R. T. Seidner*, J. Amer. Chem. Soc. *91*, 7769 (1969).

[4] a) *A. G. Anastassiou* and *J. H. Gebrian*, Tetrahedron Lett. *1970*, 825; b) J. Amer. Chem. Soc. *91*, 4011 (1969); c) *S. Masamune, K. Hojo*, and *S. Takada*, Chem. Commun. *1969*, 1204; d) *A. G. Anastassiou, R. P. Cellura*, and *J. H. Gebrian, ibid. 1970*, 375; e) *A. G. Anastassiou, S. W. Eachus, R. P. Cellura*, and *J. H. Gebrian, ibid. 1970*, 1133; f) *K. Hojo* and *S. Masamune*, J. Amer. Chem. Soc. *92*, 6690 (1970).

[5] See, *e.g., E. P. Woo* and *F. Sondheimer*, Tetrahedron *26*, 3933 (1970); *G. Schröder, R. Neuberg*, and *J. F. M. Oth*, Angew. Chem. *84*, 36 (1972); Angew. Chem. internat. Edit. *11*, 51 (1972).

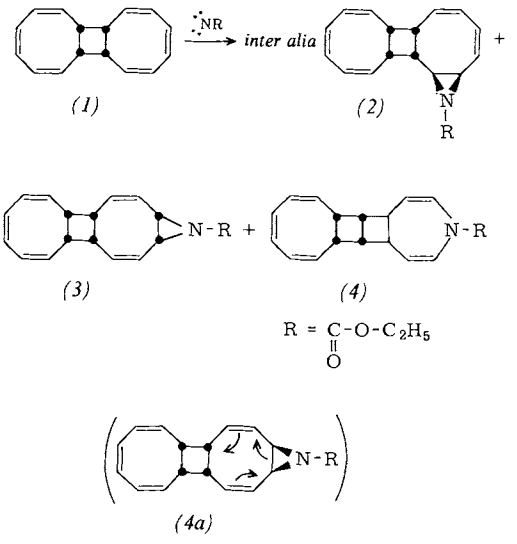
[6] See, *e.g., J. F. M. Oth* and *J.-M. Gilles*, Tetrahedron Lett. *1968*, 6259; *G. Schröder, G. Kirsch*, and *J. F. M. Oth, ibid. 1969*, 4575; *R. C. Haddon, V. R. Haddon*, and *L. M. Jackman*, Fortschr. Chem. Forsch. *16*, 103 (1971); *J. F. M. Oth*, Pure Appl. Chem. *24*, 573 (1971).

[7] *G. Schröder* and *W. Martin*, Angew. Chem. *78*, 117 (1966); Angew. Chem. internat. Edit. *5*, 130 (1966); and references cited therein.

[8] For detailed discussion of *(2)* see *M. R. Willcott, J. F. M. Oth, J. Thio, G. Plinke*, and *G. Schröder*, Tetrahedron Lett. *1971*, 1579.

[9] The compound gave satisfactory values on C,H analysis and molecular-weight determination (osmometry and mass spectrometry).

[10] Meanwhile we have been able to prepare cycloheptadecaoctaene, $C_{17}H_{18}$, by photolysis of the methylene adduct of *(1)*. No fundamental difference could be recognized between the spectroscopic data for $C_{17}H_{18}$ and those for oxa[17]annulenes.



adducts *(3)* and *(4)*. Separation and purification of *(2)*—*(4)* were effected by dry column chromatography (SiO_2; pentane/ether 9:1) and recrystallization (from methanol) (Table 1).

Table 1. Data for compounds *(2)*—*(4)*.

Cpd. [5]	Yield (%) [a]	M.p. (°C)	^{1}H-NMR, τ in ppm [b]	UV, λ in nm (ε) [c]
(2)	≈20	64	3.80–4.65 (10 H/m) 5.92 (2 H/q; J = 7 Hz) 6.50–7.75 (5 H/m) 7.76 (1 H/m) 8.77 (3 H/t; J = 7 Hz)	λ_{sh} 230 (7200) λ_{sh} 260 (2100)
(3)	≈ 9	93	4.27 (10 H/sharp m) 5.90 (2 H/q; J = 7 Hz) 6.58 (4 H/AA'BB') 7.02 (2 H/s) 8.73 (3 H/t; J = 7 Hz)	λ_{sh} 262 (1900)
(4)	≈ 9	74	3.15 (2 H/d; J = 10 Hz) 4.10 (4 H/s); 4.27 (2 H/s) 5.20 (2 H/pseudo-d; J = 10 Hz) 5.75 (2 H/q; J = 7 Hz) 6.47 (4 H/m); 7.63 (2 H/m) 8.65 (3 H/t; J = 7 Hz)	λ_{max} 230 (23000) λ_{sh} 265 (1900)

[a] Referred to the amount of *(1)* used.
[b] 60-MHz spectrum, in CCl_4, with TMS as internal standard.
[c] In cyclohexane.

Aza[17]annulenes[1,2][**]

By *Gerhard Schröder, Günter Heil, Herbert Röttele*, and *Jean F. M. Oth*[*]

Dedicated to Professor R. Criegee on the occasion of his 70th birthday.

Aza[17]annulenes are of interest for the same reasons as are oxa[17]annulenes[1].

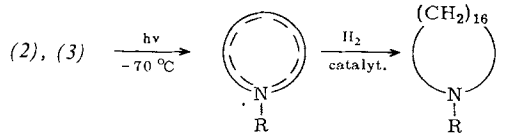
In analogy to epoxidation[1], the reaction of *(1)* in CH_2Cl_2 at 20 °C with *N*-(ethoxycarbonyl)nitrene [from *N*-(*p*-nitrobenzenesulfonyloxy)urethane and triethylamine[3]] gives an asymmetric adduct *(2)* and two symmetrical

According to their NMR spectra, *(2)* is an asymmetrical molecule, but *(3)* and *(4)* are symmetrical molecules. The steric orientation of the aziridine ring in *(2)* follows from comparison of the NMR spectrum with that of the analogous epoxide[1]. The aziridine ring in *(3)* can only be in the *anti*-position with respect to the cyclobutyl protons because with the *syn*-arrangement [*(4a)*] a Cope rearrangement (in the sense of the arrows shown) would set in, leading to *(4)*. This is the only way in which we can interpret the formation of *(4)*. This rearrangement has a precursor: the adduct of cyclooctatetraene and *N*-(ethoxycarbonyl)nitrene isomerizes when warmed, in which process a Cope rearrangement leads to ethyl 4-azabicyclo[5.2.0]nona-2,5,8-triene-4-carboxylate[4]. The doublet at τ = 3.15 and the pseudodoublet at τ = 5.20 in the NMR spectrum of *(4)* are particularly striking; they correspond in shape and chemical shift to the signals ascribed to the protons in α- and β-positions relative to the nitrogen in ethyl 4-azabicyclo[5.2.0]nonatriene-4-carboxylate[4].

[*] Prof. Dr. G. Schröder, Dr. G. Heil, and Dr. H. Röttele
Institut für Organische Chemie der Universität
75 Karlsruhe, Richard-Willstätter-Allee (Germany)
Prof. Dr. J. F. M. Oth
Organisch-chemisches Institut der ETH Zürich (Switzerland)

[**] This work was supported by the Badische Anilin- & Soda-Fabrik AG and the Deutsche Forschungsgemeinschaft.

On photolysis of the aziridines *(2)* and *(3)* in ether at −70 °C, using a low-pressure UV lamp, there are formed the aza[17]annulenes *(5a)*—*(5c)*. Under the same conditions the compound *(4)* yields extremely unstable products that we have been unable to isolate and identify.



R = $C(=O)-O-C_2H_5$ *(5a), (5b), (5c)* *(6)*

(5a), *(5b)*, and *(5c)* differ only in the sequence and individual number of *cis*- and *trans*-double bonds. On their catalytic hydrogenation the same liquid monocyclic urethane *(6)* is obtained (see Table 2).

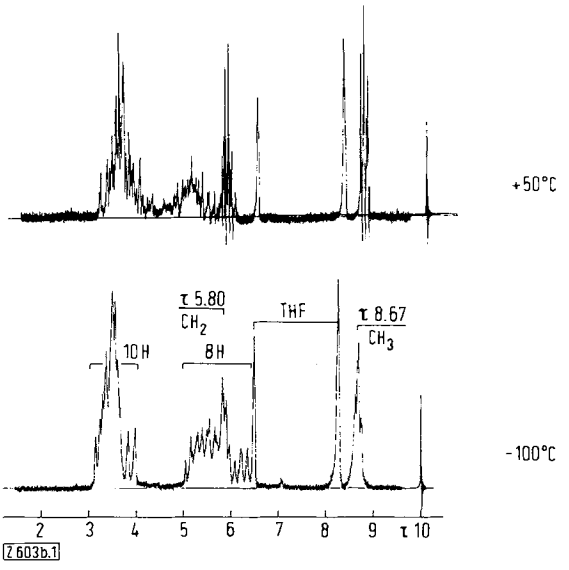


Table 2. Data for compounds *(5a)/(5b)*, *(5c)*, and *(6)*.

Cpd. [5]	Yield	M.p. (°C)	^{1}H-NMR, τ in ppm	UV, λ in nm (ε)
(5a)/(5b)	≈34% from *(2)*	83–97	2.6 (*ca.* 2 H/two d; J = 12 Hz) 3.0–4.0 (*ca.* 9 H/m) 4.8–6.5 (*ca.* 7 H/m, 2 H of which as two q at 5.8; J = 7.0 Hz) 8.6 (3 H/two t; J = 7.0 Hz) [a]	λ_{max} 246 (24000) λ_{max} 320 (60500) λ_{max} 420 (8500) [d]
(5c)	≈30% from *(3)*	111–113	3.0–4.0 (10 H/m) 5.0–6.4 (8 H/m, 2 H of which as two q at 5.8; J = 7.0 Hz) 8.67 (3 H/two t; J = 7.0 Hz) [b]	λ_{max} 242 (22000) λ_{max} 306 (71000) λ_{max} 409 (9800)
(6)	≈80%	liquid	5.96 (2 H/q; J = 7.0 Hz) 6.8 (4 H/pseudo-t; J = 7 Hz) 8.7 (28 H/pseudo-s) 8.78 (3 H/t; J = 7.0 Hz) [c]	[e] —

[a] 100-MHz spectrum, in CS_2, at −60 °C, with TMS as internal standard.
[b] 100-MHz spectrum, in CS_2/[D_8]-THF, at −100 °C, with TMS as internal standard.
[c] 60-MHz spectrum, in CCl_4, at 40 °C, with TMS as internal standard.
[d] In cyclohexane.
[e] In ether.

(5a)—*(5c)* can be separated from other reaction products by column chromatography (SiO_2; pentane/ether 30:1) and recrystallization (from pentane/ether 1:1). Photolysis of *(2)* at −70 °C and subsequent column chromatography and recrystallization give an inseparable mixture of two aza[17]annulenes *(5a)* and *(5b)*; the aza[17]-annulene *(5c)* is obtained from *(3)*. Preliminary investigations show that irradiation of *(2)* at −100 °C affords almost pure *(5a)*. An NMR spectroscopic comparison of samples obtained by photolysis of *(2)* at −70 and −100 °C show that *ca.* 20% of *(5b)* accompanies the *(5a)* in the sample obtained at −70 °C. *(5a)/(5b)* and *(5c)* are crystalline, red, thermally stable up to at least 80 °C and extremely sensitive to air.

The NMR spectra of *(5a)/(5b)* and *(5c)*, like those of the oxa[17]annulenes[1], are very complicated. Temperature-dependence of the signals is only feeble. There is no definite indication of π-electron delocalization[6]. We do not feel able to make definite statements about the configurations of the aza[17]annulenes on the basis of the spectroscopic data.

Like the oxa[17]annulenes[1], the aza[17]annulenes *(5a)/(5b)* and *(5c)* are best described as polyolefins. Here again configurational isomers can be isolated that are not interconvertible thermally.

A study of the aza[13]annulenes that have meanwhile been synthesized[7] will undoubtedly contribute to a better understanding of questions raised here.

Received: January 4, 1972 [Z 603b IE]
German version: Angew. Chem. *84*, 474 (1972)

[1] Annulenes, Part 17.—Part 16: *G. Schröder*, *G. Plinke*, and *J. F. M. Oth*, Angew. Chem. *84*, 472 (1972); Angew. Chem. internat. Edit. *11*, 424 (1972).

[2] *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972), describe a methano-bridged, doubly annelated bisdehydroaza[17]-annulene.

[3] *W. Lwowski* and *T. J. Maricich*, J. Amer. Chem. Soc. *87*, 3630 (1965).

[4] *S. Masamune* and *N. T. Castellucci*, Angew. Chem. *76*, 569 (1964); Angew. Chem. internat. Edit. *3*, 582 (1964).

[5] The compound gave satisfactory values on C,H analysis and molecular-weight determination (osmometry and mass spectrometry).

[6] Meanwhile we have succeeded in preparing cycloheptadeca-octaene, $C_{17}H_{18}$, by photolysis of the methylene adduct of *(1)*. No fundamental difference can be seen in the spectroscopic data for $C_{17}H_{18}$ and those for aza[17]annulenes.

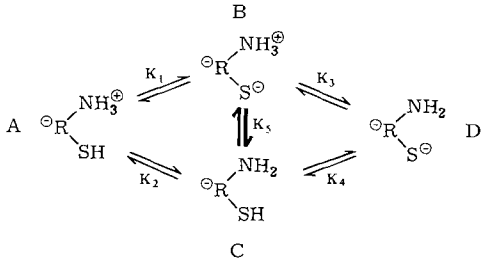
[7] *G. Frank*, Diplomarbeit, Universität Karlsruhe 1971, and part of a projected Dissertation.

Studies of Intramolecular Proton Transfer to Cysteine and Related Compounds by Relaxation Kinetics[**]

By *Günter Maass* and *Frens Peters*[*]

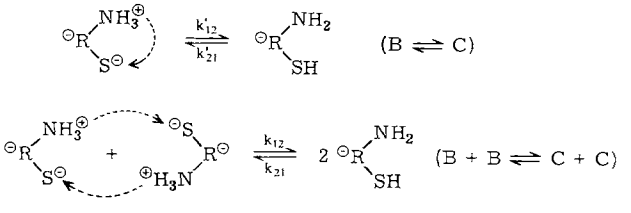
The dissociative behavior of amino acids such as cysteine and related compounds containing more than two proton donor-acceptor functions has been repeatedly investigated[1-3]. Whereas the carboxyl-proton is removed in acid solution, the amino- and thiol-protons of cysteine are liberated in about the same weakly basic media. It is, however, not possible, without further assumptions, to assign the potentiometrically determined pK values pK_{II} and pK_{III} to individual "microscopic" pK values of the two groups[1] that are linked by the relations $K_{II}=K_1+K_2$ and $1/K_{III}=1/K_3+1/K_4$.

For the dissociative behavior of cysteine and analogous di- and poly-basic acids a simple reaction scheme is usually given[4] according to which the protonated species A passes into the deprotonated form D with loss of two protons by way of B or C. We have found that this scheme must be supplemented by a direct proton transfer between B and C, whose equilibrium constant is related to the other micro-



scopic constants by $K_5=K_1/K_2=K_4/K_3$. This proton transfer can be demonstrated directly by investigation of the chemical relaxation by means of ultrasound absorption measurements[5, 6]. Similar proton transfer reactions are known for cysteamine $HS(CH_2)_2NH_2$.

The proton exchange between the two functional groups may occur intra- or inter-molecularly:



The pH values were so chosen that the concentrations of forms B and C were maximal and those of forms A and D were low. Under these conditions the reciprocal of the relaxation time for the two parallel reactions:

$$1/\tau = 2(k_{12}\gamma_B + k_{21}\gamma_C)c_0 + (k'_{12} + k'_{21})$$

($\bar{c}_B=\gamma_B c_0$, $\bar{c}_C=\gamma_C c_0$: equilibrium concentrations of B and C, respectively) gives a straight line when plotted against the initial concentration c_0 (Fig. 1).

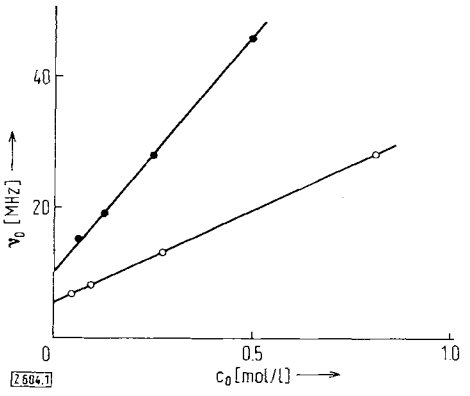


Fig. 1. Dependence of the relaxation frequencies on concentration. ● = Glutathione (pH = 9.05); ○ = cysteamine (pH = 9.7).

Thence, by extrapolation to low concentrations the time constants for the intramolecular proton transfer can be calculated. For cysteamine one thus obtains $1/\tau'=k'_{12}+k'_{21}=3.0\times10^7\ s^{-1}$ and for glutathione $1/\tau'=6.2\times10^7\ s^{-1}$. If the intramolecular proton exchange is fast compared with the intermolecular process the first terms can be neglected and the reciprocal relaxation time becomes independent of concentration; this condition is fulfilled for cysteine.

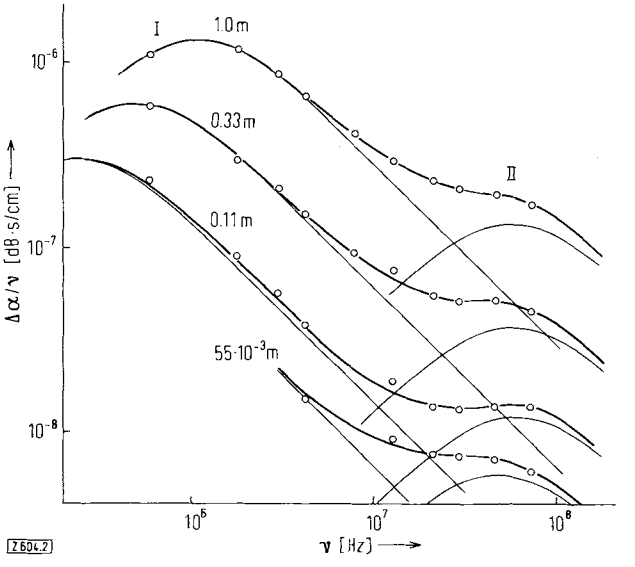


Fig. 2. Sound absorption spectra of aqueous cysteine solutions at pH = 9.5.

The sound absorption spectrum (Fig. 2) shows a rapid contribution, independent of concentration (effect II), and a second one (effect I) that is slower by an order of magnitude and can be ascribed to the intermolecular reactions. In this case, because of the markedly differing time constants, the two effects can be treated as uncoupled. For cysteine the sum of the velocity constants for intramolecular proton exchange between the thiol and the amino group has the value $1/\tau'=3.6\times10^8\ s^{-1}$.

Direct calculation of the individual velocity constants k'_{12} and k'_{21}, and thus the microscopic pK values, from the

[*] Priv.-Doz. Dr. G. Maass and Dr. F. Peters
Gesellschaft für Molekularbiologische Forschung
3301 Stöckheim/Braunschweig, Mascheroder Weg 1 (Germany)
and
Max-Planck-Institut für Biophysikalische Chemie
34 Göttingen-Nikolausberg (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 75).

relaxation measurements requires a knowledge of the equilibrium constants K_5. However, the microscopic constants can be determined by combination of potentiometric and spectrophotometric titrations[1] only under the limiting assumption that the absorption by the deprotonated thiol group is independent of the prevailing degree of protonation of the amino group. This assumption can be tested by kinetic methods if the reaction volume $\Delta V(=V_B-V_C)$ is known and provided that it can be decided upon which side the equilibrium lies. It is then possible to determine $K_5=\bar{c}_B/\bar{c}_C=\gamma/(1-\gamma)$ unambiguously by measuring the maximal sound absorption amplitude $(\Delta\alpha/\nu)_{max}=\text{const.}\gamma(1-\gamma)\Delta V^2$.

However, it can be shown that for the systems studied, the intramolecular proton exchange between neighboring groups is faster by two or three orders of magnitude than the protolysis (or hydrolysis) reactions[7] (see Table):

$$B + H^+ \rightleftharpoons A \rightleftharpoons C + H^+$$
or $B \rightleftharpoons D + H^+ \rightleftharpoons C$ [7]

Table. Relaxation times for the intramolecular proton transfers.

Compound	τ [s]
Cysteine	2.8×10^{-9}
Homocysteine	4.4×10^{-8}
Penicillamine	4.9×10^{-8}
Glutathione	1.6×10^{-8}
Cysteamine	3.3×10^{-8}

This means that the direct proton exchange between the two functional groups with interchange of hydrogen bonds can occur appreciably more easily than the corresponding reactions of the free protons or hydroxide ions.

These results are of particular interest for enzyme reactions in which mutually reacting groups are brought into close contact by rapid structural interchanges (10^{-7} s). They show that the individual steps of intramolecular proton transfer are as fast as, or faster than, the structural changes.

Received: January 14, 1972 [Z 604 IE]
German version: Angew. Chem. *84*, 430 (1972)

[1] *R. E. Benesch* and *R. Benesch*, J. Amer. Chem. Soc. *77*, 5877 (1955).
[2] *K. Wallenfels* and *Ch. Streffer*, Biochem. Z. *346*, 119 (1966).
[3] *E. Coates*, *C. Marsden*, and *B. Rigg*, Trans. Faraday Soc. *65*, 863 (1969).
[4] *J. T. Edsall* and *J. Wyman*: Biophysical Chemistry. Vol. 1. Academic Press, New York 1966.
[5] *M. Eigen* and *L. de Maeyer* in *A. Weissberger*: Technique of Organic Chemistry. Vol. 8/2, Interscience, New York 1963.
[6] *F. Peters*, Acustica, in press.
[7] *M. Eigen*, Angew. Chem. *75*, 489 (1963); Angew. Chem. internat. Edit. *3*, 1 (1964).

Trimeric 1-(Cyclohexylimino)methoxymethylgold(I), A New Type of Organometallic Compound

By *Giovanni Minghetti* and *Flavio Bonati*[*]

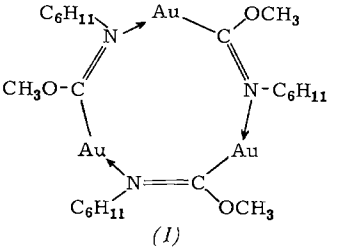
No organometallic compound corresponding to the general formula $[R-N=C(OR')-]_nM$ has hitherto been known.

[*] Dr. G. Minghetti and Prof. Dr. F. Bonati
Istituto di Chimica Generale dell'Università
I-20133 Milano, via Venezian 21 (Italy)

Such a compound ($R=C_6H_{11}$; $R'=CH_3$, $M=Au$, $n=1$) is formed (as trimer) when methanolic potassium hydroxide solution (157 mg/18.9 ml) and then, with stirring, cyclohexyl isocyanide (305 mg) are added to a suspension of chloro(triphenylphosphane)gold(I) in methanol. After 0.5 h the suspension is concentrated to half volume in a water-pump vacuum. The white precipitate is recrystallized from chloroform/methanol (m.p. $\approx$190 °C with gradual decomposition and violet coloration above 160 °C).

The ^{1}H-NMR spectrum, in $CDCl_3$, measured from $\tau=-10$ to $+30$ ppm, contains only signals that can be assigned to the cyclohexyl ($\tau=5.7$ and 8.3 ppm) and the methoxyl group ($\tau=5.99$ ppm). No N—H, O—H, or $-\overset{\oplus}{N}\equiv\overset{\ominus}{C}-$ stretching vibration was observed in the IR spectrum, but only $-\overset{|}{C}=N-$ and $=\overset{|}{C}-OCH_3$ stretching vibrations at 1535 (vs, br.) and 1130 (s) cm^{-1}, respectively. The compound is non-conducting in methylene chloride. The molecular weight in chloroform amounted to 1031 and is independent of concentration (0.81 – 3.1 wt.-%).

These findings and the position of the $-\overset{|}{C}=N-$ stretching vibration indicate a formula of type *(1)*.



(1)

If aromatic isocyanides are used instead of cyclohexyl isocyanide, monomeric (not trimeric) ligand-stabilized compounds such as $[(C_6H_5)_3P]AuC(=N-C_6H_4-CH_3)OCH_3$ are formed[1].

Except for the unstable cyclopentadienylgold(I) and $[C_6H_5-C\equiv C-Au]_x$, the compound *(1)* described here is the only organogold(I) compound[2] that does not require stabilization by ligands such as phosphanes or isocyanides.

Received: December 20, 1971 [Z 616 IE]
German version: Angew. Chem. *84*, 482 (1972)

[1] *G. Minghetti* and *F. Bonati*, Rend. Accad. Naz. Lincei, Classe Sci. fis. mat. nat. [VIII], *49*, 287 (1970).
[2] *B. Armer* and *H. Schmidbauer*, Angew. Chem. *82*, 120 (1970); Angew. Chem. internat. Edit. *9*, 101 (1970).

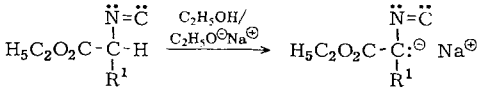
Ethyl γ-Cyano-α-isocyanoalkanoates from α-Metalated Ethyl Isocyano-acetates or -propionates and Acrylonitriles[1]

By *Ulrich Schöllkopf* and *Paul-Hermann Porsch*[*]

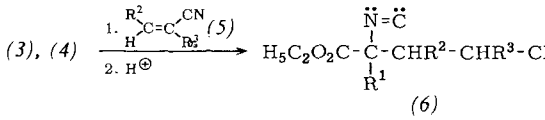
γ-Cyano-α-isocyanoalkanoic esters *(6)* deserve attention because they have several reactive centers and can react in many ways, *e.g.* by hydrolysis of the isocyano group to yield α-amino-γ-cyanoalkanoates. They are obtained by

[*] Prof. Dr. U. Schöllkopf and Dipl.-Chem. P.-H. Porsch
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

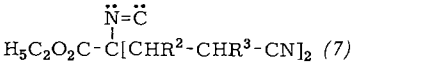
cyanoethylating, for example, ethyl isocyanoacetate *(1)* ($R^1 = H$) or isocyanopropionate *(2)* ($R^1 = CH_3$) in ethanol with sodium ethoxide as catalyst at ≈30 °C. Essential intermediates are the α-metalated isocyanoalkanoic esters *(3)* or *(4)* which add to the double bond of acrylonitrile *(5)*. The adducts *(6)* result by protonation.



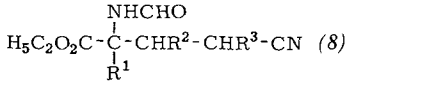
(1), (2) *(3), (4)*



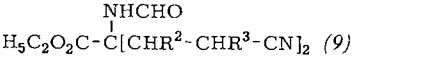
(6)



(7)



(8)



(9)

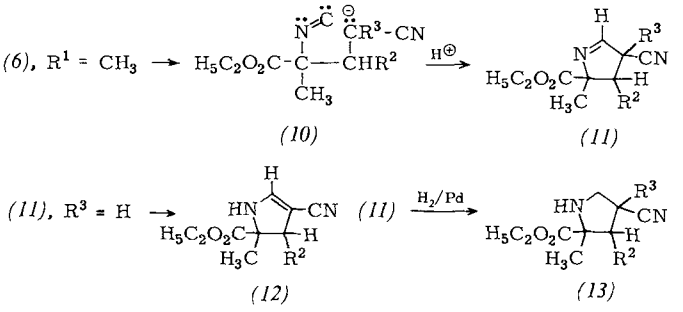
Cpd.	R^1	R^2	R^3	B.p. (°C/torr)	M.p. (°C)	Yield (%)
(6a)	H	CH_3	H	106/0.1	–	50 [a] [d]
(6b)	H	C_6H_5	H	103/0.02	–	31 [b]
(6c)	CH_3	H	H	99/0.15	–	43 [c]
(6d)	CH_3	CH_3	H	100/0.15	–	53 [c]
(6e)	CH_3	C_6H_5	H	–	110 [f]	31 [c]
(6f)	CH_3	H	CH_3	94/0.05	–	86 [c]
(7a)		H	H	175/0.1	44–46 [g]	55 [b]
(7b)		H	CH_3	–	50–52 [h]	50 [b]
(7c)		CH_3	H	173/0.1	–	41 [b] [e]

[a] Molar ratio, *(1)* or *(2)*:*(5)* = 2:1.
[b] Molar ratio, *(1)* or *(2)*:*(5)* = 1:2.
[c] Molar ratio, *(1)* or *(2)*:*(5)* = 1:1.
[d] Amount of bis adduct = about 30% of the weight of monoadduct.
[e] Amount of monoadduct = about 30% of the weight of bis adduct.
[f] From cyclohexane.
[g] From ethanol/cyclohexane.
[h] From ethanol/water.

Bis adducts of type *(7)* can be formed from isocyanoacetic esters *(1)* because the anions from compounds *(6)* can react further with acrylonitrile *(5)* when $R^1 = H$. In experiments to date, acrylonitrile *(5)* ($R^2 = R^3 = H$) and methacrylonitrile *(5)* ($R^2 = H$, $R^3 = CH_3$) afford only the bis adducts—even when an excess of isocyanoacetic ester is used—whereas, for example, crotononitrile and cinnamonitrile give monoadducts of type *(6)* as isolable products.

Compounds *(6)* and *(7)* can be hydrolyzed by 2N hydrochloric acid in ethanol to γ-cyano-α-(*N*-formylamino) esters *(8)* and *(9)*, respectively, the nitrile group remaining intact.

If the cyanoethylation of ethyl isocyanopropionate *(2)* ($R^1 = CH_3$) is carried out at 65 °C with an equimolar amount of sodium ethoxide, the 3-cyanopyrroline-5-carboxylic esters *(11)* or, if $R^3 = H$, *(12)* result; they are formed by way of the anions *(10)*.



(10) *(11)*

(12) *(13)*

The 1-pyrrolines *(11)* can be reduced to 3-cyanoproline ethyl esters (ethyl 4-cyanopyrrolidine-2-carboxylates) *(13)* by catalytic hydrogenation in ethanol over palladium on activated charcoal.

Ethyl γ-cyano-α-isocyano-β-methylbutyrate (6a)

A solution (1 ml) of sodium ethoxide (prepared from 5 g of sodium in 100 ml of anhydrous ethanol) was added to one of ethyl isocyanoacetate[2] (11.3 g, 0.1 mol) in anhydrous ethanol (30 ml). Then a solution of crotononitrile (3.35 g, 50 mmol) in anhydrous ethanol (15 ml) was added dropwise over 30 min, the temperature not rising above 30 °C. The mixture was kept at room temperature for 15 h, then neutralized with glacial acetic acid, and the solvent was removed in a vacuum (bath-temperature max. 80 °C). The residue was dissolved in methylene chloride (50 ml) and washed three times with water (20 ml portions), and the organic phase was dried with sodium sulfate and evaporated. This residue afforded 50% (4.5 g) of a 1:1 diastereoisomeric mixture *(6a)*. IR spectrum (film): 2250 (ν_{CN}), 2140 ($\nu_{N=C}$), 1750 cm^{-1} (ν_{CO}); NMR spectrum ($CDCl_3$): τ = 5.46 (d, $J_{\alpha,\beta} \approx 4$ Hz), 5.60 (d, $J_{\alpha,\beta} \approx 4$ Hz), 8.58 (d, $J \approx 7$ Hz), 7.43 ppm (m). The distillation residue contained *ca.* 1.5 g of the bis adduct *(7c)*.

4-Ethoxycarbonyl-4-isocyano-3,5-dimethylheptanedinitrile (7c):

A mixture of crotononitrile (13.4 g, 0.2 mol) and ethyl isocyanoacetate (11.3 g, 0.1 mol) in anhydrous ethanol (30 ml) is added to a mixture of anhydrous ethanol (30 ml) and sodium ethoxide solution (2 ml; from 5 g of sodium and 100 ml anhydrous ethanol) during *ca.* 30 min at such a rate that the temperature does not exceed 30 °C. Working up is as described above. Fractional distillation of the crude product afforded 3 g of monoadduct *(6a)* and 10 g (41%) of *(7c)*. IR spectrum (film): 2260 (ν_{CN}), 2140 (ν_{NC}), 1740 cm^{-1} (ν_{CO}); NMR spectrum ($CDCl_3$): τ = 8.60 (m), 7.52 (m), 5.64 (q), 8.73 ppm (m).

4-Ethoxycarbonyl-4-formylamino-3,5-dimethylheptanedinitrile (9), $R^2 = CH_3$, $R^3 = H$

A mixture of *(7c)* (3.5 g), concentrated hydrochloric acid (1 ml), and 96% ethanol (15 ml) was stirred at room temperature until (2.5 h) the isocyanide band was no longer present in the IR spectrum, neutralized with 10% potassium hydroxide solution, and worked up as usual, affording 3 g of *(9)*, $R^2 = CH_3$, $R^3 = H$, as a colorless oil. IR spectrum (film): 3360 (ν_{NH}), 2250 (ν_{CN}), 1730 (ν_{CO}), 1680 ($\nu_{amide\ I}$), 1520 cm^{-1} ($\nu_{amide\ II}$).

Ethyl 3-cyano-4,5-dimethyl-2-pyrroline-5-carboxylate (12), $R^2 = CH_3$

A solution of ethyl isocyanopropionate[2] (6.35 g, 50 mmol) and crotononitrile (3.35 g, 50 mmol) in anhydrous ethanol

(15 ml) was added with stirring and cooling (water-bath) to a solution of sodium (1.15 g, 50 mmol) in anhydrous ethanol (40 ml); the mixture was stirred at 65 °C until the isocyanide band was no longer present in the IR spectrum (1.5—2 h), and was then neutralized with glacial acetic acid. Working up as described above afforded 54% (5.2 g) of *(12)*, $R^2=CH_3$, b. p. 106 °C/0.1 torr. IR spectrum (film): 3370 (ν_{NH}), 3095 ($\nu_{H-C=C}$), 2190 (ν_{CN}), 1730 (ν_{CO}), 1600 cm^{-1} ($\nu_{C=C}$); NMR spectrum (CCl_4): $\tau=3.08$ (d, $J_{2,4}=3$ Hz), 4.47 (s), 5.82 (q), 6.9 (m), 8.7 ppm (m).

Received: December 23, 1971 [Z 605 IE]
German version: Angew. Chem. *84*, 478 (1972)
Publication delayed at authors' request

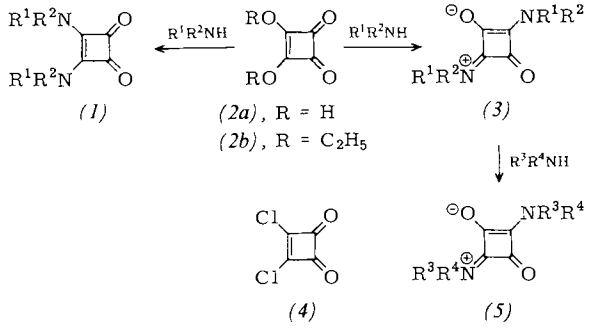
[1] Syntheses with α-Metalated Isocyanides, Part 13.—Part 12: *D. Hoppe* and *U. Schöllkopf*, Angew. Chem. *84*, 435 (1972); Angew. Chem. internat. Edit. *11*, 432 (1972).

[2] *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer*, and *K. Offermann*, Angew. Chem. *77*, 492 (1965); Angew. Chem. internat. Edit. *4*, 472 (1965).

New Routes to Squaric 1,3-Diamides

By *Siegfried Hünig* and *Hermann Pütter*[*]

Squaric acid *(2a)* reacts with amines, when heated in alcohols or DMF, to give 1,3-diamides *(3)*[1], but 1,2-diamides *(1)*[2] are formed from squaric esters, *e.g. (2b)*. This rule is broken by feebly reactive amines. Only the 1,3-diamide *(3)* ($R^1=o$-$NO_2C_6H_4$, $R^2=H$)[1] can be isolated (65%) from *o*-nitroaniline and *(2b)* (4.5 h, 180 °C)[3].

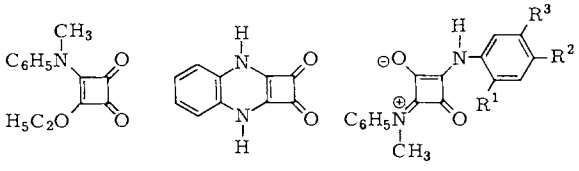


(1) *(2a)*, R = H; *(2b)*, R = C_2H_5 *(3)* *(4)* *(5)*

The isomer of type *(1)* results, however, from *o*-nitroaniline and the dichloride *(4)* (40 min, 150 °C, 54%). The isomeric amides differ characteristically in their IR spectra[1,2].

Mainly the ester amide *(6)* is formed from *(2b)* and *N*-methylaniline (1:2) in ethanol (3 h, reflux). However, *(3)* ($R^1=C_6H_5$, $R^2=Me$) is formed in *n*-butanol (3 h, reflux, 56%); even in absence of solvent (1 h, reflux, 1:13) 70% of *(3)* is obtained. This indicates a direct reaction *(2b)* → *(3)* since the rearrangement *(1)* → *(3)* occurs only under catalysis by protons[1b,3]. The isomeric 1,2-diamide *(1)* ($R^1=C_6H_5$, $R^2=CH_3$) is conveniently obtained by alkylation of *(1)* ($R^1=C_6H_5$, $R^2=H$)[2a] by methyl iodide and K *tert*-butoxide in DMF (1 h, 20 °C, 43%).

Considerable importance attaches to the finding that when the 1,3-diamides *(3)* are heated with an excess of an amine R^3R^4NH for 3—20 min with or without a solvent at 150—200 °C the amino groups are exchanged, giving *(5)*. The reaction is smooth if the entering amine is more strongly basic (nucleophilic) than the leaving amine. This method is an advantageous extension of the usual method of heating a squaric acid salt with the amine[1] and makes aliphatic 1,3-diamides, *e.g. (5d)* and *(5f)*, accessible without the difficulties previously described for the case of *(5d)*[1e] (Table 1).



(6) *(7)*

	(8a)	*(8b)*	*(8c)*
R^1	NO_2	H	Cl
R^2	H	NO_2	H
R^3	H	H	Cl

The amide *(5c)* which is important as starting material for a squaric amidine[5] can only be prepared in this way; *o*-phenylenediamine closes the ring with either *(2a)* or *(2b)*, yielding the 1,2-diamide *(7)*. The compound hitherto described as *(5)*[6a] has another structure[1e,6b]. We have confirmed also that it is impossible to reduce the nitro group of *(3)* ($R^1=o$-$NO_2C_6H_4$, $R^2=H$) to an amino group[1e].

The reduced reactivity of *N*-methylaniline is evident here too: even if the leaving amine of *(3)* is favorable, only one

Table 1. Transamidation of 1,3-diamides *(3)* by heating with R^3R^4NH, to yield *(5)* [4].

(3) R^1	R^2	Ref.	*(5)* R^3	R^4	Ref.		Yield (%)
o-$O_2NC_6H_4$	H	[1c]	C_6H_5	H	[1c]	*(5a)*	90
			α-Naphthyl	H	[1c]	*(5b)*	100
			o-$H_2NC_6H_4$	H		*(5c)*	93
			—$(CH_2)_5$—		[1e]	*(5d)*	69
			Cyclohexyl	H		*(5e)*	89
			$C_6H_5CH_2$	H		*(5f)*	90
p-$O_2NC_6H_4$	H	[1c]	$C_6H_5CH_2$	H		*(5f)*	72
2,5-$Cl_2C_6H_3$	H	[7]	—$(CH_2)_5$—		[1e]	*(5d)*	98
			$C_6H_5CH_2$	H		*(5f)*	80
			—$(CH_2)_2$—O—$(CH_2)_2$—		[1a]	*(5g)*	97
p-ClC_6H_4	H	[7]	$C_6H_5CH_2$	H		*(5f)*	44
C_6H_5	H	[1c]	—$(CH_2)_5$—		[1c]	*(5d)*	84
			$C_6H_5CH_2$	H		*(5f)*	95
C_6H_5	CH_3	[1c]	$C_6H_5CH_2$	H		*(5f)*	80

[*] Prof. Dr. S. Hünig and Dipl.-Chem. H. Pütter
Institut für Organische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie, DECHEMA, and the Badische Anilin- & Soda-Fabrik AG, as well as by Chemische Werke Hüls who supplied squaric acid derivatives.

amino group is replaced, giving *(8a)* (43%), *(8b)* (74%), or *(8c)* (90%).

Received: January 31, 1972 [Z 609a IE]
German version: Angew. Chem. *84*, 480 (1972).

[1] a) *H. E. Sprenger* and *W. Ziegenbein*, Angew. Chem. *80*, 541 (1968); Angew. Chem. internat. Edit. *7*, 530 (1968); b) *J. Gauger* and *G. Manecke*, Tetrahedron Lett. *1967*, 3509; c) Chem. Ber. *103*, 2996 (1970); d) *H. J. Roth* and *H. Sporleder*, Arch. Pharmaz. *303*, 895 (1970); e) *J. Gauger* and *G. Manecke*, Chem. Ber. *103*, 3553 (1970); f) *G. Manecke* and *J. Gauger*, Tetrahedron Lett. *1968*, 1339.

[2] a) *G. Maahs* and *P. Hegenberg*, Angew. Chem. *78*, 927 (1966); Angew. Chem. internat. Edit. *5*, 888 (1966); b) *S. G. Cohen* and *S. Cohen*, J. Amer. Chem. Soc. *88*, 1533 (1966).

[3] Dimethylaniline arylates *(2b)*, as described in [1f], also in the 1,3-position.

[4] Correct spectra and analytical data are available for all the new compounds.

[5] *S. Hünig* and *H. Pütter*, Angew. Chem. *84*, 481 (1972); Angew. Chem. internat. Edit. *11*, 433 (1972).

[6] a) *S. Skujins* and *G. A. Webb*, Chem. Commun. *1968*, 598; b) *W. Ried* and *W. Kunstmann*, Chem. Ber. *102*, 1439 (1969).

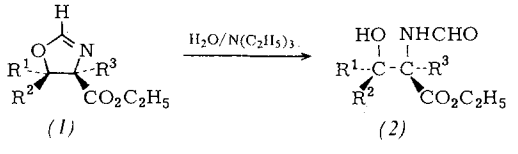
[7] Prepared analogously to the method given in [1c].

Ethyl α-Formylamino-β-hydroxy-acid Esters (β-Substituted *N*-Formylserine Esters) from Ethyl 2-Oxazoline-4-carboxylates[1]

By *Dieter Hoppe* and *Ulrich Schöllkopf*[*]

Ethyl 2-oxazoline-4-carboxylates *(1)* are obtained conveniently and in good yields from ethyl isocyanoalkanoates and carbonyl compounds in weakly basic alcoholic media[2]. Their conversion into ethyl α-formylamino-β-hydroxy-acid esters *(2)* can be accomplished almost quantitatively by warming 1 mol of *(1)* with 2—3 mol of water and 0.03 mol of triethylamine (if necessary, with addition of a little ethanol).

Alkaline hydrolysis is unusual for 2-oxazolines[3]; it can be achieved with the compounds *(1)* under relatively mild conditions, probably because the negative charge arising on the nitrogen atom when a hydroxide ion attacks C-2 is taken over by the carbonyl group at position 4 in the neighboring group effect.

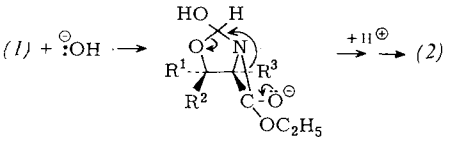


(1) *(2)*

(2)	R^1	R^2	R^3	Hydrolysis (h) [a]	Yield (%) [b]
(a)	H	H	H	0.1	90 [c]
(b)	CH_3	H	H	0.5	68
(c)	$(CH_3)_2CH$	H	H	1	91
(d)	C_6H_5	H	H	1.5 [f]	51 [d]
(e)	CH_3	CH_3	H	3	80 [e]
(f)	$-(CH_2)_5-$		H	6 [f]	92
(g)	CH_3	CH_3	CH_3	3	83
threo-(h)	C_6H_5	H	CH_3	6 [f]	20 [g]
erythro-(h)	H	C_6H_5	CH_3	6 [f]	56 [g]

[a] Until *(1)* is no longer detectable by IR spectroscopy (1620 cm^{-1}).
[b] Isolated product.
[c] Crude product.
[d] Precipitated by water.
[e] Distilled at 0.05 torr.
[f] 0.5 ml of ethanol per g of *(1)* added.
[g] After chromatographic separation of the diastereoisomers.

[*] Dr. D. Hoppe and Prof. Dr. U. Schöllkopf
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)



The plane in which the ethoxycarbonyl group lies must therefore be perpendicular to that of the five-membered ring, and this is hindered particularly by *cis*-substituents on the ring. This consideration explains satisfactorily the various times required for the hydrolyses (cf. Table).

Water-soluble α-formylamino-β-hydroxy-acid esters *(2)* are isolated by removing the excess of water in a vacuum and distilling the residue or taking it up in carbon tetrachloride or ether and awaiting crystallization; sparingly soluble esters *(2)* are precipitated by water. These esters can be converted into α-amino-β-hydroxy acids (β-substituted serines) by heating them with 5N hydrochloric acid.

N-Formylthreonine ethyl ester (2b)

Ethyl *trans*-5-methyl-2-oxazoline-4-carboxylate[2] (5.4 g, 34 mmol), water (1.8 g), and triethylamine (0.1 g, 0.1 mmol) are heated for 30 min at 100 °C. The water is then distilled off at 1 torr and 80 °C (bath-temperature), ether (10 ml) is added, and the solution is left at 0 °C for crystallization. This yields *(2b)* (3.9 g, 68%), m.p. 74 °C (from 2:1 carbon tetrachloride/chloroform). NMR spectrum (in $CDCl_3$): $\tau = 5.4$ (m/C-2-H and C-3-H), 5.6 (—OH), 8.75 ppm (d/$J = 7$ Hz, $-CH_3$).

(2b) was converted by 5N HCl into threonine. *allo*-Threonine was not detectable either by IR spectroscopy or by thin-layer chromatography.

erythro- and threo-N-Formyl-2-methyl-3-phenylserine ethyl ester (2h)[4, 5]

Ethyl 4-methyl-5-phenyl-2-oxazoline-4-carboxylate[2] (*cis*:*trans* = 2.5:1) (4.7 g, 20 mmol), water (1.0 ml), ethanol (2.5 ml) and triethylamine (0.1 g) were heated under reflux for 6 h at 100 °C. The solvent was distilled off at 100 °C in a water-pump vacuum and the residue was chromatographed on silica gel (200 g; 0.05—0.2 mm; column diameter 3 cm) with ethyl acetate/chloroform (6:4). The fractions (each 20 ml) were investigated by thin-layer chromatography (silica gel F 1500 LS 254, Schleicher and Schüll; above solvent). Removing the solvent at water-pump vacuum from the fractions containing the faster migrating substance ($R_F = 0.26$) gave *erythro-(2h)* as a residual viscous oil (2.8 g, 56%) that slowly crystallized from ether/pentane (2:1) at −10 °C (m.p. 74 °C). NMR spectrum ($CDCl_3$): $\tau = 4.15$ and 4.85 (d/$J = 8.5$ Hz, —CHOH), 8.35 (s/$-CH_3$)[5], 5.77 and 8.72 ppm ($-OCH_2-CH_3$)[5].

Concentration of the fractions containing the slower migrating component ($R_F = 0.19$) and of the mixed fractions afforded an oil (1.5 g) that, when treated with ether (10 ml), yielded crystals of *threo-(2h)* (1.0 g, 20%), m.p. 105 °C. NMR spectrum ($CDCl_3$): $\tau = 5.0$ (—CHOH), 8.6[5] and 8.73 (s/$-CH_3$), 5.75 and 5.90[5], as well as 8.70 and 8.83[5] ($-OCH_2-CH_3$). Since the relative intensities

of the groups of signals change in CD_3OD we assume that the signal splitting is caused by competition between intra- and inter-molecular hydrogen-bridge formation.

Received: January 27, 1972 [Z 606 IE]
German version: Angew. Chem. *84*, 435 (1972)

[1] Syntheses with α-Metalated Isocyanides, Part 12.—Part 11: *U. Schöllkopf* and *R. Schröder*, Angew. Chem. *84*, 289 (1972); Angew. Chem. internat. Edit. *11*, 311 (1972).

[2] *D. Hoppe* and *U. Schöllkopf*, Angew. Chem. *82*, 290 (1970); Angew. Chem. internat. Edit. *9*, 300 (1970).

[3] Review: *J. W. Cornforth* in *R. C. Elderfield*: Heterocyclic Compounds. Vol. 5, Wiley, New York 1957, p. 386.

[4] Another access to 2-methyl-3-phenylserines: a) *S. H. Pines, S. Karady*, and *M. Sletzinger*, J. Org. Chem. *33*, 1758 (1968); b) *S. H. Pines, S. Karady, M. A. Kozlowski*, and *M. Sletzinger*, *ibid. 33*, 1962 (1968).

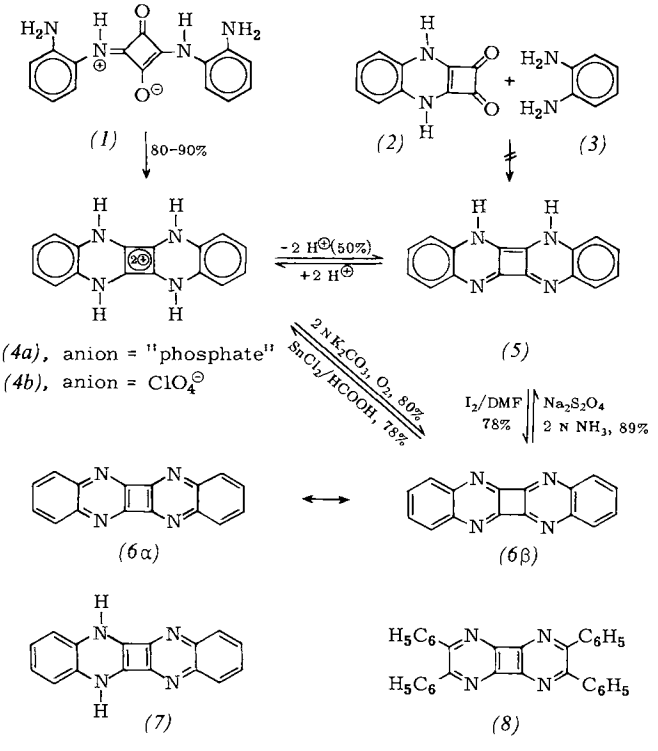
[5] The relative chemical shifts are very similar to those of the *N*-acetyl compounds; cf. [4b].

A Squaric Diamidine and an Aza Analog of Biphenylene[**]

By *Siegfried Hünig* and *Hermann Pütter*[*]

The replacement of oxygen in squaric acid by nitrogen has hitherto been extended only to provide 1,2-[1] and 1,3-diamides[1]. We here describe the first squaric acid diamidine.

All previous attempts to introduce further amino groups into the 1,2-diamide *(2)*, *e.g.*, by *o*-phenylenediamine *(3)*,



[*] Prof. Dr. S. Hünig and Dipl.-Chem. H. Pütter
Institut für Organische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie. DECHEMA, and the Badische Anilin- & Soda-Fabrik as well as by Chemische Werke Hüls who supplied squaric acid derivatives.

failed[3]. On the other hand, the 1,3-diamide[4] *(1)* has now been shown to be a useful starting material. When *(1)* is heated in polyphosphoric acid a dark green reaction mixture is formed from which a green (poly?)phosphate *(4a)* of indefinite composition is precipitated by water. Thence perchloric acid produces the extremely sparingly soluble green diperchlorate *(4b)*[5] (dec. from 295 °C; IR[6]: 3150, 1610, 1550, 1460, 1100, 1040, 780 cm^{-1}). *(4)* can be regarded as a highly stabilized cyclobutadienyl dication.

When stirred in DMF suspension in absence of air, *(4b)* changes without visible alteration into the equally very sparingly soluble diamidine *(5)*[5] (m. p. from 210 °C → *(6)*, 318 °C; [IR[6]: 3150—2800, 1610, 1580, 1510, 1460, 1420, 1230, 750 cm^{-1}]. Localization of the two H atoms in one hetero ring is unlikely since in our experience[3] structures of benzocyclobutadiene character[7] like *(7)* are avoided. The structure of the skeleton of *(4)* and *(5)* follows from the smooth oxidation to yellow quinoxalino[2',3':1,2]-cyclobuta[3,4-*b*]quinoxaline *(6)* [λ_{max} (CH_3CN) = 443 (61 700), 413 (24 200), 280 nm (50 000); m. p. 324 °C], which can be reduced back to *(5)*. Structure *(6)* is indicated by: a) the mass spectrum ($M^+ = 256$); b) an IR spectrum (1505, 1360, 1055, 760 cm^{-1}) containing few bands and no NH band but with an intense band at 760 cm^{-1} characteristic of *o*-disubstituted benzenes[8]; c) NMR signals only in the aromatic region where they are of AA'BB' type [(D_6-DMSO): $\delta = 7.86$, 8.06 ppm; $J_{AB} = 8.50$, $J_{AB'} = 1.50$, $J_{BB'} = 6.00$ Hz]. *(6)* can be described in the limiting formula *(6α)* as a cyclobutadiene annelated to two quinoxaline systems and is the first example[9] of a cyclobutadiene stabilized by incorporation into pyrazine rings.

Compound *(8)*[10] described a long time ago has a different structure[11]. Even very recent attempts to synthesize *(8)* have failed[12].

Received: January 31, 1972 [Z 609 b IE]
German version: Angew. Chem. *84*, 481 (1972)

[1] Literature cited in [4].

[2] *S. Skujins* and *G. A. Webb*, Chem. Commun. *1968*, 598.

[3] *H. Pütter*, Diploma thesis, Universität Würzburg (Germany) 1970.

[4] *S. Hünig* and *H. Pütter*, Angew. Chem. *84*, 480 (1972); Angew. Chem. internat. Edit. *11*, 431 (1972).

[5] Correct elemental analyses are available.

[6] All IR spectra were measured for Nujol suspensions.

[7] *M. P. Cava* and *M. J. Mitchell*: Cyclobutadiene and Related Compounds. Academic Press, New York 1967.

[8] *A. J. Bellamy*: Ultrarotspektrum und chemische Konstitution. Steinkopff, Darmstadt 1967.

[9] a) *M. P. Cava* and *L. Bravo*, Chem. Commun. *1968*, 1538; b) *R. F. C. Brown, N. D. Crow*, and *R. K. Solly*, Chem. Ind. (London) *1966*, 343; c) *M. P. Cava, M. J. Mitchell, D. C. de Jong*, and *R. Y. van Vossen*, Tetrahedron Lett. *1966*, 2947.

[10] *A. T. Mason* and *L. A. Dryfoot*, J. Chem. Soc. *63*, 1293 (1893).

[11] *P. England* and *R. H. McDougall*, J. Chem. Soc. *C 1971*, 2685.

[12] *P. England* and *R. H. McDougall*, J. Chem. Soc. *C 1971*, 3605.

Cyclodimerization of Heated Methylenecyclopropane

By *Paul Binger*[*]

The now readily available methylenecyclopropane *(1)*[1] dimerizes on a nickel(0) catalyst between −15 and 0 °C to

[*] Dr. P. Binger
Max-Planck-Institut für Kohlenforschung
433 Mülheim/Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

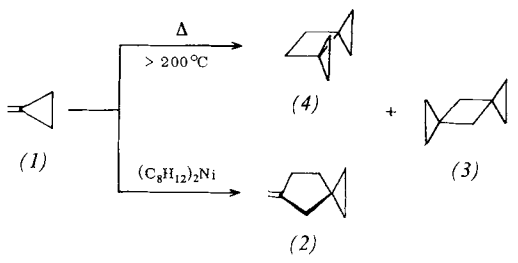


Table 1. Formation of the dispirooctanes *(3)* and *(4)* from *(1)* in an autoclave.

Conditions		Conversion	Yield of	Composition (GC; *ca.* %) [a]			
T(°C)	(h)	*(1)* (%)	C_8H_{12} (%)	*(3)*	*(4)*	2 unidentified	C_8H_{12} [b]
200	14	6	46	4	69	4	3
220	8	24	68	7	77	3	5
230	5	21	76	7	77	4	5
230	8	51	44	7	77	2	5
250	3	63	43	11	77	3	6
250	5	69	27	9	59	3	8

[a] Rest not identified.
[b] Molecular formulas determined by coupled GC/MS (GC = gas chromatography; MS = mass spectrometry).

yield mainly the cyclic C_8H_{12}-hydrocarbons *(2)* and *(3)*[2]. Contrary to previous findings[3], *(1)*, which is completely stable up to 150 °C, was found to cyclodimerize between 200 and 250 °C to the two dispirooctanes *(3)* and *(4)*; higher oligomers are also formed.

Analogous cyclodimerizations were previously successful only with the substituted methylenecyclopropanes bicyclopropylidene[4] and (dichloromethylene)cyclopropane[5].

The efficiency of the dispirooctane synthesis depends greatly on the reaction conditions (cf. Table 1). The highest yields of *(3)*/*(4)* mixture so far obtained were 76% with 20% conversion after about 5 h at 230 °C.

(3) and *(4)* were identified by spectroscopy after separation by preparative gas chromatography. The main product is the previously unknown dispiro[2.0.2.2]octane *(4)*. Dispiro[2.1.2.1]octane *(3)* has recently been obtained catalytically from *(1)*[2].

Spectroscopic data for *(4)*: Mol. wt. (mass spectr.) 108; characteristic fragments 93, 91, 80, 79, and 54. IR spectrum (neat), 3060 ($\nu_{CH\Delta}$) and 1000 cm^{-1} (δ_Δ).—^{1}H-NMR spectrum (100 MHz, neat), $\tau = 7.81$ (s/4H), 9.74 (m/4H), and 9.85 ppm (m/4H).

Dispirooctanes (3) and (4)

(1) (32 g, 0.59 mol) is shaken for 5 h at 230 °C in an autoclave (200 ml; V4A steel; $p_{max} = 68$ atm.). After release of pure (GC) *(1)* (24.8 g; trap at −78 °C), working up gives a pale yellow liquid (6.7 g) from which colorless hydrocarbons (5.1 g, 76%) of b. p. 118—120 °C containing *(3)* (7.1%) and *(4)* (77.4%) (gas chromatography) are obtained; impurities (GC/MS) are mainly two compounds C_8H_{12} (4.0 and 5.3%); an unidentified viscous oily residue (1.6 g, 6.1%) remains.

Received: March 13, 1972 [Z 615 IE]
German version: Angew. Chem. *84*, 483 (1972)

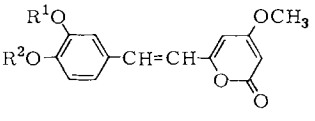
[1] *R. Köster, S. Arora*, and *P. Binger*, Synthesis *1971*, 322.
[2] *P. Binger*, Angew. Chem. *84*, 352 (1972); Angew. Chem. internat. Edit. *11*, 309 (1972).
[3] *J. P. Chesick*, J. Amer. Chem. Soc. *85*, 2720 (1963).
[4] *P. Le Perchee* and *J. M. Conia*, Tetrahedron Lett. *1970*, 1587.
[5] *W. R. Dolbier jr., D. Lomas*, and *P. Tarrant*, J. Amer. Chem. Soc. *90*, 3594 (1968).

A Light-induced [2 + 4]-Cyclodimerization in the Crystalline State[**]

By *Hans Achenbach, Wolfgang Karl*, and *Egmont Schaller*[*]

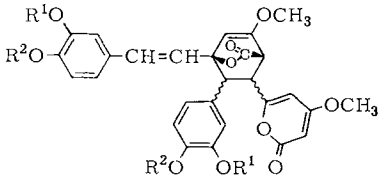
During work on the constituents of kava root (*Piper methysticum* Forst.)[1] we synthesized the known compound 5-hydroxy-3-methoxy-7-[3-methoxy-4-methoxymethoxyphenyl]-2,4,6-heptatrienoic acid δ-lactone *(1)*[2]. If the yellow needles of *(1)* [m. p. 121—123 °C (from methanol); $\lambda_{max} = 355$ nm] are exposed to daylight at room temperature, a compound *(3)* that is very sparingly soluble in methanol is formed during a few days.

Unlike *(1)*, the isomer *(2)* is stable to light.



(1), $R^1 = CH_3$, $R^2 = CH_2OCH_3$
(2), $R^1 = CH_2OCH_3$, $R^2 = CH_3$

The structure of the photoproduct *(3)* [m. p. 191—193 °C; $M^+ = 636.2197$ (dimer); $\lambda_{max} = 260$ nm; $\nu_{CO} = 1725$, 1685 cm^{-1}] is based mainly on the following arguments:



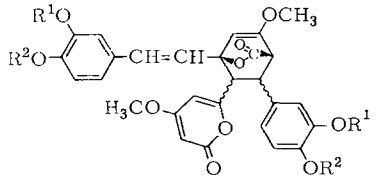
(3), $R^1 = CH_3$, $R^2 = CH_2OCH_3$

1. When heated in boiling xylene for 6 h, *(3)* decomposes almost quantitatively to *(1)*, which contraindicates a cyclobutane formulation.

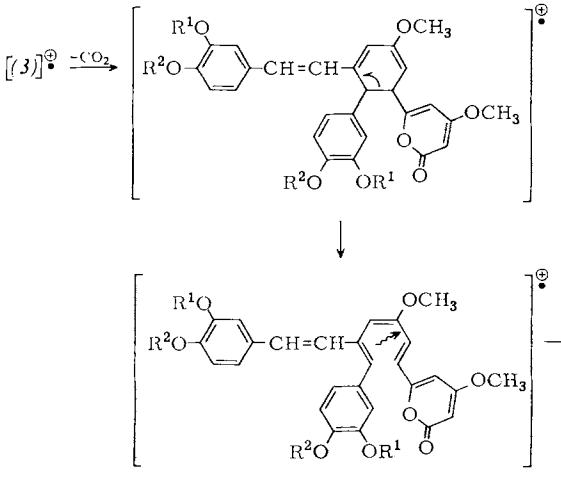
2. The NMR spectrum shows only two olefinic protons (AB system, $J = 16$ Hz), whose signals disappear on catalytic hydrogenation to the dihydro compound. Thus only one styryl double bond participates in the dimerization.

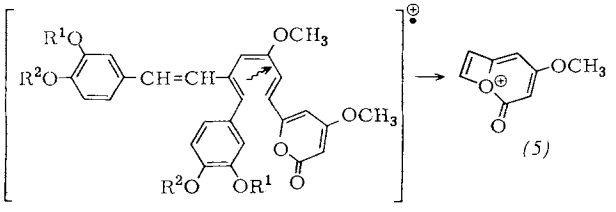
[*] Doz. Dr. H. Achenbach, Dipl.-Chem. W. Karl, and E. Schaller
Chemisches Laboratorium der Universität
78 Freiburg, Albertstr. 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.



(4), $R^1 = CH_3$, $R^2 = CH_2OCH_3$





3. In the mass spectrum of *(3)* the relatively weak molecular ion splits off CO_2 preferentially ($m/e = 592$; base peak). Thus the double bond system in one of the δ-lactone rings from *(1)* must have been altered. The position of the unchanged lactone ring can also be deduced from the mass-spectrometric fragmentation: formation of an observed fragment *(5)* at $m/e = 151.0393$ cannot be explained plausibly from the alternative structure *(4)*.

(1) did not dimerize to *(3)* under the conditions of the Diels-Alder reaction (xylene, 80 and 100 °C, up to 18 h). Also on irradiation of *(1)* with UV light (Hg-lamp, pyrex filter, $CHCl_3$ solution) a reaction could not be observed.

Whereas photo-induced [2+2]-cyclodimerizations in the crystalline state are known[3], photo-induced [2+4]-cyclodimerizations have been observed only in isolated cases together with other types of dimerizations and in liquid phase only[4].

Received: January 31, 1972 [Z 608 IE]
German version: Angew. Chem. *84*, 479 (1972)

[1] *H. Achenbach, W. Karl,* and *W. Regel,* Chem. Ber., in press.

[2] *R. Hänsel, H. Sauer,* and *H. Rimpler,* Arch. Pharmaz. *299*, 507 (1966).

[3] *M. D. Cohen* and *G. M. J. Schmidt,* J. Chem. Soc. *1964*, 1996; *B. S. Green, M. Lahav,* and *G. M. J. Schmidt,* J. Chem. Soc. *B 1970*, 1552.

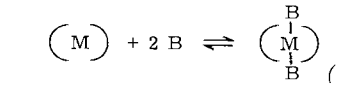
[4] See *e.g. G. O. Schenck, S.-P. Mannsfeld, G. Schomburg,* and *C. H. Krauch,* Z. Naturforsch. *19b*, 18 (1964); *D. V. Valentine, N. J. Turro,* and *G. S. Hammond,* J. Amer. Chem. Soc. *86*, 5202 (1964).

Coordination-Polymeric Metal Complexes of Bifunctional Dithiophosphinic Acids and Their Use as Adsorbents in Chromatography

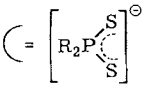
By *Wilhelm Kuchen, Jürgen Delventhal,* and *Helmut Keck*[*]

We have previously reported that planar Ni(II) and tetrahedral Co(II) dithiophosphinato complexes can add certain Lewis bases readily and reversibly to form octahedral complexes of type *(1)*[1-3].

After the recent discovery of an elegant synthesis of bifunctional dithiophosphinic acids of type *(2)* in our



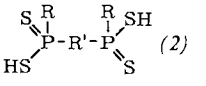
(1)



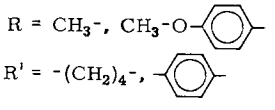
M = Co^{II}, Ni^{II}

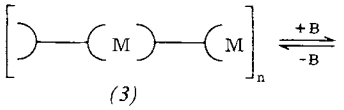
B = Pyridine, pyrazine, thiophene, etc.

laboratories[4,5] our attention was directed toward the complexing properties of these acids. We hoped thus to obtain coordination polymers of the composition *(3)* which should be able to expand their coordination

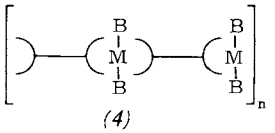


(2)





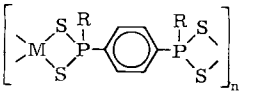
(3)



(4)

sphere reversibly to give the adducts *(4)*. These products would then be, *inter alia*, specific adsorbents for particular Lewis bases.

To prepare coordination polymers of type *(3)* we united aqueous solutions of the metal salts and the sodium salt of *p*-phenylenebis(methoxyphenyldithiophosphinic acid)[5] in the presence of CCl_4 and allowed the vigorously stirred mixture to react for several hours at room temperature.



(5a), M = Zn^{II}
(5b), M = Cd^{II}
(5c), M = Co^{II}
(5d), M = Ni^{II}
(5e), M = Pd^{II}

(5), R = CH_3-O-C$_6$H$_4$-

The coordination polymers $[ML]_n$ then separated in *ca.* 90% yields, being of type *(5)* or, for the chromium(III) complex, of type $[CrL_{1.5}]_n$ *(6)*. They are solids, insoluble in water or organic solvents, and very stable thermally and chemically; some of them are deeply colored. Magnetic and electron-spectroscopic findings show that the metal ion in *(6)* has octahedral, in *(5c)* tetrahedral, and in *(5d)* and *(5e)* planar coordination geometry.

[*] Prof. W. Kuchen, Dipl.-Chem. J. Delventhal, and Dipl.-Chem. H. Keck
Institut für Anorganische Chemie der Universität
4 Düsseldorf, Ulenbergstrasse 127/129 (Germany)

On treatment of *(5b)*, *(5c)*, or *(5d)* with Lewis bases, *e.g.* secondary or tertiary amines, adducts are formed, in some cases with change of color, corresponding in the case of pyridine to compounds *(4)* in stoichiometry.

The specific adsorbing power of such compounds was studied in detail for the Co(II) and Ni(II) complexes. For this purpose, *(5c)* and *(5d)*, mixed with an inert material, were packed into columns to which pentane solutions of the Lewis bases were then added. The separations effected were determined by gas chromatography of the pentane eluates.

It was thus shown that the complexes *(5c)* and *(5d)* are able to adsorb different amines to differing extents, so that, *e.g.* the strongly adsorbed pyridine can thus be separated from diethyl-, triethyl- and tributyl-amine, and diethylamine separated from tributylamine. Further, by use of *(5c)* a triethylamine/tributylamine mixture can also be separated.

The column packing can be regenerated by protic solvents such as a mixture of methanol/benzene and dilute acetic acid. *Ca.* 90% of the theoretical capacity could be reached experimentally with pyridine.

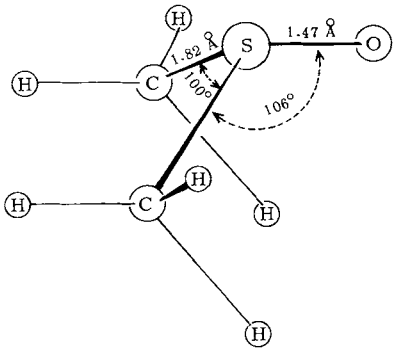
Received: March 13, 1972 [Z 618 IE]
German version: Angew. Chem. *84*, 485 (1972)

[1] *A. Judat*, Dissertation, Technische Hochschule Aachen 1964.
[2] *W. Kuchen* and *A. Judat*, Chem. Ber. *100*, 991 (1967).
[3] *K. Diemert* and *W. Kuchen*, Chem. Ber. *104*, 2592 (1971).
[4] *K. Diemert* and *W. Kuchen*, Angew. Chem. *83*, 544 (1971); Angew. Chem. internat. Edit. *10*, 508 (1971).
[5] *K. Diemert*, Dissertation, Universität Düsseldorf 1972.

The "Sulfoxide Bond"[1]

By *Hans Bock* and *Bahman Solouki*[*]

In the sulfoxides[2] R^1—SO—R^2 such as



(1)

it is assumed from the short distance d_{SO} that a S=O double bond exists and from the pyramidal C_s conformation that there is an electron pair n_S on sulfur. Since the sulfur is surrounded by a total of ten valence electrons, the π_{SO} system is formulated with a 3d orbital. CNDO/2 calculations including the 3d orbitals[3] give the correlation diagram shown in Figure 1 for the five highest occupied molecular orbitals of dimethyl sulfoxide within the CSC- and CSO-angular range 90—120°.

[*] Prof. Dr. H. Bock and Dipl.-Chem. B. Solouki
Chemische Institute der Universität
6 Frankfurt 70, Ludwig-Rehn-Str. 14 (Germany)

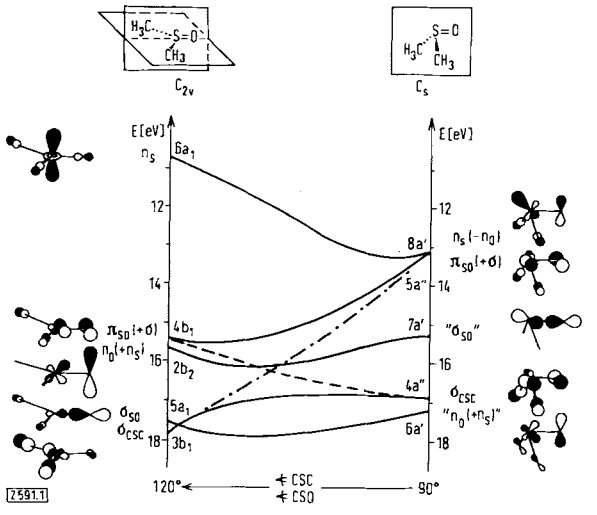


Fig. 1. Correlation diagram for dimethyl sulfoxide.

From the CNDO/2 orbitals shown in Fig. 1 it is clear that characterization is difficult because of the electron delocalization over the whole molecular skeleton: as the central angle ∢ CSC is decreased, the n_S electron pair is stabilized by increasing admixture of n_O and σ contributions, and the second-highest $\pi_{SO}(+\sigma)$ orbital is destabilized by further decrease of the π contribution. Successive molecular orbitals can be crudely characterized as $n_O(+n_S)$, σ_{SO}, and σ_{CSC}; the correlation of symmetry equivalent orbitals, $4b_1 \rightarrow 5a''$ and $3b_1 \rightarrow 4a''$, follows the non-crossing rule[4].

According to the correlation diagram (Fig. 1) it is to be expected that, for example, in dialkyl sulfoxides with a central CSC angle $\lesssim 90°$, the sulfur electron pair $n_S(-n_O)$ and the $\pi_{SO}(+\sigma)$ orbital will fortuitously be energetically equal. This expectation is confirmed by comparison of the photoelectron (PE) spectra of dimethyl sulfoxide and ethylene sulfoxide (Fig. 2).

The assignment of the dimethyl sulfoxide spectrum according to the calculated orbital sequence—

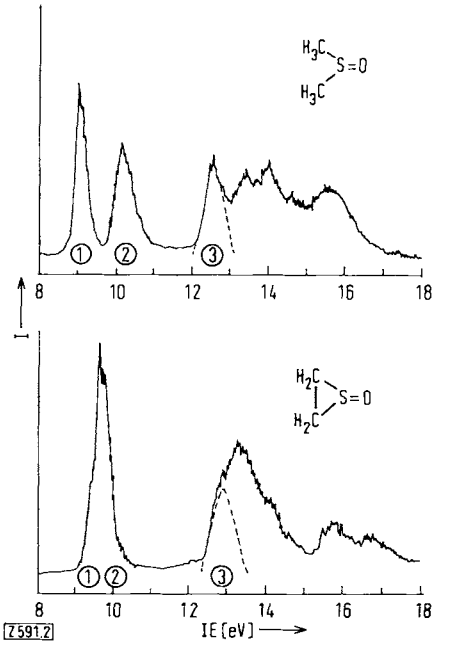
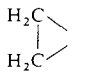
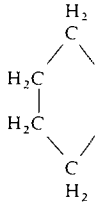
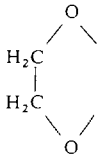


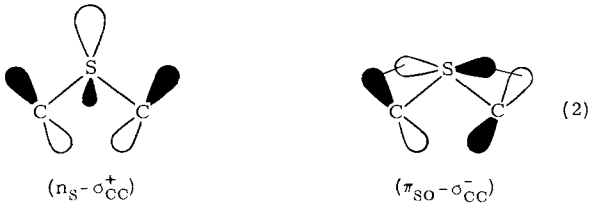
Fig. 2. PE spectra of dimethyl sulfoxide and ethylene sulfoxide.

Table 1. Vertical ionization energies IE_n [eV] of sulfoxides.

R_2SO	IE_1	IE_2	ΔIE	$\Delta IE_{corr.}$
	9.66	9.78	0.12	0.12
	8.77	9.75	0.98	1.07
H_3C-	9.01	10.17	1.16 ≡	1.16
H_3CCH_2-	8.76	9.83	1.07	1.16
$(H_3C)_2CH-$	8.46	9.52	1.06	1.24
$(H_3C)_3C-$	8.18	9.20	1.02	1.29
X_2SO	IE_1	IE_2	IE_3	IE_4
$(H_3C)_2N-$	8.53	9.06	9.82	10.82
H_3CO-	10.25	10.95	11.60	11.90
	10.93	10.93	11.96	12.48
Br—	10.54	10.82	11.15	11.64
Cl—	11.13	11.78	12.08	12.48
F—	12.58	14.0	14.75	16.02

$n_S(-n_O)/\pi_{SO}(+\sigma)/n_O(+n_S)$— is best supported by the dynamic behavior of the system as a function of geometrical perturbation, as well as by band forms (n, unsymmetrical and sharp; π symmetrical and broad)[5].

For open-chain dialkyl sulfoxides the ionization energy IE_2 decreases more than does IE_1 with increasing degree of methylation, and this can be understood as an effective hyperconjugative destabilization of the π_{SO} relative to the n_S orbital:



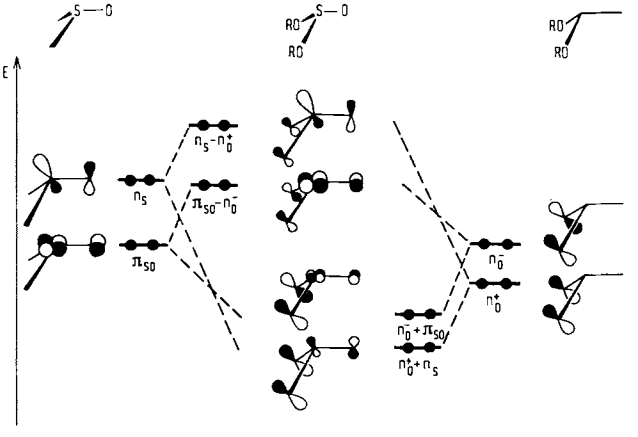
$(n_S - \sigma^+_{CC})$ $(\pi_{SO} - \sigma^-_{CC})$ (2)

If the donor effect of α-methyl groups (Table 1: ΔIE CH_3/CH_2CH_3)

$$\Delta n_S = \tfrac{1}{2}(8.76—9.01)\,eV = -0.12\,eV$$
$$\Delta \pi_{SO} = \tfrac{1}{2}(9.83—10.17)\,eV = -0.17\,eV \quad (3)$$

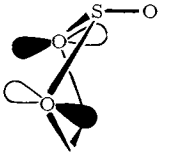
is subtracted, for example, from the ionization energies of the *tert*-butyl derivative ($IE_1 = 8.18 - 6(-0.12) = 8.9$ eV and $IE_2 = 9.20 - 6(-0.17) = 10.2$ eV), the resulting difference, $\Delta IE_{corr} = 1.3$ eV, is smaller than the separation of 0.16 eV in dimethyl sulfoxide. This increased energetic separation can be explained in terms of widening of the CSC-angle due to the bulk of the alkyl group in accordance with Figure 1.

For sulfoxides X_2SO in which the atom X next to sulfur carries an electron pair n_X, the energy level scheme (Fig. 1) is to be correspondingly expanded: for alkyl sulfites (X = OR) there result the following symmetry-correct combinations, with the assumptions that $E(n_O) \approx E(\pi_{SO})$ and $\Delta E(n_O^-/n_O^+) > 0.3$ eV[6]:



(4)

Again it is possible to test this by geometrical perturbation: In the *endo*-conformation of ethylene sulfite, which is the stable one according to CNDO/2 calculations, the electron pairs of the ring-oxygen atoms are oriented at an angle of about 45° to each other:



(5)

The steric rigidity, an unfavorable condition relative to that of dimethyl sulfite, decreases the antibonding interaction in the orbital $(n_S - n_O^+)$ and increases the antibonding interaction in the orbital $(n_O^- - \pi_{SO})$ [cf. (4)]; according to CNDO/2 calculations these two should have equal energy. As expected, the PE spectrum of ethylene sulfite shows the first band to have doubled intensity (Table 1).

The other derivatives X_2SO in Table 1 round out the picture: If $X = N(CH_3)_2$, then unlike (4), $E(n_N) \approx E(n_S)$, and if X = F[7], Cl or Br, then the "horizontal" electron pairs must also be taken into account. Collectively, the perturbations of the sulfoxides shown by PE spectroscopy indicate that

[1] Part 9 of Photoelectron Spectra and Molecular Properties.— Part 8: *C. Pitt* and *H. Bock*, Chem. Commun. *1972*, 28.

[2] Cf. *H. H. Szmant*: "The Sulfur-Oxygen Bond" in: Sulfur in Organic and Inorganic Chemistry. Dekker Inc., New York 1971; and literature cited therein.

[3] *B. Solouki*, Diplomarbeit, Universität Frankfurt 1971.

[4] *C. A. Coulson*, Chem. Britain *4*, 113 (1968).

[5] Cf., *e.g. D. W. Turner, C. Baker, A. D. Baker*, and *C. R. Brundle*: Molecular Photoelectron Spectroscopy. Wiley-Intersience, London 1970.

[6] *P. Mollère* and *H. Bock*, unpublished work.

[7] We are indebted to Prof. *H. W. Roesky*, Universität Frankfurt, for providing us with a sample of thionyl fluoride.

there are many possibilities for delocalization of the electrons. Therefore, as part of a more complex total system the "SO bond" cannot be treated as an isolated moiety.

Received: December 30, 1971 [Z 591 IE]
German version: Angew. Chem. *84*, 436 (1972)

Preparation of Pure Triacetylene, Tetraacetylene, and Pentaacetylene and Investigation of Their Electronic Spectra[**]

By *Else Kloster-Jensen*[*]

Unsubstituted polyacetylenes $(1)_n$ are among the simplest parent compounds in organic chemistry. Although their physical and chemical properties are of central importance, particularly for theoretical chemistry, only the first two members of the series ($n=1, 2$) have hitherto been studied in detail; the higher polyynes are extremely unstable.

$H-(C\equiv C)_n-H$ $(1)_n$

We report here the preparation of pure $(1)_3$, $(1)_4$, and $(1)_5$ which can be isolated at low temperatures *in vacuo* as colorless, crystalline (?) solids. $(1)_3$ and $(1)_4$ are sufficiently stable and volatile for their electron spectra to be measured in the gas phase in the far UV region (see Table 1).

Triacetylene (hexatriyne) $(1)_3$[2] was prepared from 1,6-dichloro-2,4-hexadiyne[2a, 3] by a slightly modified procedure given by *Bohlmann*[2b]. Working up at a low temperature and in a vacuum afforded a colorless, completely sublimable product. Photoelectron spectrum[4]: vertical ionization potentials $I_v(\pi_1)=9.50$ eV, $I_v(\pi_2)=11.55$ eV, $I_v(\pi_3)=12.89$ eV. IR spectrum (gas phase, 10 torr) (bands in cm^{-1}): ν(H—C), $\parallel$ band 3327, 3318 (s); ν(C≡C) 2115 (w); δ(H—C≡C; 1st overtone), $\parallel$ band 1243, 1234 (s); δ(H—C≡C), $\perp$ band 628, 623, 618 (s). The NMR spectrum ($CDCl_3$: $\delta=7.29$ ppm at -50°C) was measured for a mixture of $(1)_2$ and $(1)_3$: $(1)_3$, $\delta=2.14$ ppm; $(1)_2$, $\delta=2.06$ ppm[5]. Under the same conditions $(1)_1$ gives $\delta=2.01$ ppm[5].

Tetraacetylene (octatetrayne) $(1)_4$[6, 7] was prepared by oxidative coupling of (trimethylsilyl)diacetylene[8] and subsequent alkaline hydrolysis of the resulting bis-(trimethylsilyl)tetraacetylene $(2)_4$[9]:

$$2\,(CH_3)_3Si-C\equiv C-C\equiv C-H \xrightarrow[CH_3OH/H_2O/\text{pyridine}]{Cu(OAc)_2,\ Cu_2Cl_2} (CH_3)_3Si-C\equiv C-C\equiv C-C\equiv C-C\equiv C-Si(CH_3)_3 \quad (2)_4$$

$$(2)_4 \xrightarrow{NaOH/CH_3OH} H-C\equiv C-C\equiv C-C\equiv C-C\equiv C-H \quad (1)_4$$

Bis(trimethylsilyl)tetraacetylene could be isolated as colorless transparent crystals of m.p. 94.0—94.2 °C [IR spectrum (in KBr): characteristic bands (in cm^{-1}) at *ca.* 2957, 2895, 1402, 1245, 835, 754, 697 ($Si(CH_3)_3$); 2045 (s) ν(C≡C); further strong bands at 1028, 960, 625, 443, 352 cm^{-1}]. The hydrolyzate of tetraacetylene was acidified,

Table 1. Electronic spectra of the polyacetylenes (positions of maxima in nm) [***].

Compound		$^1\Sigma_g^+ \rightarrow {}^1\Delta_u$ Solution	$^1\Sigma_g^+ \rightarrow {}^1\Delta_u$ Gas phase	$^1\Sigma_g^+ \rightarrow {}^1\Sigma_u^+$ Solution	$^1\Sigma_g^+ \rightarrow {}^1\Sigma_u^+$ Gas phase
$(1)_2$	H—(C≡C)$_2$—H [1]	247 [a]	243.4		164.5
		235	231.5		159.2
		224	220.7		154
		214	211.1		
$(1)_3$	H—(C≡C)$_3$—H	300 [a]	293.3		183.1 [d]
		284	275.9		179.2
		268.4	260.7		172.7
		254.5	246.9		166.5
		242	234.8		
$(1)_4$	H—(C≡C)$_4$—H	345.5 [a]		226.2 [a]	207.3
		322		215.9	198.7
		301.6		206.6	190.8
		283.7		198.1	183.8
$(1)_5$	H—(C≡C)$_5$—H	384.6 [b]		251.3 [b]	[e]
		356.3		239	
		332.2		227.9	
		311.3		217.8	
$(2)_4$	$(CH_3)_3Si$—(C≡C)$_4$—$Si(CH_3)_3$	371 [a]		254 [c]	
		344.6		241.2	
		321.6		229.8	
		301.6		219.2	
$(2)_5$	$(CH_3)_3Si$—(C≡C)$_5$—$Si(CH_3)_3$			274.3 [b]	
				259.8	
				247.1	
				235.2	
				224.9	

[a] *n*-Pentane/2,2-dimethylbutane 3:8. [b] *n*-Pentane. [c] Cyclohexane. [d] Provisional assignment. [e] Not measurable in the gas phase because intensity was too low.

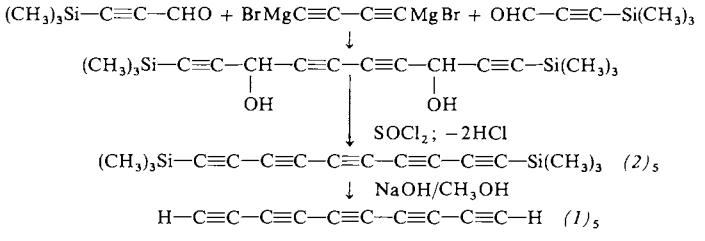
[*] Dr. Else Kloster-Jensen
Physikalisch-Chemisches Institut der Universität
CH-4056 Basel, Klingelbergstrasse 80 (Switzerland)
Permanent address: Department of Chemistry, University of Oslo, Blindern, Oslo 3 (Norway)

[**] This work was supported by the Schweizerischer Nationalfonds as part of Project No. 2.477.71, and by CIBA-GEIGY AG, Basel.

[***] For previous data see [2—7].

washed until neutral, and then chromatographed; the eluate was concentrated to dryness under vacuum in the cold. The NMR spectrum ($CDCl_3$, $\delta = 7.28$ ppm, $-50\,°C$) was measured for a mixture of $(1)_2$ and $(1)_4$: $(1)_4$, $\delta = 2.14$ ppm; $(1)_2$, $\delta = 2.03$ ppm. The minor discrepancy in the value for $(1)_2$ is probably due to a difference in concentration.

Pentaacetylene (decapentayne) $(1)_5$[6] was prepared as shown in the following scheme:



Trimethylsilylpropiolaldehyde[10] was coupled with butadiynylenebis(magnesium bromide) to give 1,10-bis(trimethylsilyl)-1,4,6,9-decatetrayne-3,8-diol, m.p. 118–119 °C [electronic spectrum: $\lambda_{max} = 259.5$, 246, 234, 222 (sh) nm]. Treatment with thionyl chloride and two-fold 1,6-elimination of hydrogen chloride gave bis(trimethylsilyl)pentaacetylene $(2)_5$. Subsequent alkaline hydrolysis and chromatographic separation yielded spectroscopically pure pentaacetylene $(1)_5$. After removal of the solvent under vacuum in the cold there remained a colorless, crystalline solid. The vapor pressure of $(1)_5$ was insufficient for an electronic spectrum to be recorded in the gas phase.

Received: February 16, 1972 [Z 617 IE]
German version: Angew. Chem. 84, 483 (1972)

[8] *B. G. Shakovskoi, M. D. Stadnichuk,* and *A. A. Petrov,* Zh. Obshch. Khim. *35*, 1714 (1965); Chem. Abstr. *64*, 2119 (1966).

[9] Bis(trimethylsilyl)tetraacetylene, m.p. 95–97 °C; Dr. *D. R. M. Walton,* private communication after completion of the present work; cf. [7].

[10] *N. V. Komarov, O. G. Yarosh,* and *L. N. Astaf'eva,* Zh. Obshch. Khim. *36*, 907 (1966); Chem. Abstr. *65*, 10607 (1966).

Cleavage of 1-Arylarsoles by Alkali Metals

By *Gottfried Märkl* and *Hagen Hauptmann*[*]

1-Phenyl-substituted aromatic arsoles, which are readily accessible by base-catalyzed cycloaddition of phenylarsane to 1,3-butadiyne[1], react with alkali metals in dimethoxyethane by stepwise addition of two electrons. 1,2,5-Triphenylarsole *(1a)* yields first the blue-green radical anion *(2a)* (λ_{max} 650 nm), whose ESR spectrum (Fig. 1) exhibits no fine structure and then the red-violet arsenide *(4)* (λ_{max} 610 nm); the resulting phenyl-Li(K) is decomposed by reaction with the solvent:

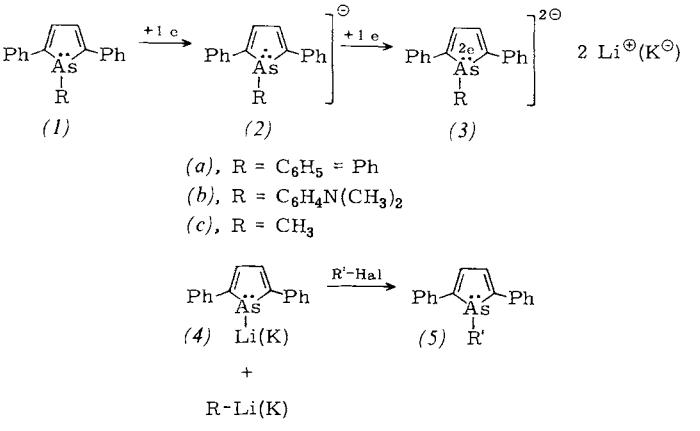


Table 1. Reaction of halides R'—Hal with *(2a)* or *(4)* to give arsole derivatives *(5)*.

(5), R'=	Yield (%) from *(2)*	Yield (%) from *(4)*	M.p. (°C)	UV λ_{max} (nm) (log ε) (in ethanol)	^{1}H-NMR (τ)	
(a), CH_3	63	52	101–102	367.5 (4.27) 218 (4.16)	$-CH_3$:	8.74 (s)
(b), $CH_2C_6H_5$	23	63	90– 91	373 (4.23) 225 (4.39)	$-CH_2-$:	6.66 (s)
(c), CH_2OCH_3	—	63	82.5–84.5	368 (4.04) 225 (4.22)	$-OCH_3$: $-CH_2O-$:	6.69 (s) 5.81 (s)
(d), CH_2Cl	10	28	80.5–81.5	375 (4.19) 238 (4.15)	$-CH_2Cl$:	6.17 (s)
(e), $CHCl_2$	10	—	105–107	380 (4.14) 244 (4.19)	$-CHCl_2$:	4.19 (s)
(f), $CHClC_6H_5$	26	—	107–109	379 (4.04) 230 (4.31) 213 (4.33)	$-CHCl-$:	4.94 (s)

The dianion *(3a)*, isoelectronic with the stable 1,1-dimethyl-2,5-diphenylsilole dianion[2], could not be detected. Deuterolysis of the dianion *(3b)* formed by reaction of 1-(*p*-dimethylaminophenyl)-2,5-diphenylarsole *(1b)* with two equivalents of alkali metal should give only 4-D-*N*,*N*-dimethylaniline alongside 1-D-2,5-diphenylarsole; however, the dimethylaniline formed actually contains no deuterium.

[*] Prof. Dr. G. Märkl and Dr. H. Hauptmann
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

[1] a) Synthesis according to *B. J. Armitage, E. R. H. Jones,* and *M. C. Whiting,* J. Chem. Soc. *1952*, 1993; b) For UV spectra see *K. K. Georgieff* and *Y. Richard,* Can. J. Chem. *36*, 1280 (1958), and references cited therein.

[2] a) *W. Hunsmann,* Ber. Dtsch. Chem. Ges. *83*, 213 (1950); b) *F. Bohlmann, ibid. 84*, 785 (1951); c) *J. B. Armitage, C. L. Cook, E. R. H. Jones,* and *M. C. Whiting,* J. Chem. Soc. *1952*, 2010.

[3] *J. B. Armitage* and *M. C. Whiting,* J. Chem. Soc. *1952*, 2005.

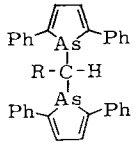
[4] *E. Heilbronner, V. Hornung,* and *E. Kloster-Jensen,* unpublished work.

[5] *E. Kloster-Jensen, C. Pascual,* and *R. Tabacchi,* unpublished work.

[6] *C. L. Cook, E. R. H. Jones,* and *M. C. Whiting,* J. Chem. Soc. *1952*, 2883.

[7] *R. Eastmond* and *D. R. M. Walton,* Chem. Commun. *1968*, 204.

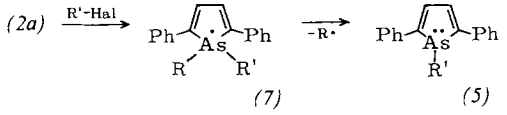
Reaction of *(2a)* with methylene chloride and benzal chloride yields not only the monochloroalkylarsoles *(5d)* and *(5f)*, respectively, but also the dinuclear arsoles *(6a)* and *(6b)* by double nucleophilic substitution:



(6)

(6a), R = H: yield 10%; m. p. 225—227 °C; UV spectrum: λ_{max} 382 (log ε 4.42), 342 (4.28), 220 nm (4.52). *(6b)*, R = C_6H_5: yield 6%; m. p. 194—195 °C; UV spectrum: λ_{max} 376 (log ε 4.12), 346 (4.08), 230 nm (4.81).

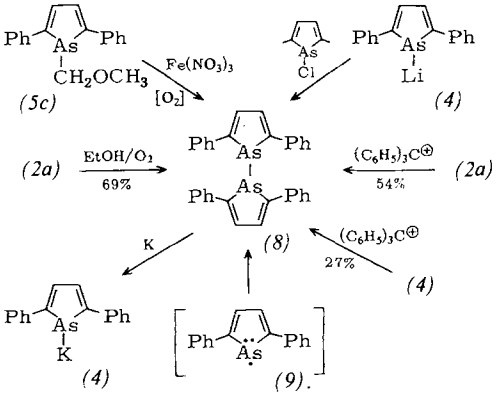
The mechanism of alkylation of the radical anion *(2a)* has not yet been fully elucidated. The derivative *(7)* containing pentavalent arsenic is probably formed initially *via* reaction of the lone pair; loss of a phenyl radical then affords the arsole.



(7) *(5)*

Both the radical ion *(2a)* and the anion of *(4)* react in a surprising manner with trityl perchlorate: The deep red product consists of diarsolyl *(8)*, m. p. 209—212 °C, yield 54 and 27%, respectively. UV spectrum (in dimethoxyethane): λ_{max} 414 (log ε 3.96), 338 (4.38), 262.5 nm (4.23). ^{1}H-NMR spectrum: arsole ring H: 3.22 τ, 4H (s); aryl H: 2.92—2.34 τ, 20H (m). Mass spectrum (SM 1; 40 eV): M ($C_{32}H_{24}As_2$), *m/e* 558, rel. int. 100%; M/2 ($C_{16}H_{12}As$), *m/e* 279, 29%.

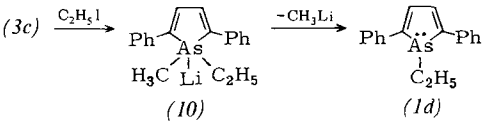
The tendency of formation and the stability of diarsolyl are unusual. Various routes to *(8)* are summarized in the following scheme.



(4) *(9)*

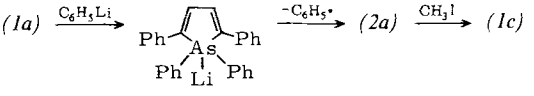
Oxidative formation of *(8)* probably proceeds by dimerization of the arsolyl radical *(9)*. On treatment with an alkali metal, *e. g.* potassium, *(8)* is smoothly cleaved to give the K arsenide *(4)* which gives the methylarsole *(1c)* on reaction with *e. g.* CH_3I.

Unlike triphenylarsole *(1a)*, 1-methyl-2,5-diphenylarsole *(1c)* produces a stable dianion *(3c)* on treatment with two equivalents of alkali metal; ethyl iodide reacts with *(3c)*, probably *via* the pentacoordinate species *(10)* to yield a mixture of 1-methyl- and 1-ethylarsole *(1c)* and *(1d)* (R = C_2H_5), respectively.



(10) *(1d)*

With respect to *(10)* the expected reactivity of the arsole system toward organolithium compounds has been confirmed experimentally. *(1a)* reacts with phenyl-Li at room temperature to give a radical species (Fig. 2), shown by chemical evidence to be the radical anion *(2a)* (*e. g.* reaction with methyl iodide affording *(1c)*).



According to the well-resolved, multiple-line ESR spectrum (Fig. 2), no polyaryl radicals appear to be present[3]; however, phenyl radical can be detected by ESR spectroscopy for a short while in a freshly prepared solution.

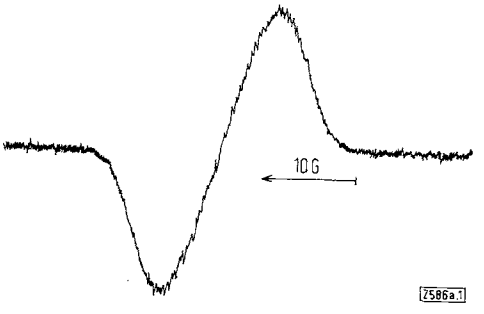


Fig. 1. ESR spectrum of the radical anion *(2a)*.

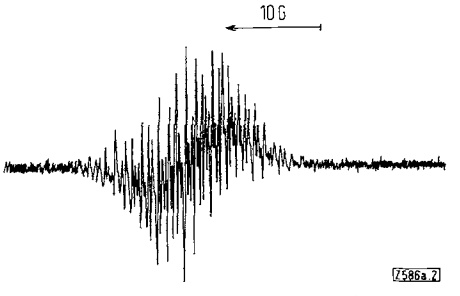


Fig. 2. ESR spectrum of the radical species formed on reaction of *(1a)* with C_6H_5Li.

Received: November 16, 1971 [Z 586a IE]
German version: Angew. Chem. *84*, 438 (1972)

[1] *G. Märkl* and *H. Hauptmann*, Tetrahedron Lett. *1968*, 3257.

[2] *E. G. Janzen, J. B. Pickett*, and *W. H. Atwell*, J. Organometal. Chem. *10*, P 6 (1967).

[3] *K. W. Böddeker, G. Lang*, and *U. Schindewolf*, Angew. Chem. *80*, 998 (1968); Angew. Chem. internat. Edit. *7*, 954 (1968); *P. Wormington* and *J. R. Bolton, ibid. 80*, 997 (1968) and *7*, 954 (1968) resp.; *C. Thomson* and *D. Kilcast, ibid. 82*, 325 (1970) and *9*, 310 (1970), resp.

Unusual Substitution in an Arsole Ring

By *Gottfried Märkl* and *Hagen Hauptmann*[*]

The less pronounced nucleophilic character of tertiary arsanes[1, 2] compared to phosphanes is further reduced in the aromatic arsole system *(1)*. The chemistry of the arsoles resembles that of pyrrole rather than the phospholes.

1,2,5-Triphenylarsole and 1-phenyl-2,5-dimethylarsole are unable to form quaternary salts and sulfides; arsole oxides are formed only in moderate yields alongside arsenic-free decomposition products on oxidation with H_2O_2.

However, these arsoles react smoothly with elemental chlorine (as phenyl iodide dichloride) to give the stable 1,1-dichloro derivatives *(2)* (Table 1), and with *tert*-butyl hypochlorite to give the 1-chloro-1-*tert*-butoxy derivatives *(3)*:

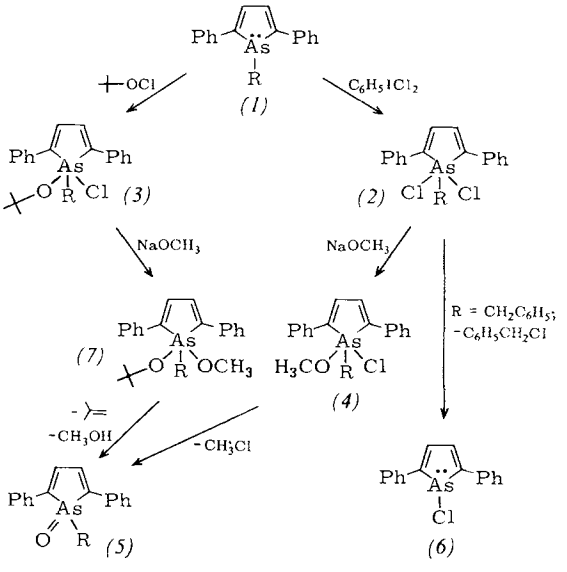


Table 1. 1,1-Dichloro derivatives *(2)* of 1,2,5-trisubstituted arsoles.

(2), R =	Yield (%)	M. p. (°C)	UV λ_{max} (nm) (log ε) (in ethanol)	^{1}H-NMR (τ) (in $CDCl_3$)
C_6H_5	96	168–169	395 (4.19) 239 (4.14) 220 (4.32)	
$CH_2C_6H_5$	88	85 (dec.)		
CH_3	83	170	400 (4.18) 237 (4.25)	—CH_3: 7.05 (s) aryl-H: 2.06–3.06 (m)

The dichlorides are thermolabile [1,1-dichloro-1-benzylarsole *(2)*, R = $C_6H_5CH_2$, decomposes at room temperature to 1-chloro-2,5-diphenylarsole *(6)*, fine red needles, m. p. 136—137 °C; yield 85%; UV spectrum (in CH_2Cl_2): λ_{max} (log ε): 402 (4.07), 246 nm (4.23)] but surprisingly stable toward water and alcohols (recrystallized from ethanol). Reaction with one equivalent of Na methoxide furnishes the unstable 1-chloro-1-methoxyarsoles *(4)* which spontaneously lose methyl chloride to give the arsole oxide *(5)* in good yield (R = C_6H_5, yield 80%; m. p. 226—227 °C. R = CH_3, yield 64%; m. p. 199 °C. R = $CH_2C_6H_5$, yield 35%; m. p. 115 °C (decomp.)).

[*] Prof. Dr. G. Märkl and Dr. H. Hauptmann
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

The yellow-orange voluminous *tert*-butyl hypochlorite adducts *(3)* (R = C_6H_5, $CH_2C_6H_5$) resemble *(4)* in structure but do not decompose to the arsole oxides; however, they disproportionate in solution at room temperature to give *(2)*. In the case of R = $CH_2C_6H_5$ the reaction proceeds further to give the 1-chloroarsole *(6)* directly in 41% yield.

Reaction of *(3)*, R = C_6H_5, with $NaOCH_3$ proceeds directly to the arsole oxide *(5)*, R = C_6H_5, *via* the 1-methoxy-1-*tert*-butoxy derivative *(7)*.

These results suggested that the reaction of the *tert*-butyl hypochlorite adducts *(3)* with organolithium compounds should give pentacoordinate arsoles *(8)* or their reaction products. Surprisingly, the pale yellow crystalline reaction products are actually 3-substituted arsoles *(9)* (Table 2):

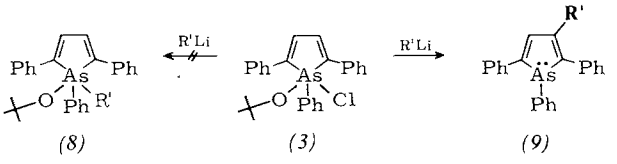


Table 2. 1,2,3,5-Tetrasubstituted arsoles *(9)*.

(9), R =	Yield (%)	M. p. (°C)	UV λ_{max} (nm) (log ε) (in ethanol)	^{1}H-NMR (τ) (in $CDCl_3$)
CH_3	36	122–124	353 (4.17) 234 (4.35)	—CH_3: 7.80 (s)
C_6H_5	40	151–152.5	370 (4.11) 265 (4.25) 240 (4.41)	aryl-H: 2.26–3.30
$C_6H_4N(CH_3)_2$	16	154–155	385 (4.00) sh 330 (4.30) 265 (4.32) 230 (4.39) sh	$N(CH_3)_2$: 7.08 (s) aryl-H: 2.24–3.46

Formation of *(9)* can be rationalized mechanistically as S_N2' substitution and subsequent aromatization by elimination of *tert*-butanol.

The bulky *tert*-butyl group induces the S_N2' mechanism by blocking nucleophilic attack at the heteroatom.

Received: November 16, 1971 [Z 586b IE]
German version: Angew. Chem. *84*, 439 (1972)

[1] *W. C. Davis* and *W. P. G. Lewis*, J. Chem. Soc. *1934*, 1599; *L. Maier*, Progr. Inorg. Chem. *5*, 126 (1963).
[2] *E. Bergmann* and *W. Schütz*, Z. Phys. Chem. *B 19*, 401 (1932).

General Synthesis of Aryl-Substituted Arsabenzenes

By *Gottfried Märkl*, *Hagen Hauptmann*, and *Jürgen Advena*[*]

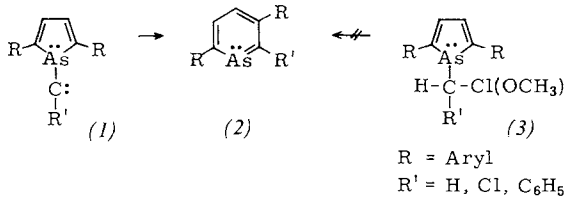
Both the "phenarsazine" described by *Wieland*[1] in 1921 and the "arsanthrene" of *Kalb*[2] have been shown by *Bickelhaupt et al.*[3, 4] to be dimers and therefore not arsa-aromatic compounds containing —As=C< (4pπ—2pπ) double bonds.

Evidence for the existence of this bond system was first provided by the preparation of arsamethinecyanines[5].

[*] Prof. Dr. G. Märkl, Dr. H. Hauptmann, and Dipl.-Chem. J. Advena
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

Following the spectroscopic detection of the unstable 9-arsaanthracene[6, 7], *Vermeer* and *Bickelhaupt*[8] successfully isolated a dibenzoarsabenzene, *viz.* 10-phenyl-9-arsaanthracene; *Ashe*[9] subsequently described unsubstituted arsabenzene itself.

In the present communication we report a general synthesis of arsabenzenes *(2)* bearing three or more aryl substituents by an intramolecular carbene insertion reaction of arsoles *(1)*.

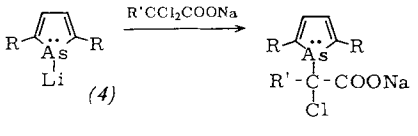


(1) *(2)* *(3)*

Previous attempts to prepare six-membered arsenic heterocycles from halo-(methoxy-)alkyl-substituted arsoles *(3)*[10] by ring expansion *via* carbonium, carbenoid, or carbene intermediates were unsuccessful. The organometallic bases required for deprotonation or α-elimination in these arsoles also attack the arsole ring; moreover, under such conditions —in analogy to the phosphabenzenes[11]—one must not forget that the expected arsabenzenes may react further.

In order to prepare arsolylcarbene species *(1)* while avoiding basic reactions we applied the method of generating dichlorocarbene by thermolysis of Na trichloroacetate to arsole chemistry.

The lithium arsenide *(4)*, which is readily accessible by lithium-induced cleavage of 1,2,5-triphenylarsole in dimethoxyethane[10], reacts with Na trichloroacetate and also with Na phenyldichloroacetate[12] to give the mono-substituted products *(5)* and *(6)*, respectively (Table 1), as potential carbene precursors:



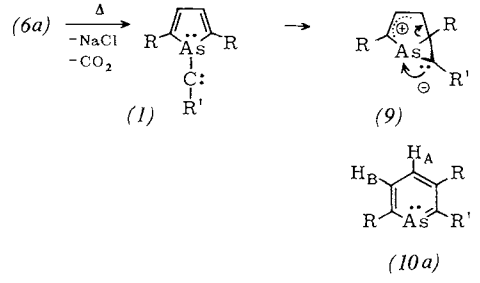
(4) *(5)*, R' = Cl; *(6)*, R' = C_6H_5

Table 1.

(5), (6)	Yield (%)	M. p. (°C)	UV λ_{max} (nm) (ε) (in ethanol)
(5a), R = C_6H_5	32	170 (dec.)	385 (12600) 246 (16000)
(6a), R = C_6H_5	11	140 (dec.)	222 (15000) 263 (8850) 380 (10500)
(6b), R = naphthyl	60	125 (dec.)	223 (61700) 264 (24600) sh 286 (17000) 303 (14250) 398 (15400)
(6c) = 3-phenyl-*(6a)*	38	153–155 (dec.)	223 (25900) sh 268 (18600) 377 (5950)

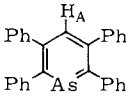
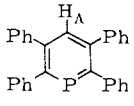
Whereas Na arsolyldichloroacetate *(5a)* is degraded in an undefined manner at 170°C, its phenyl derivative *(6a)* decomposes a little above its melting point (140°C) to give a 77% yield of stable, non-autoxidable 2,3,6-triphenylarsabenzene *(10a)* as colorless crystals of m. p. 146°C.

This rearrangement results from an intramolecular carbene insertion, probably *via* the arsacyclopropane of the bicyclic betaine *(9)* (non-symmetrical arsoles should give two isomeric arsabenzenes—by insertion at position 2 or 5; see Table 2):

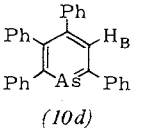


(1) *(9)* *(10a)*

Table 2.

	Yield (%)	M. p. (°C)	MS *m/e* (rel. int.)	UV λ_{max} (nm) (ε) (in ethanol)	^{1}H-NMR (τ) (in $CDCl_3$)
(10b), R = naphthyl, R' = C_6H_5	40	170–172	468 (100%)	218 (69600) 272 (42400) 297 (30200) sh 326 (16400) sh	AB part of H_AH_B: 1.73, 1.89, 1H; aromatic protons: 1.90–2.96, 20H (m)
 *(10c)* [a]	80	223–225	444 (100%)	225 (27800) sh 283 (37100) 358 (1200)	H_A: 2.39, 1H (s); aromatic protons: 2.43–3.15, 20H (m)
For comparison					
	—	239–240	—	225 (29600) 272 (36900) 344 (1200)	H_A: 2.38, 1H (d), $^4J_{P-H}$ 3 Hz; aromatic protons: 2.60–3.02, 20H (m)

[a] The isomeric 2,3,4,6-tetraphenylarsabenzene *(10d)* [NMR spectrum H_B: 2.05 τ 1H (s); aromatic protons: 2.43–3.34 τ, 20H (m)], which is formed at the same time and is predicted by the discussion of the reaction mechanism, has not yet been obtained pure.



(10d)

Mass spectrum (SM1; 70 eV): M ($C_{23}H_{17}As$), *m/e* 368, 100% rel. int.; M − C_6H_5, *m/e* 291, 11.6%; M − (2 × C_6H_5),

m/e 214, 11.9%; M−(AsC—C_6H_5), *m/e* 204, 6.3%; M−((C_6H_5)$_2C_2$), *m/e* 190, 11.5%. The aromatic stability of the arsabenzene system is indicated by the large molecular ion peak and the occurrence of the molecular dication (M^{2+} 184), and the dications of higher molecular fragments.

^{1}H-NMR spectrum (Fig. 1): AB spectrum of the arsabenzene ring protons, H_A 2.29 τ, H_B 1.98 τ; $J_{H_AH_B}$ 9 Hz; aromatic protons at 2.21—2.94 τ.

The chemical shifts of the H_A, H_B ring protons are almost identical with those in the corresponding phosphabenzenes.

Figure 2 compares the UV spectra of *(10a)* (λ_{max} 268 (ε = 34000), 285 (34600), 360 nm (3390) sh) with those of the aromatic hydrocarbon (λ_{max} 247 (ε = 32500), 268 nm (23400)

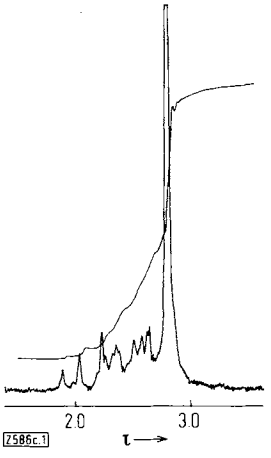


Fig. 1. ^{1}H-NMR spectrum of *(10a)*.

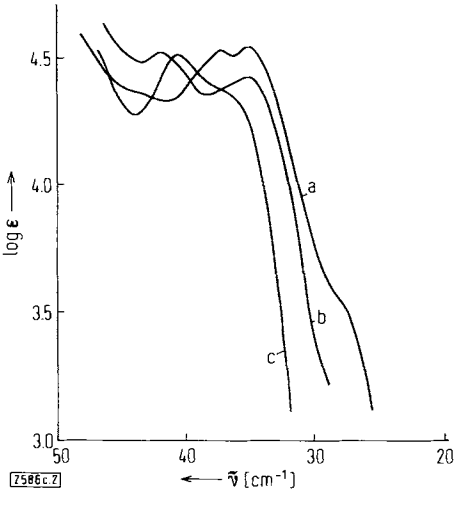


Fig. 2. UV spectra of a) 2,3,6-triphenylarsabenzene *(10a)*, b) 2,3,6-triphenylpyridine, and c) 1,2,4-triphenylbenzene.

sh) and 2,3,6-triphenylpyridine[13] (λ_{max} 243 (ε = 32000), 286 nm (26400)).

Whereas the position of the ^1L_b (α) band at 287 nm for arsabenzene *(10a)* is constant at 287 nm with respect to that of 2,3,6-triphenylpyridine, the ^1L_a (p) band at 268 nm shows a bathochromic shift of 21 and 25 nm compared to the benzene and pyridine derivatives.

IR spectrum: C—H stretching vibrations: 2970, 3020, and 3075 cm^{-1}; the spectra of the arsabenzenes are largely identical with those of the corresponding pyridines and phosphabenzenes.

The arsabenzenes obtained from the Na salts *(6b)* and *(6c)* are characterized in Table 2.

Received: November 16, 1971 [Z 586c IE]
German version: Angew. Chem. *84*, 440 (1972)

[1] *H. Wieland* and *W. Rheinheimer*, Liebigs Ann. Chem. *423*, 1 (1921).
[2] *L. Kalb*, Liebigs Ann. Chem. *423*, 39 (1921).
[3] *H. Vermeer* and *F. Bickelhaupt*, Tetrahedron Lett. *1970*, 1007; *C. Jongsma* and *H. van der Meer*, *ibid.* *1970*, 1323.
[4] *H. Vermeer*, *R. Lourens*, and *F. Bickelhaupt*, Tetrahedron Lett. *1970*, 3255, ref. 10.
[5] *G. Märkl* and *F. Lieb*, Tetrahedron Lett. *1967*, 3489.
[6] *P. Jutzi* and *K. Deuchert*, Angew. Chem. *81*, 1051 (1969); Angew. Chem. internat. Edit. *8*, 991 (1969).
[7] *H. Vermeer* and *F. Bickelhaupt*, Angew. Chem. *81*, 1052 (1969); Angew. Chem. internat. Edit. *8*, 992 (1969).
[8] *H. Vermeer* and *F. Bickelhaupt*, Tetrahedron Lett. *1970*, 3255.
[9] *A. J. Ashe*, J. Amer. Chem. Soc. *93*, 3294 (1971).
[10] *G. Märkl* and *H. Hauptmann*, Angew. Chem. *84*, 438 (1972); Angew. Chem. internat. Edit. *11*, 439 (1972).
[11] *G. Märkl*, *F. Lieb*, and *A. Merz*, Angew. Chem. *79*, 59 (1967); Angew. Chem. internat. Edit. *6*, 87 (1967); *G. Märkl* and *A. Merz*, Tetrahedron Lett. *1968*, 3611.
[12] *J. Advena*, Diplomarbeit, Universität Würzburg 1970.
[13] *C. F. H. Allen* and *W. E. Barter*, J. Amer. Chem. Soc. *54*, 742 (1932).
[14] *F. Lieb*, Dissertation, Universität Würzburg 1969.

Ketene Thioacetals by "Peterson Carbonyl Olefination"[1] with Metalated Formyl Trimethylsilyl Thioacetals[**]

By *Dieter Seebach*, *B.-Th. Gröbel*, *A. K. Beck*, *Manfred Braun*, and *K.-H. Geiss*[*]

Dedicated to Professor R. Criegee on the occasion of his 70th birthday

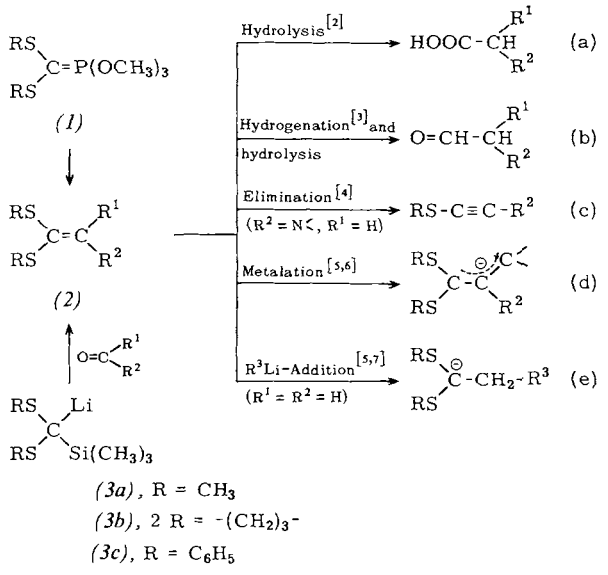
As shown in the reactions (a)—(e) of the following scheme, ketene thioacetals *(2)* are useful synthetic intermediates.

A generally applicable method of preparation of these compounds is, however, not available[3, 5–8]. Thus Wittig-Horner olefination succeeds only with aldehydes (R^1 = H) as carbonyl components [*(1)* → *(2)*][3, 8b, 8d].

We report here a simple access to *(2)* by reaction of the metalated silyl thioacetals *(3a)*—*(3c)*[9] with carbonyl derivatives (Peterson olefination). The ketene thioacetals *(2)* are obtained in high yields when solutions of *(3a)* to *(3c)* in THF are combined at −80 °C with the aldehydes, ketones, and carboxamides[10] listed in the Table. The reaction mixture is left overnight at room temperature prior to product isolation. Even ketones such as cyclopentanone and cyclohexenone, which are readily enolized by other organometallic reagents, react smoothly.

[*] Prof. Dr. D. Seebach, B.-Th. Gröbel, A. K. Beck, Dipl.-Chem. M. Braun, and Dipl.-Chem. K.-H. Geiss
Institute für Organische Chemie der Universitäten
75 Karlsruhe und
63 Giessen, Ludwigstrasse 21 (Germany) (present address)

[**] This work was supported by the Deutsche Forschungsgemeinschaft. We thank Professor *Carey* of the University of Virginia for informing us about his independent work in this area prior to publication.



into methylene chloride/water. Yield of colorless, dry crude product: 4.00 g (100%); after recrystallization from methanol more than 3.6 g of pure 2-cyclohexylidene-1,3-dithiane (see Table 1) is obtained.

Received: March 20, 1972 [Z 619 IE]
German version: Angew. Chem. *84*, 476 (1972)

[1] *D. J. Peterson*, J. Org. Chem. *33*, 780 (1968), cf. *T. H. Chan*, *E. Chang*, and *E. Vinokur*, Tetrahedron Lett. *1970*, 1137.

[2] *E. J. Corey* and *R. G. Parker*, unpublished results 1968; *J. A. Marshall* and *J. L. Belletire*, Tetrahedron Lett. *1971*, 871.

[3] *F. A. Carey* and *J. R. Neergaard*, J. Org. Chem. *36*, 2731 (1971).

[4] Strong bases such as butyllithium eliminate thiol (RSH) from these enamines (C≡C band of the resulting acetylenes at 2120 cm^{-1}).

[5] See literature cited in *D. Seebach*, Synthesis *1969*, 17.

[6] *D. L. Coffen*, *T. E. McEntee, jr.*, and *D. R. Williams*, Chem. Commun. *1970*, 913.

[7] *R. M. Carlson* and *P. M. Helquist*, Tetrahedron Lett. *1969*, 173.

Table 1. Yields and physical constants of ketene thioacetals *(2)* [a].

Carbonyl compound	*(3)*	Olefin *(2)* R^1	Olefin *(2)* R^2	Yield (%)	B. p. (°C torr) m. p. (°C)
Formaldehyde	*b*	H	H	71	80/10 (79–80/9.5 [5, 7, 8d])
Benzaldehyde	*b*	H	C_6H_5	>95	148/0.2 (150/0.14; 142/0.1 [5, 8b, 8c])
Hydratropaaldehyde	*c*	H	C_6H_5—CH(CH$_3$)	85	210/0.005
Cyclopentanone	*b*	—$(CH_2)_4$—		60	44.0–44.8
Cyclohexanone	*b*	—$(CH_2)_5$—		92	92.4–93.4 (93.6–94.0 [5, 8c])
2-Methyl-1-cyclohexanone	*b*	—CH(CH$_3$)—$(CH_2)_4$—		61	24–25
2-Cyclohexenone	*b*	—CH=CH—$(CH_2)_3$—		63	58.5–59.5
Benzophenone	*a*	C_6H_5	C_6H_5	85	83–84
	b			87	132.8–133.6 (134.5–135.0 [5, 8c])
N-Formylpyrrolidine	*b*	H	Pyrrolidino	82	63.5–64.5 [b]
	c			30	109.4–109.9 [b]
N-Formylmorpholine	*b*	H	Morpholino	59	55.8–57.8 [b]

[a] All new compounds give correct elemental analyses. C=C band in the IR spectrum between 1575 and 1600 cm^{-1}.
[b] Elimination reaction, see [4].

Procedure:

A solution of 2-lithio-1,3-dithiane [prepared from dithiane (24.0 g, 0.200 mol) in THF (200 ml) and 130 ml of a 1.58 M *n*-butyllithium solution in *n*-hexane] cooled to −30 °C is added to freshly distilled chlorotrimethylsilane (40 ml) stirred at −55 °C. The mixture is kept for 20 min at this temperature and for 5 h at +20 °C. Workup with pentane/water furnishes 35.1 g (91%) of 2-trimethylsilyl-1,3-dithiane, b. p. 96—97 °C/5 torr, $n_D^{22} = 1.5308$.—A solution of 2-lithio-2-trimethylsilyl-1,3-dithiane (20 mmol) prepared as usual[5] is combined at −50 °C with neat cyclohexanone (2.00 g, 20.4 mmol). The temperature is allowed to rise to +20 °C within 1 h. After 14 h the reaction mixture is poured

[8] a) *R. Gompper* and *H. Schaefer*, Chem. Ber. *100*, 591 (1967), and earlier work cited therein; b) *E. J. Corey* and *G. Märkl*, Tetrahedron Lett. *1967*, 3201; c) *E. J. Corey* and *D. Seebach*, Angew. Chem. *77*, 1134 (1965); Angew. Chem. internat. Edit. *4*, 1075 (1965); d) *D. M. Lemal* and *E. H. Banitt*, Tetrahedron Lett. *1964*, 245; *D. Seebach*, Chem. Ber. *105*, 487 (1972).

[9] *(3a)* and *(3c)* were prepared similarly to the dithiane derivative *(3b)* (modification of the original procedure given by *E. J. Corey*, *D. Seebach*, and *R. Freedman*, J. Amer. Chem. Soc. *89*, 434 (1967), see procedure given there) from the corresponding silyl thioacetals *(3)* (H instead of Li, R = CH_3: b. p. 68 °C/10 torr, $n_D^{20} = 1.5071$; R = C_6H_5: b. p. 110 °C/0.005 torr).

[10] *(3b)* and tetramethylurea form an extremely sensitive substance whose NMR spectrum is in accord with the structure of an olefin $(RS)_2C{=}C[N(CH_3)_2]_2$ (N—CH_3 singlet at δ = 3.15 ppm). With water it decomposes quantitatively to give *N,N*-dimethyl-1,3-dithiane-2-carboxamide [5], m. p. 82 °C.

Isoelectric Focusing: Present and Future State of a New Method

By *B. J. Radola*[*]

Isoelectric focusing is a new method of separation in which amphoteric substances, in particular proteins, can be separated in a stable pH gradient owing to the differences in their isoelectric points. The method is extremely efficient and permits separation of proteins whose isoelectric points differ by only 0.02 pH unit. Further, the method enables the separated components to be characterized by a physicochemical constant, namely the isoelectric point. It is only recently that development of appropriate "carrier ampholytes" provided the prerequisites for practical use of the method. Several techniques of isoelectric focusing can be distinguished by the way in which the pH gradient is stabilized: 1. Focusing in a density gradient (*e. g.* saccharose); 2. focusing in polyacrylamide gel (either in flat gels or in an arrangement corresponding to disk electrophoresis); and 3. focusing in granulated gels (*e. g.* Sephadex or Bio-Gel).

Isoelectric focusing in layers of granulated gels can be used as a thin-layer method for analytical separations on plates of various lengths and widths. If the thickness of the layer is increased the work can be done preparatively in throughs. The separations are carried out in a double chamber developed for isoelectric focusing (Desaga, Heidelberg). After the focusing, the separated components are detected densitometrically directly in the gel layer or can be localized by dyeing in a paper print. Enzymes can be made visible by means of a buffered paper impregnated with substrate. Microgram to gram quantities of amphoteric substances can be separated by isoelectric focusing in gel-stabilized layers. For a number of proteins and enzymes it was possible, by thin-layer isoelectric focusing, to detect a heterogeneity that was not found previously by any other method. Preparative isoelectric focusing in gel-stabilized layers opens a completely new perspective for purification of proteins in respect of both the excellent resolution and of the capacity of the method; the latter exceeds greatly the capacity of preparative electrophoretic methods.

For protein chemistry isoelectric focusing is today one of the most efficient methods of separation. Analytical and preparative separation of proteins will in the future be supplemented to an increasing degree by introduction of this method for determination of isoelectric points as well as for studies of conformation and for modification of proteins by group-specific reagents.

Lecture at Aachen on February 18, 1972 [VB 336 IE]
German version: Angew. Chem. *84*, 444 (1972)

[*] Dr. B. J. Radola
Bundesforschungsanstalt für Lebensmittelfrischhaltung
75 Karlsruhe 1, Engesserstrasse 20 (Germany)

Studies of Reaction Kinetics in the Solid State: First and Second Order Reaction Constants

By *Hermann Schmalzried*[*]

The kinetics of reactions involved in spinel and silicate formation have been studied by a thermogravimetric method. In all cases, initial results follow a linear rate law analogous to many oxidation processes. Interpretation of the rate determining mechanism of the phase boundary reactions is not yet certain, although dislocation movements are suspected at the solid-solid phase boundary, at least for spinels.

For spinel formation, the parabolic rate law followed as the reaction progresses allows quantitative interpretation based on counterdiffusion of cations. For formation of simple orthosilicates matters are more complicated. In independent diffusion measurements it was found that the mobilities of silicon and oxygen ions are of the same order of magnitude and astonishingly high [$D_{Si}(Zn_2SiO_4 \approx 10^{-13}$ cm^2/s (1300 °C); $D_O(Co_2SiO_4) \approx 10^{-13}$ cm^2/s (1300 °C)]. Diffusion measurements in glass, however, seem to confirm the behavior of these components of the SiO_4 tetrahedra.

If the starting oxides are mutually soluble, transport processes occur in them that must be taken into account when determining the overall reaction kinetics. First and second order reaction constants have therefore been defined and related mathematically to one another. First order reaction constants describe solid state reactions for pure starting oxides; second order reaction constants describe solid state reactions in which a single phase product is formed from its two saturated neighboring phases.

Lecture at Berlin, February 7, 1972 [VB 335 IE]
German version: Angew. Chem. *84*, 486 (1972)

[*] Prof. Dr. H. Schmalzried
Institut für Theoretische Hüttenkunde der
Technischen Universität Clausthal
3392 Clausthal-Zellerfeld (Germany)

Polycations of Group VI, which have received considerable attention during recent years, are the subject of a review by *R. J. Gillespie* and *T. Passmore*. The unusual colors of solutions of S, Se, and Te in strong acid solutions, which have been known for more than 150 years, have recently been shown to be due to polyatomic cations. At least nine of these cations have now been characterized and isolated in the form of crystalline compounds. Discussed are, *inter alia*, the preparation and physical properties of compounds containing $O_2^{\oplus}$, $S_{16}^{2\oplus}$, $S_8^{2\oplus}$, $S_4^{2\oplus}$, $Se_4^{2\oplus}$, and $Se_8^{2\oplus}$ ions, and Te polycations; the structures of $Se_4^{2\oplus}$ and of $Se_8^{2\oplus}$ are also discussed. The high π-bond energy and low σ-bond energy of oxygen favor $O_2^{\oplus}$ formation rather than $O_4^{2\oplus}$. The reverse is the case for sulfur. The more metallic nature of tellurium is reflected in the formation of $Te_n^{n\oplus}$. [Polycations of Group VI. Accounts Chem. Res. *4*, 413–419 (1971); 69 references]

[Rd 479 –M IE]

The growth of large diamond crystals is reviewed by *H. M. Strong* and *R. H. Wentorf, jr.* Large crystals up to 6 mm in diameter are obtained at high pressures (55–60 kbar) and temperatures (1400–1500 °C) by causing diamantiferous material as carbon source to dissolve in a molten catalyst metal (such as Fe, Ni, or Co) in a hot region and to crystallize out in a cooler region on a seed crystal. The procedure requires several days and is influenced by several parameters. [The Growth of Large Diamond Crystals. Naturwissenschaften *59*, 1–7 (1972); 22 references]

[Rd 480 –M IE]

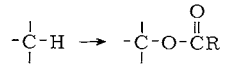
Molecular deficiencies of human blood coagulation are discussed in a review by *E. A. Beck*. Blood coagulation is a complex biochemical process; deficiencies in thrombin or fibrin formation lead to hemorrhages. Congenital hemophilia is due to a deficiency in the amount of or structural anomalies of the coagulation factor. Investigations on the functional breakdowns of anomalous fibrinogens indicate the existence of numerous structural variants which influence interaction with thrombin, fibrin polymerization, or fibrin stabilization differently. Analogous studies on the coagulation factors II, VII, VIII, IX, X, and XIII also suggest structural anomalies as the cause of most hemophilic disorders. [Molecular Deficiencies of Human Blood Coagulation. Experientia *28*, 1–7 (1972); 67 references]

[Rd 481 –M IE]

Organic geochemistry is reviewed by *J. R. Maxwell, C. T. Pillinger*, and *G. Eglinton*. Much more carbon is present in the earth's crust than in the biosphere. In spite of the great age of sedimentary rocks (up to 3.5×10^9 a) they are found to contain biogenic substances such as pristane, phytane, triterpenoids, and porphyrins. The authors go into the methods available for isolation and identification of organic compounds from geological sources and into the modifications of the initially deposited compound upon transformation of the sediments into solid rocks.—Extraterrestrial occurrence of organic compounds is also discussed. [Organic Geochemistry. Quart. Rev. Chem. Soc. *25*, 571–628 (1971); 296 references]

[Rd 488 –L IE]

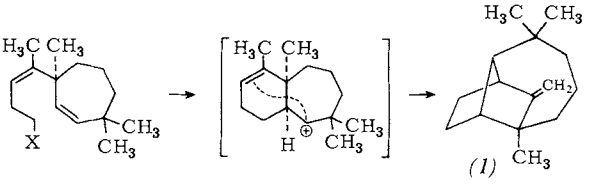
One-step substitutive acyloxylation at carbon involving reactions with organic peroxy compounds is reviewed by *D. J. Rawlinson* and *G. Sosnovsky*. The article covers acyloxylations—with and without catalysis by transition metal ions—of, *inter alia*, hydrocarbons, ethers, esters, aldehydes, ketones, amides, thioethers, phenols. Suitable peroxy com-



pounds are, *e.g.*, peroxy esters, hydroperoxides, dialkyl peroxides, peroxy acids, diacyl peroxides, and diaroyl peroxides. [One-step Substitutive Acyloxylation at Carbon. Synthesis *1972*, 1–28; 179 references]

[Rd 482 –M IE]

Computer-assisted analysis of complex synthetic problems, with particular regard to the derivation of synthetic routes to complex molecules, is described by *E. J. Corey*. The dialog is essentially between man and computer; *inter alia*, structural formulas serve as a means of communication. The capability of the method is illustrated using the hypo-

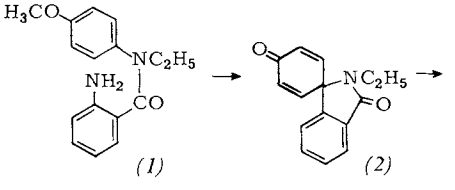


(1)

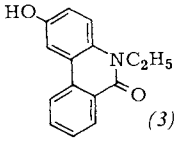
thetical synthesis of longifolene *(1)* as example. [Computer-assisted Analysis of Complex Synthetic Problems. Quart. Rev. Chem. Soc. *25*, 455–482 (1971); 23 references]

[Rd 483 –L IE]

Spirodiene rearrangements are summarized in a review by *D. H. Hey*. As an example of the formation of a spirodiene and its rearrangement into a phenanthridone derivative, the reaction sequence *(1)*→*(2)*→*(3)* is discussed. The reaction *(2)*→*(3)* only proceeds in 100% phosphoric acid at 170 °C.—The author also gives a comprehensive account of the photochemical rearrangement of spirodienes and of



(1) *(2)*



(3)

other reactions of compounds of type *(1)*, *e. g.* the formation of dimers, in dependence upon substituents and reaction conditions. [Spirodiene Rearrangements. Quart. Rev. Chem. Soc. *25*, 483–499 (1971); 18 references]

[Rd 484 –L IE]

Electrochemical measurements with amalgam electrodes are reviewed by *H. P. Bennetto* and *A. R. Willmot*. Numerous experimental difficulties that formerly limited the use of such electrodes have now been overcome. Apart from an historical introduction and experimental procedures, the article includes a discussion of the application of such measurements in two special cases, *viz.*, the association of ions in aqueous cadmium chloride solutions and the solvation of alkali metal ions. [Electrochemical Measurements with Amalgam Electrodes. Quart. Rev. Chem. Soc. *25*, 501–520 (1971); 77 references]

[Rd 485 –L IE]

The effect of polar substituents on the ionization of organic acids is the subject of a review by *P. D. Bolton* and *L. G. Hepler*. The authors attach importance not only to "internal" polar and steric effects of substituents but also to the reaction medium. An introduction to the thermodynamics of ionization is followed by a discussion of the effects of polar groups on the free energy of ionization, taking ω-amino acids, chloroacetic acid, and similar acids, as well as phenol and substituted phenols as examples. Further conclusions are drawn from entropy values. Such considerations and measurements could provide a theoretical basis for the (empirical) Hammett relation. [Polar Substituent Effects and the Ionization of Acids. Quart. Rev. Chem. Soc. *25*, 521–532 (1971); 22 references]

[Rd 486 –L IE]

Halogen and interhalogen cations are the topic of a review authored by *R. J. Gillespie* and *M. J. Morton*. The highly electrophilic cations can only be prepared and studied in very weakly basic solvents, *e. g.* fluorosulfuric acid, disulfuric acid, antimony pentafluoride, and sulfur dioxide. These cations form stable crystalline compounds only with extremely weakly basic anions such as $Sb_3F_{16}^{\ominus}$ [see eq. (1)–(4)].

$$2I_2 + S_2O_6F_2 \rightarrow 2I_2^{\oplus} + 2SO_3F^{\ominus} \quad (1)$$

$$Br_2 + BrSO_3F \rightleftharpoons Br_3^{\oplus} + SO_3F^{\ominus} \quad (2)$$

$$Cl_2 + ClF + AsF_5 \rightarrow Cl_3^{\oplus}AsF_6^{\ominus} \quad (3)$$

$$2ICl_3 \rightarrow ICl_2^{\oplus} + ICl_4^{\ominus} \quad (4)$$

Interhalogen cations are also present in the known adducts of ClF_3 and AsF_5 ($ClF_2^{\oplus}AsF_6^{\ominus}$) or BrF_3 and SbF_5 ($BrF_2^{\oplus}SbF_6^{\ominus}$).—The crystal structure of $Br_2^{\oplus}Sb_3F_{16}^{\ominus}$, $ClF_2^{\oplus}SbF_6^{\ominus}$, and $BrF_2^{\oplus}SbF_6^{\ominus}$ are also reported. [Halogen and Interhalogen Cations. Quart. Rev. Chem. Soc. *25*, 553–570 (1971); 50 references]

[Rd 487 –L IE]

Substitution reactions of platinum(IV) complexes catalyzed by platinum(II) or reducing agents are treated by *W. R. Mason*. The general rate law and the mechanism of these reactions are given, and kinetic data are tabulated for individual reactions. The kinetic data are analyzed for the influence of the ligands involved; medium effects (solvent, ionic strength) and some more common side-reactions are also discussed. [Platinum(II)-Catalyzed Substitutions of Platinum(IV) Complexes. Coord. Chem. Rev. *7*, 241–255 (1972); 41 references]

[Rd 489 –H IE]

The vibrational spectra of octahedral hexahalogen compounds are analyzed by *P. Labonville, J. R. Ferraro, M. C. Wall*, and *L. J. Basile*. Starting from the observed frequencies, different sets of force constants are calculated depending on the form of the intramolecular force field assumed. The best fit of frequencies calculated from the force constants with the observed frequencies is achieved by use of a Modified Orbital Valence Force Field (MOVFF). Finally, the effects of mass and oxidation number and the influence of nonbonding valence electrons (in transition metal compounds) are discussed. [Force Fields in Octahedral Hexahalogen Molecules. Coord. Chem. Rev. *7*, 257–287 (1972); 42 references]

[Rd 490 –H IE]

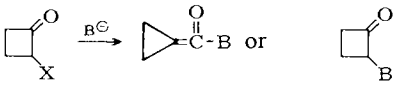
The literature on manganese-porphyrin complexes is surveyed by *L. J. Boucher*. The most stable compounds are formed by trivalent manganese; complexes with bi- and tetravalent manganese are accessible by redox reactions starting from the trivalent state. Minor sections on complexes derived from chlorophyll and phthalocyanine are included; finally, a comparison is made with the corresponding iron complexes and the relevance of these compounds for the investigation of biological problems is discussed. [Manganese Porphyrin Complexes. Coord. Chem. Rev. *7*, 289–329 (1972); 112 references]

[Rd 491 –H IE]

The circular dichroism (CD) of cobalt(III) chelates is the subject of a review by *L. I. Katzin* and *I. Eliezer*. The qualitative features (sign and order of magnitude) of the CD spectra of about 150 chelates in the spectral region of the first two ligand field transitions in the low spin d^6 system are tabulated and discussed throughly. An important topic is the determination of "absolute configurations" from CD spectra. In the authors' opinion the details of these spectra are not sufficiently understood to allow conclusions by analogy even to closely related compounds; also comparison with sufficient X-ray data is lacking. [Bonding Effects in Circularly Dichroic Co(III) Complexes. Coord. Chem. Rev. *7*, 331–343 (1972); 65 references]

[Rd 492 –H IE]

Cyclobutane ring contractions not involving carbonium ions have been reviewed by *J. M. Conia* and *J. R. Salaun*. The reaction of 2-bromo-(or 2-tosyloxy)-cyclobutanones *(1)* with nucleophilic reagents is not to be considered as a classical Favorskii rearrangement, but rather as a type of semibenzil rearrangement. Depending on the reagent used, one obtains compound *(2)* and/or *(3)*. This contraction, like the ring contraction of 2-halo(or 2-tosyloxy)-cyclobutanols with nucleophiles, which take place particularly readily (*e. g.* even in water), is apparently to be compared with the base-catalyzed rearrangement of cyclic glyco-



(1), X = Br, OTs *(2)* *(3)*

monotosylate or 1,2-halohydrin of the pinacol type. The ring contractions of 2-bromocyclobutanone hydrate, -hemiketal, and -ketals, as well as those of bromohydroxy- dihydroxy-, and epoxycyclobutanones on heating are obviously closely related to these rearrangements. [Cyclobutane Ring Contractions not Involving Carbonium Ions. Accounts Chem. Res. *5*, 33—40 (1972); 123 references]

[Rd 497 IE -M]

The versatility of organocopper(I) compounds and organocuprates in organic syntheses is dealt with in a review by *J. F. Normant*. Both these reagents frequently prove to be more useful than the common organometal compounds. Condensations with organocopper(I) compounds R—Cu sometimes necessitate the use of an aprotic solvent (DMF, DMSO) and sometimes of a salt or a neutral complexing agent (phosphane, thioether, pyridine). The homocuprates, R_2CuLi, are often better reagents than organolithium compounds—especially for nucleophilic substitution of halogen derivatives. In the acetylene series mixed cuprates, RR CuLi, have to be employed. [Organocopper(I) Compounds and Organocuprates in Synthesis. Synthesis *1972*, 63—80; 142 references]

[Rd 493 IF -M]

Structure, biosynthesis, and heterogeneity of chondroitin sulfate proteins, which are important structural units of the primary component of the connective tissue of vertebrates are reviewed in an article by *T. O. Kleine*. Many details concerning the biosynthesis, regulation, and structure of these compounds are still unknown. The considerable chemical and metabolic heterogeneity of chondroitin sulfate proteins can be understood in terms of the different sizes and turnover rates of acceptor protein pools and by the different activities and specificities of monosaccharide and sulfo-transferases. [Naturwissenschaften *59*, 64—71 (1972); 88 references]

[Rd 494 IF -M]

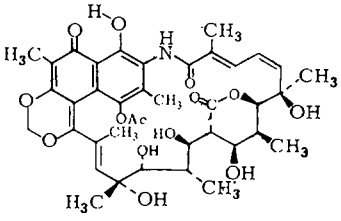
Investigations of the antibody-complement interaction with lipid model membranes are summarized, with special references to the author's own work, in a review by *S. C. Kinsky*. The immune damage of natural membranes can be imitated in very simple systems, thus opening up possibilities for further investigations of the molecular basis of the complement effect. Liposomes of the fractions IIa and IIb from the erythrocyte membranes of sheep serve as model systems. [Antibody-Complement Interaction with Lipid Model Membranes. Biochem. Biophys. Acta *265*, 1—23 (1972); 34 references]

[Rd 495 IE -M]

Investigation of the protein conformation in chemically unchanged, functionally and enzymatically active biomembranes by measurement of optical rotation and UV- and visual light-absorption is discussed in a review by *D. W. Urry*. At present, these methods afford the best information regarding conformation. The spectral data are complicated by artefacts and absorption by nonprotein material. The author deals in particular with special conformations for ion transport (valinomycin-cation complex gramicidin-A transmembrane canal). [Protein Conformation in Biomembranes: Optical Rotation and Absorption of Membrane Suspensions. Biochim. Biophys. Acta *265*, 115—168 (1972); 62 references]

[Rd 496 IE -M]

Ansamycins, a new class of antibiotics in which two nonadjacent sites of an aromatic nucleus are coupled by an aliphatic bridge, are reviewed by *K. L. Rinehart jr*. Up to now, four groups of the *Streptomyces*-type ansamycins have been recognized: Rifamycins *(S. mediterranei)*, Streptovaricins *(S. spectabilis)*, Tolypomycins *(S. tolyphorus)*, and Geldanamycins *(S. hygroscopicus* var. *geldanus)*. The structure of streptovaricin F *(1)* is given as example. The molec-

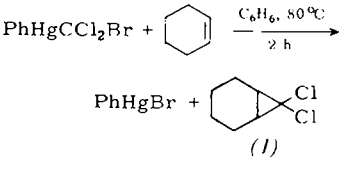


(1)

ular structures of the ansamycins can be varied considerably without lowering their antibiotic activity. Many derivatives are more active than the parent compound.—The author deals also with the biosynthesis. [Antibiotics with Ansa Rings. Accounts Chem. Res. *5*, 57 –64 (1972); 95 references]

[Rd 498 IE -M]

The chemistry of phenyl(trihalomethyl)mercury compounds, which are exceptionally versatile dihalocarbene precursors, is the subject of a review by *D. Seyferth*. $PhHgCX_3$ and other halomethylmercury compounds are suitable reagents for divalent carbon transfer:



(1)

In this reaction, 7,7-dichloronorcarane *(1)* is formed almost quantitatively with exclusive elimination of PhHgBr. A few of these compounds, such as $PhHgCCl_2I$, PhHgCClBrI, and $PhHgCBr_2F$ yield dihalocarbenes even at room temperature. [Phenyl(trihalomethyl)mercury Compounds Exceptionally Versatile Dihalocarbene Precursors. Accounts Chem. Res. *5*, 65—74 (1972); 120 references]

[Rd 499 IE -M]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften under the direction of *Margot Becke-Goehring*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. *Supplement to the 8th edition*, vol. 2/3: Organometallic Compounds of Vanadium and Chromium. Volume 2: Organovanadium Compounds, iii, 79 pp., 22 figures. Volume 3: Organochromium Compounds. x, 452 pp., 55 figures. Balacron, together DM 622.—.

The chemistry of organometallic compounds has developed explosively during the past two decades. This field is currently being dominated by the cyclopentadienyl, allyl, and olefin complexes and the π complexes with aromatic ligands. Their discovery and characterization have given fresh impetus in particular to theoretical chemistry. The carbonyl-metal compounds have also attracted renewed interest. New physical methods of investigation, including the latest type of spectroscopy, photoelectron spectroscopy, have led to extensive further information on structure and bonding in this class of compounds. Corresponding to this newness of much of the material discussed in both volumes, the literature has been evaluated up to the end of 1970, and in part even to early 1971.

The first chapter of Volume 2 deals with the mononuclear organovanadium compounds, divided into compounds with ligands bonded *via* one, two, three, five, six, and seven C atoms. Polynuclear compounds are discussed similarly in Chapter 2, again in sections on compounds with ligands bonded to the central atom *via* one, two, four, and five C atoms. The volume ends with a formula index of ligands. The main emphasis in the volume is placed on compounds of the classes mentioned earlier, such as bis(π-cyclopentadienyl)vanadium or dibenzenevanadium.

The organochromium compounds are arranged in the same manner in Volume 3. The chapter "Mononuclear Compounds" includes the sections dealing with compounds having ligands bonded to the central chromium atom *via* one, two, three, four, five, six, and twelve C atoms. Chapter 2 first describes dinuclear compounds with ligands bonded *via* one, two, three, four, five, six, and twelve C atoms. Trinuclear, tetranuclear, and polymeric compounds are then described in three chapters.

Both volumes contain shortcomings and inconsistencies in terminology, such as many terms taken too literally from English and different names for similar diagrams, methods, or quantities.

A table of reference substances at the beginning or at the end of a volume for physical measurements that occur very frequently would be useful, as would a list of abbreviations for common solvents. Finally, in the interests of the international readership, the reviewer would suggest that it is worth considering whether the symbol I should be used for the element iodine; this practice is now being followed in some German textbooks, though the official German version of the IUPAC rules for nomenclature in inorganic chemistry prescribes the symbol J.

The two supplementary volumes together are a valuable addition to Gmelin's Handbook. In conclusion, it should be emphasized that like some of the other recent volumes, they are very "readable" in two senses. Despite the concise presentation of the results of the investigations and of the many data, the text can be read continuously. Another contributory factor is the new types that have been used.

Ekkehard Fluck [NB 30 IE]

Handbook of Chemistry and Physics. By *R. C. Weast*. The Chemical Rubber Co., Cleveland, Ohio/USA 1972. 52nd Edit., xxvii, 2313 pp., bound DM 99.80.

A handbook, according to the preface of the 52nd edition of the present work, is an information system in miniature, and what one can retrieve from this system can only be as good as what has been stored in it. This imposes two duties on the publisher: he must strive after quality through expert advice (145 scientists are mentioned by name in the introductory part of the book), and he must try to keep up to date through annually improved, revised, and supplemented editions. The Handbook of Chemistry and Physics is in fact one of the few books (together with hotel guides and street plans) that are good for only one year, since they have already been improved by the time the next year comes.

The 52nd edition again contains a number of new tables, including the permissible intake of radionuclides by man, the equivalent conductivities of aqueous halohydric acids, the thermal properties of pure metals, and standard test sieves, to name but a few that are of interest to chemists. Chemistry is rightly named first in the title of the book, since out of a total of about 2300 pages (on India paper), nearly 70% carry exclusively, and the remainder predominantly, tables and data of a chemical nature. The publishers have made a start with the conversion of all the units used in the Handbook to the new SI system.

In this age of data banks and computers, anyone who would like to have his own compendium (because it rarely fails, and because its use requires only a sharp eye and a moist forefinger) will find the best solution in this work, which, as always, is supplied with 23 carat gold leaf for inscribing one's own name on the cover. What electronic data processor can offer *that*?

Helmut Grünewald [NB 41 IE]

Stabilisierung und Alterung von Plastwerkstoffen (Stabilization and Aging of Plastics). Vol. 2. Aging of Plastics. By *K. Thinius*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 1st Edit., 498 pp., 95 figures, 58 tables, cloth DM 84.—.

As in the first volume[1], the author has again collected a large body of experimental material originating in his school or taken from the literature, which is relatively fully evaluated up to about 1968/1969. The excellently chosen and expertly described subject matter is divided into seven chapters and provided with subject and author indexes.

In Chapter 1, the aging processes are defined, and general principles and problems of aging investigations on plastics are described. The equipment and methods presented in Chapter 2, for the aging of plastics are discussed critically, with the inclusion of many details from the author's own experience. Detailed data on weather and radiation rela-

tions in outdoor weathering and artificial irradiation and weathering fit well into this discussion. The description of methods for checking biological damage provides a full insight into this special field.

Chapter 3 gives a number of methods for the recognition and determination of aging processes. These lead over to Chapter 4, in which the results of natural aging are described, and to the results of artificial aging in Chapter 5. These two comprehensive chapters contain many results of the author's own investigations and experience and numerous detailed findings. The literature has been critically scanned, and here again many single results have been reported. The separation of Chapters 4 and 5 on the basis of the type of aging is very appropriate in view of the different problems that arise in natural and in artificial weathering.

Chapter 6 deals with the increasingly important problem of the relation between the results of aging under natural and under experimental conditions. The author here exercises the necessary restraint not to overgeneralize. Chapter 7 gives only a loose survey of theoretical views on the mechanism of the aging process. There has been no critical sorting to present a picture of current ideas.

It is understandably not easy to deal in an easily comprehensible manner with the many aspects of this subject in about 450 pages. The numerous results collected from the literature and the notable investigations of the author and his students, who are outstanding experts on stability problems in plastics, is unfortunately presented too unsystematically and unclearly. Parts of the book are merely successions of individual results and conclusions. It is therefore difficult to use the book as a reference work, which would have been of great value in view of the volume of reading matter that is currently in existence. For those who are directly concerned with this many-faceted field, it is tedious to read through the book, but still worth the effort.

Gerhard Menzel [NB 28 IE]

[1] Cf. Angew. Chem. internat. Edit. *9*, 542 (1970).

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 4036/4037, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A.J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N.Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P.O. Box 129/149 Germany, Telephone Weinheim (06201) 4031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 6
June 1972
Pages 451–550

International Edition in English

Chemical Synthesis of Polynucleotides[**]

By K. L. Agarwal, A. Yamazaki, P. J. Cashion, and H. G. Khorana[*]

Current methodology for the chemical synthesis of short chains (up to about twenty nucleotide units) of deoxyribopolynucleotides is reviewed.

1. Introduction

Methods have been developed in recent years for the chemical synthesis of short deoxyribopolynucleotide chains[1]. The availability of the synthetic deoxyribopolynucleotides with completely defined nucleotide sequences has permitted precise studies on the problems of protein biosynthesis, on the genetic code, and on DNA and RNA polymerases. Further studies of the biological functions of DNA at macromolecular level will also require the synthesis of bihelical products with defined nucleotide sequences. To this end, a general methodology has been developed which has been successfully used in the total synthesis of the gene corresponding to yeast alanine tRNA[2] (Fig. 1).

[*] Dr. K. L. Agarwal, Dr. A. Yamazaki, Dr. P. J. Cashion, and Prof. Dr. H. G. Khorana
Departments of Biology and Chemistry,
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139 (USA)

Presented at the XXIII International Union of Pure and Applied Chemistry, Boston, July 1971.

[**] The following abbreviations have been used:
Ac = acetyl
An = anisoyl
iBu = isobutyryl
Bz = benzoyl
DCC = dicyclohexylcarbodiimide
Me = methyl
MMTr = monomethoxytriphenylmethyl (= monomethoxytrityl)
MS = mesitylenesulfonyl chloride
TEAB = triethylammonium hydrogen carbonate
TPS = 2,4,6-triisopropylbenzenesulfonyl chloride
Tr = triphenylmethyl (= trityl)

The methodology developed consists of the following three steps: 1. Chemical synthesis of deoxyribopolynucleotide segments containing eight to twelve nucleotide units. These should represent the entire two strands of the intended DNA and those belonging to the complementary strands should have an overlap of four to six nucleotides (see Fig. 1). 2. Enzymatic phosphorylation of the 5'-hydroxyl group with ATP carrying a suitable radioactive label in the γ-phosphoryl group in presence of T4 polynucleotide kinase. 3. The head-to-tail joining of the appropriate segments when they are aligned to form bihelical complexes using T4 polynucleotide ligase.

It is clear that the concept outlined in the above strategy will continue to form the basis of future syntheses of genes[2a] and manipulation of synthetic or natural DNA. Because of the relative rapidity with which steps 2 and 3 described above can be carried out, the progress-determining step in rapid and efficient syntheses of DNA will undoubtedly be the chemical synthesis of the deoxyribooligonucleotides. The aim of the present paper will principally be (1) to review the methodology which is currently available, (2) to describe some recent improvements and refinements which have been effected in our laboratory, and (3) to briefly mention the outstanding problems awaiting satisfactory solution.

2. Synthesis of the Internucleotide Bond and the Protecting Groups

The synthesis of the simplest dinucleoside phosphate, thymidylyl-thymidine (TpT), is shown in Figure 2.

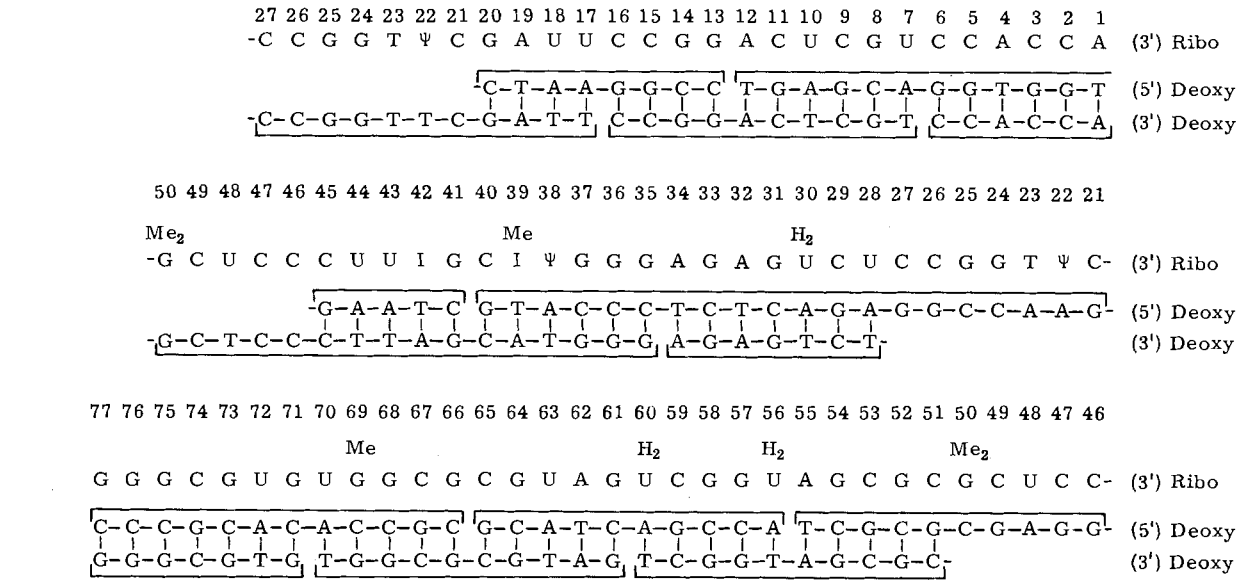


Fig. 1. Total plan for the synthesis of a $tRNA_{ala}$ gene. The chemically synthesized segments are shown in the brackets. 1st row, serial numbers; 2nd row, sequence of tRNA; 3rd and 4th row, sequence of the two strands of the $tRNA_{ala}$ gene.

In a synthesis of this kind one must note that: 1. The 5'-hydroxyl group of the nucleoside component is blocked by the classical bulky trityl group which can be removed by acid treatment when desired. 2. The 3'-hydroxyl of this component is free. 3. The second component involved in the reaction is a 5'-mononucleotide whose 3'-hydroxyl group is blocked by an acetyl group. This group is removed by very mild alkaline treatment when required. 4. The phosphate group has been used as the monoesterified component directly for the condensation step. An approach where diesterified nucleotide components were used has been suggested by *Eckstein, Letsinger*, and *Reese*, and their coworkers[3].

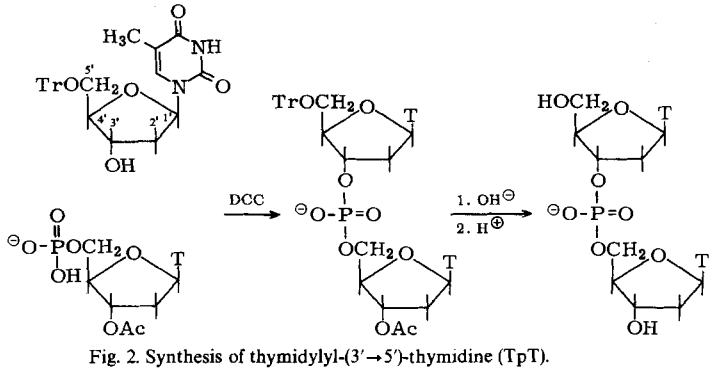


Fig. 2. Synthesis of thymidylyl-(3'→5')-thymidine (TpT).

These two components (Fig. 2) appropriately protected were condensed with dicyclohexylcarbodiimide (DCC). The condensing agents (Fig. 3), apart from DCC, currently used by us and others are aromatic sulfonyl chlorides, in particular mesitylenesulfonyl chloride (MS)[4] and 2,4,6-triisopropylbenzenesulfonyl chloride (TPS)[5]. The reason for using the trisubstituted aromatic sulfonyl chloride is to avoid sulfonation, especially of the 3'-hydroxyl end of the nucleoside or oligonucleotide component in deoxyribo-

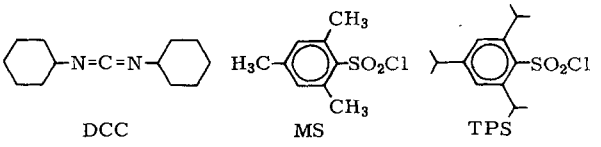


Fig. 3. Condensing agents dicyclohexylcarbodiimide (DCC), mesitylenesulfonyl chloride (MS), and 2,4,6-triisopropylbenzenesulfonyl chloride (TPS).

oligonucleotide synthesis. The activation of phosphate by DCC, MS, or TPS and the condensation of this activated intermediate with the 3'-hydroxyl of the nucleoside component is usually carried out in one step in anhydrous pyridine.

In a condensation reaction mixture, protected dinucleoside phosphate is the main product; the other minor products are the unreacted nucleoside derivative, and unreacted 3'-acetylated nucleotide component and its symmetrical pyrophosphate. The protected dinucleoside phosphate blocked at both the 3' and 5' ends is isolated by an organic solvent extraction procedure. Mild alkaline treatment hydrolyzes the acetyl group from the 3'-hydroxyl end. Under these conditions the trityl group blocking the 5' end is completely stable.

This product can now be used for further extension of the chain simply by reaction with another nucleotide component blocked at its 3'-hydroxyl end by an acetyl group. Repetition of the condensation and alkaline treatment followed by purification of products yields a polynucleotide of desired chain length. At the end of the synthesis the trityl group is removed by acidic treatment.

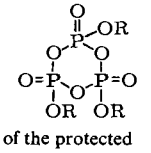


Fig. 4. Trimetaphosphate formed in the DCC reaction of the protected mononucleotide. R = amino protected nucleoside.

The mechanism of activation of phosphate by DCC, MS, or TPS is quite complex. In the case of DCC, it has been shown[6] that the initial phosphorylating species is a trimetaphosphate of the structure shown in Figure 4. The 3'-hydroxyl of the nucleoside component attacks the trimetaphosphate in a nucleophilic fashion to give an internucleotide bond. The trimetaphosphate of this type is a slow phosphorylating species. In the case of the arylsulfonyl chlorides, the activation and condensation steps are much faster, thereby suggesting that trimetaphosphates are probably not the phosphorylating species in this case[4].

We now return to the problem of the protecting groups which becomes important when nucleosides and nucleotides other than thymidine and thymidylic acid are included in the polynucleotide chains to be synthesized. Introduction of deoxyadenosine, deoxyguanosine, deoxycytidine, and their nucleotides in the synthesis of oligonucleotides requires the protection of their amino groups. If their amino groups are not protected, reaction with activated phosphate will be observed at least to some extent during the condensation reactions. The other reason for requiring the protecting groups is to increase the solubility of the nucleoside and nucleotide derivatives.

Selection of the protecting groups now requires the following considerations: 1. 3'-Hydroxyl protecting groups should be easily removed without disturbing the amino and 5'-hydroxyl protecting groups. 2. The selection of the amino protecting groups should be such that they can be removed in one step without affecting the phosphodiester bond, the 5'-hydroxyl protecting group, or the sensitive glycosyl bonds. 3. Conditions used for the removal of the 5'-hydroxyl protecting group should be such that no harm is caused to the intact oligonucleotide chain.

and specific for 5'-hydroxyl group is required. This is obtained by introduction of a *p*-methoxy substituent[8, 9] into the parent trityl group which has made removal possible under very mild acid or buffered conditions without causing any glycosyl bond cleavage. Such a modification of the trityl moiety did not lessen its 5'-hydroxyl group specificity. Introduction of each *p*-methoxy group into one or more phenyl rings increased the acid lability by a factor of 10. Both monomethoxy- and dimethoxy-trityl groups were used in our earlier studies for the protection of 5'-hydroxyl end; the group most favored and currently in use is the monomethoxytrityl group. The acetyl group is still satisfactory for 3'-hydroxyl protection and continues to be used in our current work. Other alternative groups such as β-benzoylpropionyl[10] and methoxyacetyl[11] have been suggested recently for protection of the 3'-hydroxyl group.

The amino protecting groups commonly used in syntheses are anisoyl for the cytosine, benzoyl for the adenine, and isobutyryl or 2-methylbutyryl[12] for the guanine rings. These protecting groups are removed in one step by concentrated ammonium hydroxide treatment without any side reactions. The reason for choosing different protecting groups for different nucleosides and nucleotides is due to their different stabilities. It should be noted that all of the protecting groups have to survive all the chemical manipulations during the very prolonged synthesis of an oligonucleotide.

The reaction shown in Figure 5 is an example of a general method now available for preparing deoxynucleosides containing blocked amino and 5'-hydroxyl groups. Acylation of the unprotected deoxycytidine is carried out with an excess of the acylating agent. The fully protected

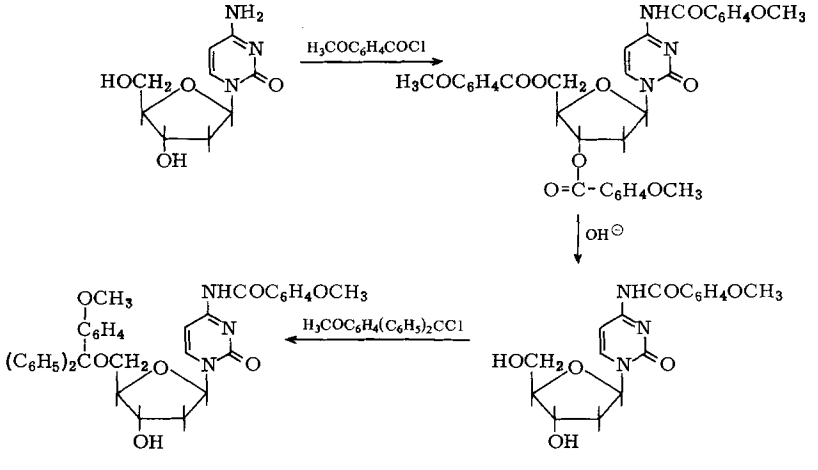


Fig. 5. Preparation of protected deoxycytidine derivatives.

The protecting groups which have already been introduced in the synthesis of thymidylyl-thymidine require reconsideration in the light of these new requirements. While the use of trityl group for the protection of the 5'-hydroxyl end is satisfactory for the synthesis of oligothymidylic acid, acidic conditions required for its removal at the end also cause appreciable cleavage of glycosidic bond in purines. Therefore, a group labile to very mild acidic[7] conditions

derivative thus obtained is treated with alkali under carefully controlled conditions to give the desired *N*-protected deoxycytidine. Selective hydrolysis is made possible by the ionization of the amide group in the aromatic system at alkaline pH which extends the resonating system and thus stabilizes the acyl group on the amino function. The rate of hydrolysis is simply proportional to the hydroxyl ion concentration.

In this way, all of the deoxynucleosides and nucleotides can be obtained in the *N*-protected form. Protection of the 5′-hydroxyl function with monomethoxytrityl group was carried out by the standard procedure used for tritylation. Protection of the amino function of the nucleotides followed the procedure described for the nucleosides. Protection for their 3′-hydroxyl group was carried out by treatment with acetic anhydride in pyridine. The three appropriately protected nucleosides and nucleotides (apart from thymidine and thymidylic acid) are shown in Figure 6.

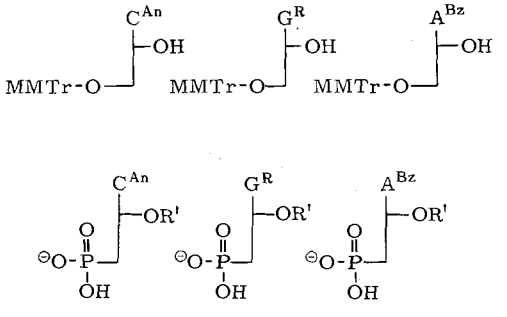


Fig. 6. Protected deoxyribonucleosides and deoxyribonucleotides (schematic). R = isobutyryl or 2-methylbutyryl, R′ = H or acetyl.

3. Synthesis of Higher Deoxyribopolynucleotides of Specific Sequences

The aim of chemical synthesis is to build deoxyribopolynucleotides of defined and specific sequences. Two approaches can be imagined: one in which mononucleotides are added one by one to a growing polynucleotide chain and a second approach involving the use of preformed oligonucleotide blocks to form successively longer chains. Both of these approaches have been investigated systematically and used in synthetic work in the last few years.

3.1. Stepwise Synthesis Using Protected Mononucleotides

The approach used first with greater success was that which involves the stepwise addition of protected mononucleotide units to the 3′-hydroxyl end of a growing oligonucleotide chain[13]. An example is given in Figure 7.

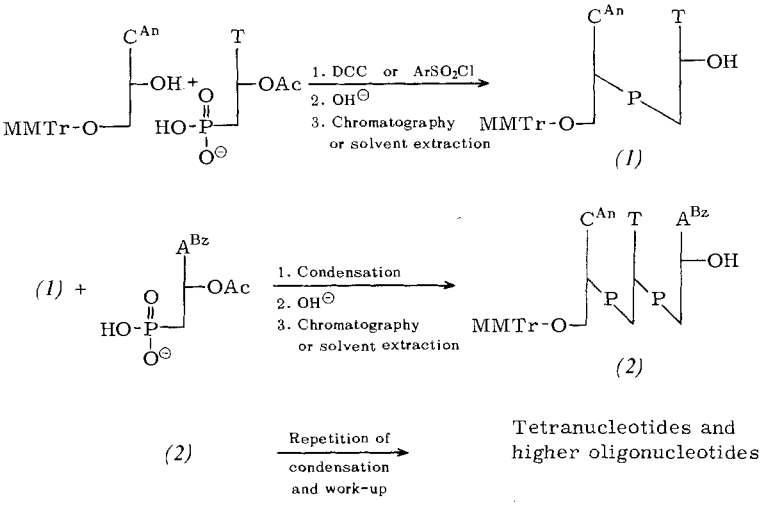


Fig. 7. Stepwise chemical synthesis of tetranucleoside triphosphate or higher oligonucleotides.

Although this approach requires a maximum number of synthetic steps in putting together a polynucleotide chain of desired size, it most often has the advantage of giving high yields in successive condensations. It has been used and continues to be used, either alone or in combination with the blockwise addition approach described below, in a great deal of synthetic work.

3.2. Stepwise Synthesis Using Preformed Protected Oligonucleotides Bearing 5′-Phosphate Groups

The second approach which utilizes preformed blocks[14,15] proceeds faster due to the fewer synthetic steps required for the oligonucleotide synthesis and provides a better system for chromatographic separation. However, the yields at the individual condensation steps are generally lower. On the whole, the blockwise approach is to be preferred in polynucleotide synthesis provided that the preformed protected oligonucleotides, especially the dinucleotides, can be readily prepared in quantity.

3.3. Synthesis of Protected Di- and Higher Oligonucleotides Carrying 5′-Phosphate Groups

Synthesis of the di- or trinucleotide blocks carrying 5′-phosphate end groups requires protection of the phosphomonoester group of the 5′-mononucleotide. Until recently this was done by condensation of the amino-protected nucleotides with cyanoethanol using DCC or $ArSO_2Cl$ as illustrated in Figure 8. The cyanoethylated derivative is

then brought into condensation with the second nucleotide component, appropriately blocked on the amino and the 3'-hydroxyl functions. The condensation is usually carried out with DCC or $ArSO_2Cl$ to give a fully protected dinucleotide. Cyanoethyl and acetyl groups are then removed from the dinucleotide by mild alkaline treatment. Purification of the reaction products is carried out by DEAE cellulose column chromatography, which is time consuming. By repeating the operations (cyanoethylation and condensation) higher blocks are prepared and used directly in the synthesis.

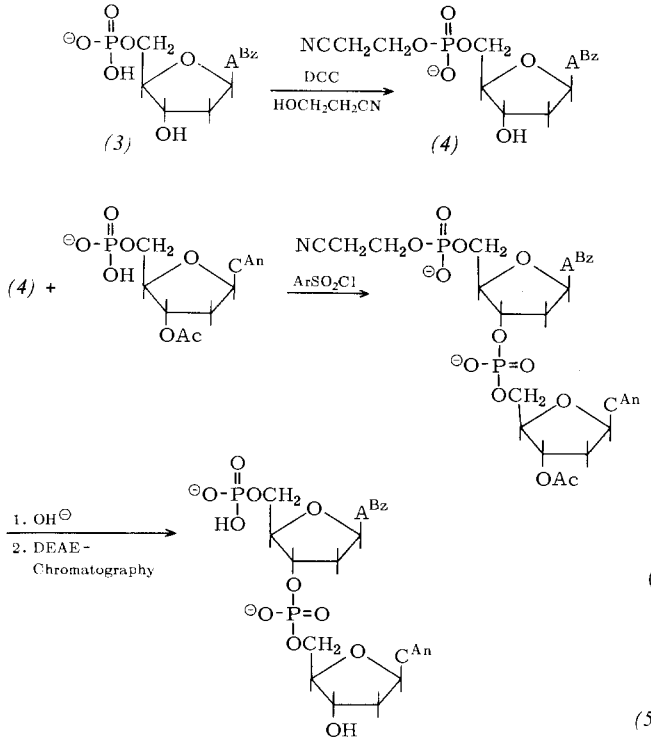


Fig. 8. Synthesis of an *N*-protected dinucleotide carrying a 5'-phosphate end group.

Alternative phosphate-protecting groups have been suggested from time to time and are shown in Figure 9. The trichloroethyl group originally introduced by *Woodward et al.*[16a] in the synthesis of cephalosporin has been suggested as a phosphate-protecting group by *Eckstein*[16b]. This group is removed by treatment with zinc in DMF. Use of substituted phosphorothioate has been suggested by *Nussbaum et al.*[17]. Conversion of phosphorothioate into phosphate was carried out by treatment with iodine in aqueous conditions. The third type, *N*-(*p*-methoxyphenyl)-carbamoylethyl, was introduced by *Narang et al.*[18] and is cleaved by alkaline treatment. The fourth type is a simple aromatic phosphoramidate. Compounds of this type were first prepared by *Moffatt* and *Khorana*[19] and used in the synthesis of nucleotide coenzymes. Recently, *Ohtsuka et al.*[20] have investigated the possible use of aromatic phosphoramidates for protection of the phosphate group and have shown that the amidate group can be cleaved by isoamyl-nitrite treatment under very mild conditions at pH 7.

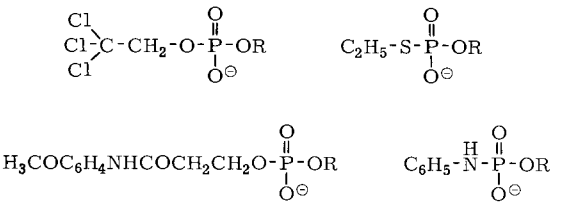


Fig. 9. Nucleosides with phosphate-protecting groups. R = thymidine or *N*-protected nucleosides.

As pointed out above, the greater part of the effort in the preparation of the protected dinucleotide blocks goes into the purification of the synthetic products by ion exchange chromatography, which requires several days. Clearly, a procedure which would eliminate the ion exchange chromatography would certainly reduce the time and effort required for the synthesis of the dinucleotide blocks. With this aim in view, an isolation procedure involving the principle of solvent extraction has been developed[21]. A highly lipophilic amine, *p*-(triphenylmethyl)aniline (see Fig. 10) was used for protecting the phosphate group of the nucleotide as the phosphoramidate. The reason for choosing the phosphoramidate type of linkage was because it could be cleaved by isoamyl nitrite under very mild conditions without any side reactions or loss of other protecting groups. All of the four phosphoramidates of the appropriately protected nucleotides were prepared by reaction of the nucleotide and the amine with DCC. These phosphoramidates were isolated in pure form by simple organic solvent extraction procedures and were shown to exist as the salts of the substituted guanidine. Formation of this guanidine inhibits the DCC reaction which is catalyzed by phosphate. Use of alternative activating agents gave lower yields of phosphoramidates. The phosphoramidate was then condensed with protected mononucleotide in the presence of TPS to give a protected dinucleotide as shown in Figure 11.

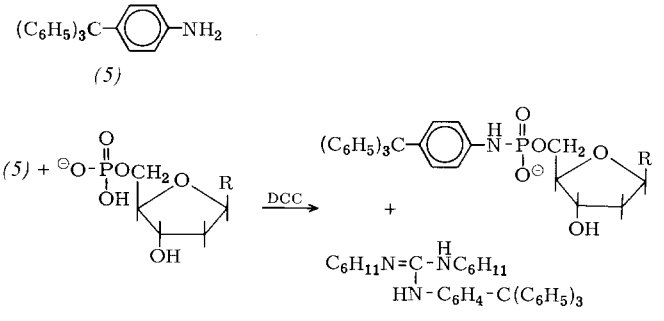


Fig. 10. Synthesis of *N*-protected phosphoramidates of nucleotides. R = thymine, *N*-anisoylcytosine, *N*-benzoyladenine, or *N*-isobutyryl-guanine.

The yields of the various dinucleotides prepared in this manner were in the range of 55 to 70%. The dinucleotide phosphoramidates were isolated free from the mononucleotide and its symmetrical pyrophosphate by solvent extraction. The yield of the dinucleotides protected on the amino functions were in the range of 50 to 65% determined after isoamyl-nitrite treatment. All the sixteen dinucleotides could be prepared in relatively short time and well characterized.

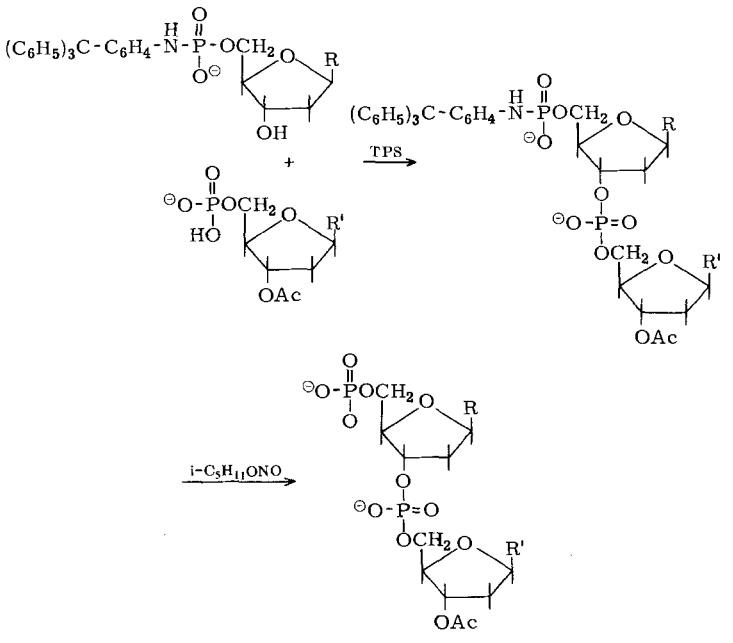


Fig. 11. Synthesis of *N*-protected dinucleotide using *p*-(triphenylmethyl)aniline as the 5′-phosphate protecting group [21]. R or R′ = thymine, *N*-benzoyladenine, *N*-anisoylcytosine, or *N*-isobutyrylguanine.

3.4. Synthesis of an Icosanucleotide

The approach using preformed oligonucleotide blocks, as mentioned above, is potentially more useful and continues to be used extensively in current work on polynucleotide synthesis. This is further illustrated by its use in the stepwise synthesis of the icosanucleotide complementary in sequence to nucleotide 21 through 40 of ala-tRNA (see Fig. 1). The synthetic steps used are shown in Figure 12. The bottom line shows the ultimate product.

The synthesis started from the 5′-end of the chain with guanosine whose 5′-hydroxyl function was protected with the monomethoxytrityl group and the amino function with isobutyryl. This was first condensed with the mononucleotide $pA^{Bz}OAc$ and the product dinucleoside phosphate was isolated by solvent extraction. Further steps involved the condensations between the 3′-hydroxyl end of the growing chain and the appropriately protected mononucleotide or di-, tri-, and tetranucleotide blocks.

At each step, the products were purified by prolonged ion exchange chromatography on DEAE cellulose. The purity of these compounds was further checked before use in the subsequent steps as follows:

1. Extensive paper chromatography of the products before and after removal of the protecting groups.

2. Determination of nucleoside and nucleotide ratios after enzymatic hydrolysis of the unprotected products.

3. DEAE cellulose chromatography in urea, a technique developed by *Tener et al.*[26] which offers very high resolution.

In syntheses of this kind, the yields tend to drop as the chain length increases and the use of large amounts of blocks becomes necessary—and even then the yields of the desired final products are only moderate in the final stages. It is, therefore, important that the choice of blocks is made after careful considerations, *e.g.*, condensations between two purines must be avoided if possible because of the low yields obtained. Pyrimidine to pyrimidine condensations are mostly favored because of the satisfactory yields obtained. The size of the blocks sometimes becomes very important because it determines the total negative charge difference between the starting chain and the product, which plays an important role in the separation of polynucleotides on ion exchange chromatography. A typical separation profile on DEAE cellulose chromatography of the reaction mixture obtained in condensation of hexadecanucleotide and tetranucleotide is shown in

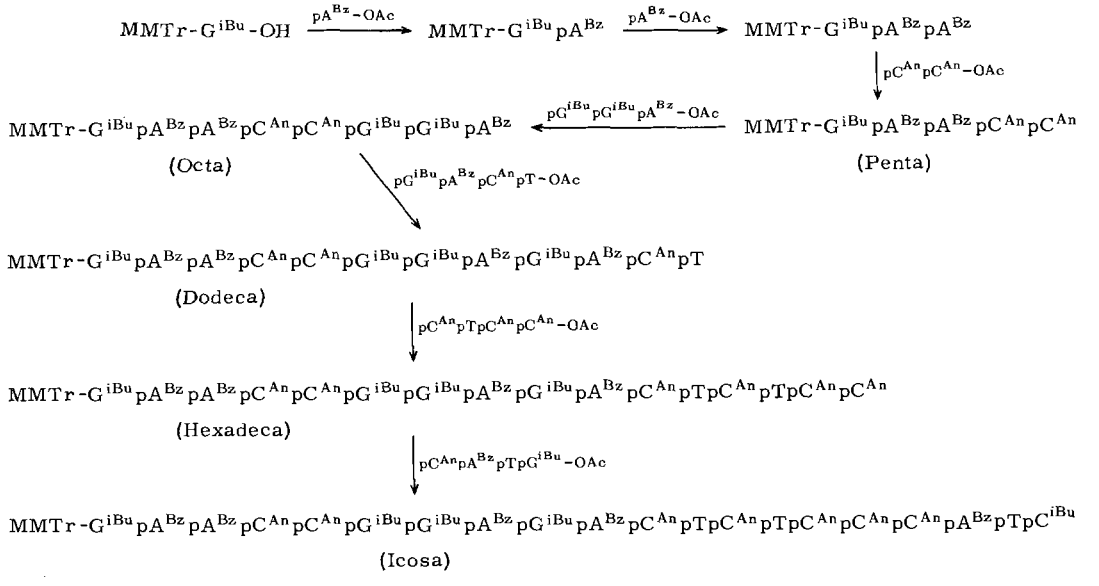


Fig. 12. Chemical synthesis of an icosanucleotide using preformed blocks.

Figure 13. The tetranucleotide block carried a tritium label so that the icosanucleotide could be distinguished from the hexadecanucleotide. Peak IV was identified as the icosanucleotide and had a constant ratio of radioactivity to ultraviolet absorbance.

formed in the synthesis of a hexanucleotide on trityl cellulose is shown in Figure 15.

The solid line shows the UV absorption and the dashed line shows the trityl estimation. Products eluted first

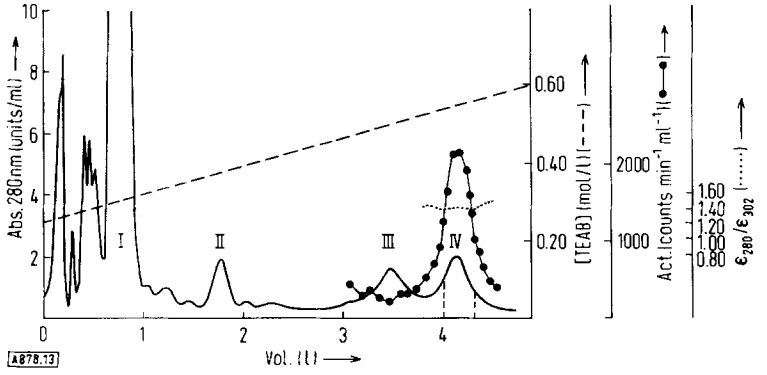


Fig. 13. Condensation of a protected hexadecanucleotide with a protected tetranucleotide (see Fig. 12). Separation of the reaction products on a DEAE cellulose (bicarbonate) column (1.8 × 60 cm) preequilibrated at 4 °C with 0.05 M triethylammonium bicarbonate (TEAB) (pH 7.5) in 40% ethanol. The bicarbonate concentration gradient used for elution was as shown by the dotted line, the solvent being 40% ethanol.

3.5. Use of Trityl Cellulose in Purification of Condensation Reaction Mixtures

The purpose of this new column adsorbent is best explained by examining the reaction products in a typical condensation reaction (Fig. 14).

1. The first type of product contains a monomethoxytrityl group at its 5'-hydroxyl function. These comprise the unreacted MMTr component and the required product.

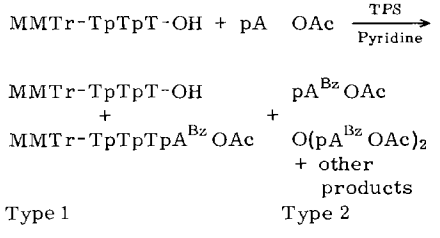


Fig. 14. Nature of products formed in a condensation reaction.

2. The second type of product includes the unreacted nucleotide and its pyrophosphate. Selective adsorption of the first type of products and consequent separation from the second type have recently been investigated using naphthoyl cellulose and trityl cellulose as the column adsorbents. The adsorbed products can then be eluted from the column simply by raising the alcohol concentration to 90%. Naphthoyl cellulose was found to be rather unstable due to the slow hydrolysis of the ester bond in presence of triethylammonium bicarbonate (TEAB) pH 7.5 to 8.0. Trityl cellulose is found to be quite stable under these conditions and is now being routinely used in our synthetic work. The elution profile of a reaction mixture (Type 2) with low alcohol concentration (45%; 0.05 mol/l TEAB) were free from trityl-containing components. When all the second type of products were washed off with low

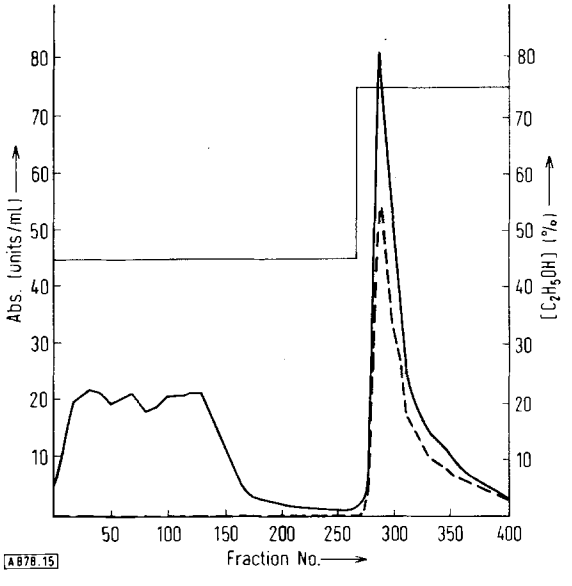


Fig. 15. Purification of condensation reaction mixture of MMTr—TpC^{An}pG^{iBu}pA^{Bz}OH and pC^{An}pC^{An}—OAc on trityl cellulose. ——, absorption at 280 nm; – – –, absorption at 472 (corresponds to content of monomethoxytrityl groups); ——, ethanol concentration.

alcohol concentration, the alcohol and TEAB concentrations were increased to 75% and 0.5 mol/l TEAB to elute the trityl-containing products. Examination of these products (Type 1) by extensive paper chromatography showed the absence of Type 2 products. Type 1 products were further purified by DEAE cellulose chromatography. A separation pattern is shown in Figure 16.

Only trityl-containing components were eluted from the column and the pattern thus obtained is relatively simple. This example clearly indicates that the introduction of trityl cellulose as a purification step prior to DEAE cellulose chromatography, not only increases the efficiency of the purification, but also reduces the overall time required.

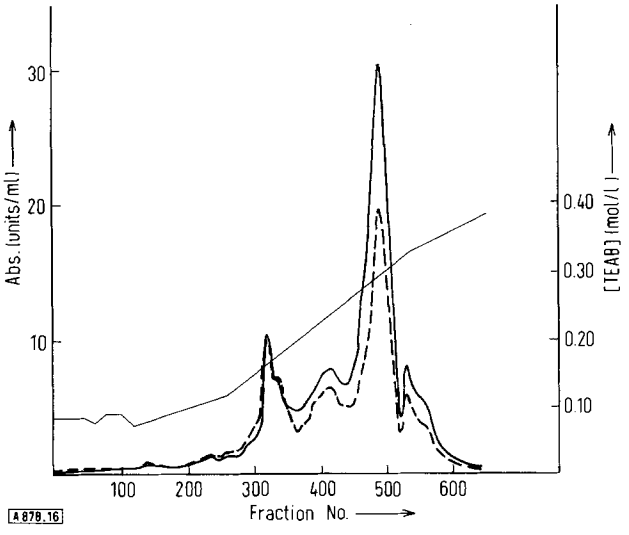


Fig. 16. Separation of monomethoxytrityl containing hexa- and tetranucleotide on DEAE cellulose. ——, absorption at 280 nm; – – –, absorption at 472 nm (corresponds to content of monomethoxytrityl groups); ——, TEAB concentration.

3.6. Polynucleotide Synthesis on Polymer Supports

There has been a great deal of interest in carrying out synthesis of biopolymers on polymer supports. This concept has been used with striking success by *Merrifield* in the synthesis of peptides and enzymes[22], and by *Katchalsky*[23] in the synthesis of insoluble enzymes. Naturally the question arises whether similar concepts can be developed in the polynucleotide field. This would accelerate the synthesis of polynucleotides and would avoid separation of products at every condensation step. A number of groups have been investigating various approaches. We, ourselves, have investigated both insoluble and organic-solvent-soluble polymers[27] for this purpose, as suggested by *Shemyakin et al.*[24]. This concept is very attractive because the condensation reactions could be carried out in homogeneous medium. In our approach, commercially available polystyrene was converted into a polymer containing a few percent of methoxytrityl chloride groups by the reaction sequence shown in Figure 17.

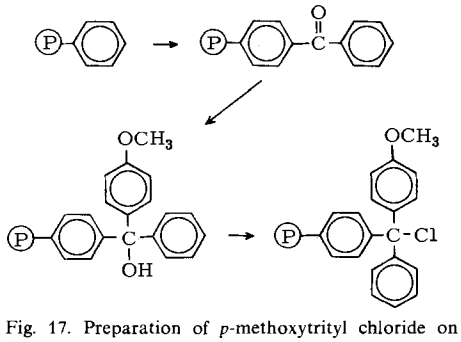


Fig. 17. Preparation of *p*-methoxytrityl chloride on a polystyrene backbone. Ⓟ = polystyrene backbone.

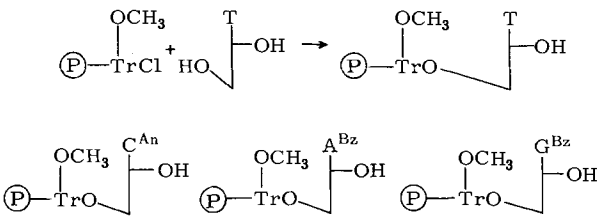


Fig. 18. Preparation of 5′-methoxytrityl-*N*-protected deoxyribonucleosides linked to a polystyrene backbone (= Ⓟ).

Deoxynucleosides appropriately protected on their amino functions were then allowed to react with this polystyrene derivative to give all four 5′-*O*-protected deoxynucleosides linked to a polystyrene backbone (Fig. 18). The subsequent chain elongation by stepwise addition of appropriately protected mononucleotides gave di- and trinucleoside phosphates as shown in Figure 19.

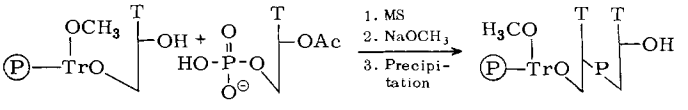


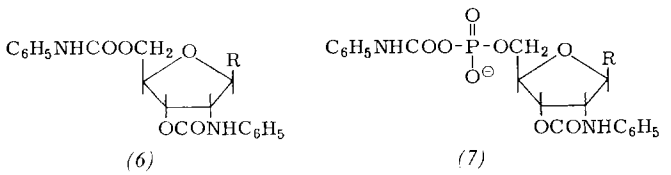
Fig. 19. Synthesis of a dinucleoside phosphate on a polystyrene backbone (= Ⓟ).

At the end of the synthesis the products were removed from the polymer by acid treatment. Although the yields were quite high in the condensation steps, they were not close to quantitative. A similar technique was investigated independently by *Cramer et al.*[25]. This approach seems quite promising but there are still some problems to be solved.

3.7. Selective Blocking of the 3′-Hydroxyl End Groups in Protected Deoxyribooligonucleotides

One main problem in the synthesis of deoxyribopolynucleotides is that the yields of the individual condensation steps are not quantitative. Synthesis cannot therefore be carried out on polymer supports because sequential isomers would result. Synthesis in solution requires time-consuming separation of starting material and elongated chain. An important advantage would accrue if the 3′-hydroxyl end groups in the unreacted components could be *specifically* and *quantitatively* blocked. A method of doing so has been found[28].

Aromatic isocyanates have been found to react with the appropriately *N*-protected nucleosides to give dicarbamoyl derivatives *(6)* (Fig. 20) in quantitative yields. Fully protected nucleosides (3′,5′-hydroxyl and amino functions appropriately blocked) did not react with the aromatic isocyanate. On the other hand, mononucleotides protected on the amino function reacted with aromatic isocyanate to give dicarbamoyl derivatives *(7)* (Fig. 20), the reaction occurring with the 3′-hydroxyl and the phosphomonoester groups. Phosphodiesters (internucleotide bonds) were resistant to aromatic isocyanate reaction, *e.g.*, the dinucleoside phosphate MMTr-TpG^{iBu}-OH reacted only on the 3′-hydroxyl group to give MMTr-TpG^{iBu}OCONHAr. Higher oligodeoxynucleotides of the size of a pentanu-



(6) (7)

Fig. 20. Dicarbamoyl derivatives of *N*-protected nucleosides (left) and mononucleotides (right). R = thymine, *N*-benzoyladenine, *N*-anisoylcytosine, or *N*-isobutyrylguanine.

cleotide appropriately protected on the 5'-hydroxyl end and the amino functions were also found to undergo quantitative reaction with the aromatic isocyanate on the 3'-hydroxyl group.

A practical application of the principle of blocking the 3'-hydroxyl end after every condensation step has been made in the synthesis of a pentanucleotide. The synthetic steps

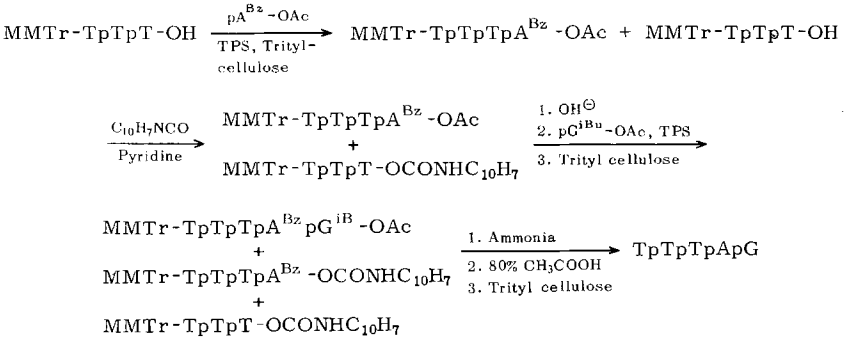


Fig. 21. Synthesis of a pentanucleotide.

are shown in Figure 21. After the condensation, the reaction mixture was first partially purified on trityl cellulose and then treated with naphthyl isocyanate to block the unreacted 3'-hydroxyl groups. Starting from a trinucleotide, the cycle: addition of appropriate mononucleotide, purification on trityl cellulose, and reaction with naphthyl isocyanate is repeated twice to give a pentanucleotide. At the end of the synthesis, the protecting groups were removed by standard procedures followed by filtration through trityl cellulose. The oligonucleotides bearing the 3'-naphthylcarbamoyl groups were selectively retained on the trityl cellulose whereas the product was present in the eluate. The product was about 90% pure. The application of this approach is now being studied in detail for the synthesis of oligonucleotides in both solution phase and solid phase synthesis.

The work has been generously supported by the National Cancer Institute of the National Institutes of Health (Grants No. 72576, CA05178), The National Science Foundation Washington (Grants No. 73078, GB-7484X), and The Life Insurance Medical Research Fund.

Received: November 25, 1971 [A 878 IE]
German version: Angew. Chem. *84*, 489 (1972)

[1] *H. G. Khorana*, Pure Appl. Chem. *17*, 349 (1968).

[2] *K. L. Agarwal, H. Büchi, M. H. Caruthers, N. Gupta, H. G. Khorana, K. Kleppe, A. Kumar, E. Ohtsuka, U. L. RajBhandary, J. H. van de Sande, V. Sgaramella, H. Weber*, and *T. Yamada*, Nature *227*, 27 (1970).

[2a] *P. Besmer, K. L. Agarwal, M. H. Caruthers, P. J. Cashion, M. Fridkin, E. Jay, A. Kumar, P. C. Loewen, K. Minamoto, E. Ohtsuka, J. H. van de Sande, N. Siderova*, and *U. L. RajBhandary*, Fed. Proc. *30*, 1413 (1971).

[3] a) *F. Eckstein* and *I. Rizk*, Angew. Chem. *79*, 684 (1967); Angew. internat. Edit. *6*, 695 (1967); b) *R. L. Letsinger* and *V. Mahadevan*, J. Amer. Chem. Soc. *87*, 3526 (1965); c) *C. B. Reese* and *R. Saffhill*. Chem. Commun. *1968*, 767.

[4] *T. M. Jacob* and *H. G. Khorana*, J. Amer. Chem. Soc. *86*, 1630 (1964).

[5] *R. Lohrmann* and *H. G. Khorana*, J. Amer. Chem. Soc. *88*, 829 (1966).

[6] *G. Weimann* and *H. G. Khorana*, J. Amer. Chem. Soc. *84*, 4329 (1962).

[7] *P. T. Gilham* and *H. G. Khorana*, J. Amer. Chem. Soc. *81*, 4647 (1959).

[8] *M. Smith, D. H. Rammler, I. H. Goldberg*, and *H. G. Khorana*, J. Amer. Chem. Soc. *85*, 3821 (1963).

[9] *H. Schaller, G. Weimann, B. Lerch*, and *H. G. Khorana*, J. Amer. Chem. Soc. *85*, 3821 (1963).

[10] *R. L. Letsinger* and *P. S. Miller*, J. Amer. Chem. Soc. *91*, 3356 (1969).

[11] *C. B. Reese* and *J. C. M. Stewart*, Tetrahedron Lett. *1968*, 4273.

[12] *E. Jay*, unpublished work.

[13] *T. M. Jacob* and *H. G. Khorana*, J. Amer. Chem. Soc. *87*, 2971 (1965).

[14] *H. Kössel, M. W. Moon*, and *H. G. Khorana*, J. Amer. Chem. Soc. *89*, 2148 (1967).

[15] *J. Hachmann* and *H. G. Khorana*, J. Amer. Chem. Soc. *91*, 2749 (1969).

[16] a) *R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan*, and *H. Vorbrüggen*, J. Amer. Chem. Soc. *88*, 852 (1966); b) *F. Eckstein*, Angew. Chem. *78*, 682 (1966); Angew. Chem. internat. Edit. *5*, 671 (1966).

[17] *A. F. Cook, M. J. Holman*, and *A. L. Nussbaum*, J. Amer. Chem. Soc. *91*, 6479 (1969).

[18] *S. A. Narang, O. S. Bhanot, J. Goodchild, J. Michniewicz, R. H. Wightman*, and *S. K. Dheer*, Chem. Commun. *1970*, 516.

[19] *J. G. Moffatt* and *H. G. Khorana*, J. Amer. Chem. Soc. *83*, 649 (1961).

[20] *E. Ohtsuka, K. Murao, M. Ubasawa*, and *M. Ikehara*, J. Amer. Chem. Soc. *92*, 3441 (1970).

[21] *K. L. Agarwal, A. Yamazaki*, and *H. G. Khorana*, J. Amer. Chem. Soc. *93*, 2754 (1971).

[22] *R. B. Merrifield*, Advan. Enzymol. *32*, 221 (1969).

[23] *I. Silman* and *E. Katchalski*, Annu. Rev. Biochem. *35*, 873 (1966).

[24] *M. M. Shemyakin, Y. A. Ovchinikov, A. A. Kinyushkin*, and *I. V. Kozhevnikova*, Tetrahedron Lett. *1965*, 2323.

[25] *F. Cramer, R. Helbig, H. Hettler, H. K. Scheit*, and *H. Seliger*, Angew. Chem. *78*, 640 (1966); Angew. Chem. internat. Edit. *5*, 601 (1966).

[26] *R. V. Tomlinson* and *G. M. Tener*, J. Amer. Chem. Soc. *84*, 2644 (1962).

[27] *H. Hayatsu* and *H. G. Khorana*, J. Amer. Chem. Soc. *89*, 3880 (1967).

[28] *K. L. Agarwal* and *H. G. Khorana*, J. Amer. Chem. Soc. *94*, 3578 (1972).

Perspectives in Nonsteroidal Anti-inflammatory Agents

By T. Y. Shen[*]

Among numerous nonsteroidal anti-imflammatory agents synthesized in the past few years, various analogs of indomethacin, phenylacetic acid and heteroarylacetic acid have reached the stage of clinical evaluation. Their biochemical mechanisms of action are exemplified by the broad activity profile of indomethacin which includes inhibition of mediators and enzymes, effects on cell membranes, and, most recently, inhibition of prostaglandin biosynthesis. The importance of pharmacodynamic properties to clinical efficacy was clearly demonstrated in some cases. Several candidates were eliminated because of their side-effects. A group of α-methylarylacetic acids showed a high degree of stereospecificity in their potency and metabolisms *in vivo*, as well as inhibition of prostaglandin synthetase and albumin binding *in vitro*. Extrinsic Cotton effect provides a sensitive technique in the study of interactions of these drugs with biopolymers. Competitive binding and antagonistic interactions between nonsteroidal drugs, particularly salicylate, were observed *in vitro* and *in vivo*. Progress in salicylate research was marked by the synthesis of flufenisal as a new derivative with enhanced potency and longer duration of action. Several fenamate analogs and new chemical types have shown promise in preliminary clinical trials. Various immunological approaches are under investigation for the treatment of rheumatoid arthritis. Newer concepts are still needed to achieve more effective control of arthritic disorders.

1. Introduction[1]

Despite the intensive and ever-increasing efforts in anti-inflammatory studies during the past decade, the treatment of rheumatoid arthritis remains a major challenge for biologists and medicinal chemists alike. A better understanding of the disease, particularly its etiology and pathogenesis, the development of more significant animal models, new medicinal chemical concepts and novel chemical structures are still much needed to achieve a major breakthrough in this difficult field.

As was noted in the Annual Report in Medicinal Chemistry for 1966[2], a wide-spread interest in the search for new anti-inflammatory agents at that time was evidenced by the disclosure of more than one hundred groups of anti-inflammatory structures in the patent literature within one year. This feverish pace of screening and synthesis has apparently been maintained, if not accelerated. However, judging from the scientific literature, apparently only a small number of leads showed adequate potency and short-term tolerance to merit further consideration. An even smaller fraction of these eventually qualified as preclinical candidates after chronic toxicity studies. This process of elimination of anti-inflammatory compounds is certainly a costly and frustrating one.

Since the general background of arthritis research, *e.g.*, clinical aspects[3-6], pharmacological studies[7-10] and new active structures[11,12], is regularly reviewed by many excellent articles, the main emphasis of this review will be on the current status of a selected group which has advanced to the clinical stage or beyond. The selection is necessarily limited by the scarcity of clinical data on new drugs under development, but it may help to focus the attention of medicinal chemists on a few significant compounds among a maze of literature claims. It is also hoped that by examining the case history of these examples, the success of very few, the near-miss of many, the limitation of their clinical efficacy and, most of all, the tremendous amount of time and effort invested by so many will illustrate some critical problems in the field of arthritis research and underscore the need for realignment of our strategy and biological approaches.

[*] Dr. T. Y. Shen
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065 (USA)

2. Arylacetic Acids

2.1. General

Interest in arylacetic acids as nonsteroidal anti-inflammatory agents was developed independently in several laboratories about 15 years ago. Although not explicitly considered by the investigators at that time, it is of interest to note that two plant growth regulators, indolylacetic acid and phenoxyacetic acid served as the basic structure for the earlier studies at Boots[13] and at Merck[14]. Hydrophobic substitutions, so effectively employed as activity-enhancing groups in many pharmacological agents, in the form of aryl, aralkyl or aroyl, readily converted these plant growth regulators into derivatives highly active in animal assays such as foot-edema, UV erythema, granuloma pellet, and adjuvant arthritis assays[15]. More recently, *in vitro* cytotoxicity and moderate *in vivo* anti-inflammatory activity have also been observed with analogs or derivatives of several other plant regulants[16].

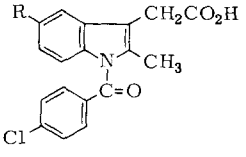
The predominance of arylacetic acids in anti-inflammatory research is reminiscent of the association of antihistaminic activity with diarylalkylamines or central nervous activity

with phenothiazinylalkylamines. Not surprisingly, the optimal aryl moieties seem to be different in each case. Several attempts to interchange the dialkylamino side-chain with an acetic acid in each series resulted in mediocre analogs only[17].

2.2. Biochemical Modes of Action of Indomethacin

The primary modes of action of anti-inflammatory aryl acids are still being elucidated, but it seems likely that they exert a multitude of actions on the complex inflammatory process. Their broad activity-profiles are probably the basis for their rather nonspecific clinical efficacy and also for some potential side effects.

The introduction of indomethacin *(1)*[14,18] appeared to coincide with the recent interest in biochemical pharma-



(1), R = OCH_3 (Indomethacin)
(2), R = $N(CH_3)_2$

cology of nonsteroidal anti-inflammatory agents. As a new reference compound it has been evaluated in various biochemical systems. Although the significance of some observations remains to be substantiated, a selection of its biochemical properties reported in the literature is listed in Table 1. As noted before, most of these properties are commonly shared with other anti-inflammatory aryl acids.

Table 1. The biochemical profile of indomethacin

1.	Effect on Enzymes and Mediators ($10^{-4}-10^{-3}$ mol/l)
1.1.	Inhibition of proteolytic enzymes, *e.g.*, trypsin, α-chymotrypsin and "tissue proteases"
1.2.	Inhibition of histidine decarboxylase *in vitro*
1.3.	Inhibition of lymph node permeability factor (LNPF)
1.4.	Marginal effect on kinin systems, Hageman factor and fibrinolysis
1.5.	Antagonism of slow reacting substances (SRS)
1.6.	Uncoupling of oxidative phosphorylation
1.7.	Inhibition of mucopolysaccharide biosynthesis
1.8.	Stabilization of serum protein
1.9.	Inhibition of prostaglandin synthetase (10^{-6} mol/l)
2.	Effect on Membrane Structures ($10^{-5}-10^{-4}$ mol/l)
2.1.	Stabilization of erythrocytes
2.2.	Inhibition of platelet functions Aggregation and release of mediators
2.3.	Inhibition of neutrophil participation in Shwartzman Reaction
2.4.	Inhibition of fibroblast-leukocytes interaction *in vitro*
2.5.	Inhibition of leukocytes migration Chemotaxis and PMN motility
2.6.	Stabilization of human skin lysosomes *vs.* histamine

The biochemical profile of indomethacin may be broadly described in two parts: inhibition of enzymes and mediators, and effect on cellular membranes. The latter, in particular, seems to be the basis of many recent observations. As shown in Table 1, indomethacin, along with other anti-inflammatory aryl acids, inhibits several proteolytic enzymes *in vitro* at 10^{-4}—10^{-3} mol/l[19,20]. Some of those proteases may be involved in tissue degradation, immunoglobulin metabolism, and the activation of inflammatory mediators[21]. The possible roles of collagenase[22-24] and of a lysosomal enzyme, cathepsin D[25], in the degeneration of arthritic joints have received much attention recently[4]. The recognition of several mammalian collagenases with different pH optima and sensitivity to serum inhibitors suggests caution in interpreting the data obtained from model *in vitro* studies[26].

Interest in histamine as the prime mediator of inflammation has decreased with time. It was found earlier that indomethacin inhibits fetal histidine decarboxylase *in vitro* at a concentration of 0.4 mmol/l[27]. However, *in vivo*, the effect seems to vary with the tissue origin of the enzyme[28,29]. Conceptually, the inhibition of histidine decarboxylase was further complicated by the postulation of an "induced" enzyme[30]. Lymph node permeability factor (LNPF) is an inflammatory mediator derived from lymphocytes and associated with a variety of phenomena involved in delayed hypersensitivity[31]. The factor produces an increase in vascular permeability, leukocyte emigration, and fibrinoid deposition. The vasoactive effects of LNPF are antagonized by indomethacin. On the other hand, indomethacin has little or no effect on the formation and activity of bradykinin[32,33]. It has marginal effect on the activation of the Hageman factor in the dog knee joint[33] and it has very weak activity in fibrinolysis *in vitro*[34].

Indomethacin antagonizes the ability of "slow reacting substances" (SRS-A, SRS-C), arachidonic acid, and bradykinin, to increase the resistance of guinea-pig lungs to inflation[35]. This drug blocks directly the spasmogenic effect of SRS-C[36] and its possible release of an aorta-contracting substance[37].

Most nonsteroid anti-inflammatory agents uncouple oxidative phosphorylation and inhibit the biosynthesis of mucopolysaccharide[38]. The correlation of these properties with anti-inflammatory actions, however, was weakened by the lack of structure specificity and by the pharmacodynamic requirements for *in vivo* activities. The effect of these drugs on the ATP level do not seem to parallel the effect on ^{35}S incorporation[39]. There appears to be no direct correlation between these two actions.

The binding of serum protein by many anti-inflammatory aryl acids and their mutual interference have been well investigated. The ε-amino group of lysine, tryptophan, and tyrosine groups in serum albumin are possibly involved in the three strong binding sites[40]. As a result of the binding, the denaturation of protein is inhibited. Whether the free SH-disulfide exchange[41] is actually involved in pathological protein denaturation *in vivo* remains speculative. Some anti-inflammatory agents displace albumin-bound warfarin and interfere with its anticoagulant action[42], but the alleged effect of indomethacin was refuted[43]. In the clinic, indomethacin does not seem to have any effect on blood clotting in patients undergoing anticoagulant therapy.

The stabilization of protein denaturation was originally proposed by *Mitsushima* as a simple screening assay for compounds with potential anti-inflammatory properties[44]. At concentrations of 0.4 mmol/l indomethacin in-

hibits the heat denaturation of serum albumin[44]. It has been suggested that similar interaction of anti-inflammatory agents with membrane proteins may be the basis of their multiple effects on cells. Indomethacin at 0.05—0.3 mmol/l inhibits the lysis of human and animal erythrocytes induced by heat or hypotonicity[45,46]. It inhibits the *in vitro* aggregation of erythrocytes induced by gelatin or fibrinogen[47]. Indomethacin and salicylate inhibit the aggregation of platelets induced by collagen, epinephrine, ADP, *etc.*[48,49].

A transient but demonstrable effect was produced by a single oral dose of indomethacin in man[49]. At concentrations of 5 μmol/l indomethacin is one of the most potent compounds to inhibit the release of serotonin and other mediators by platelets in the presence of connective tissues, ADP, or other stimulants[50]. It also inhibits the function, though not the migration, of neutrophils in the Shwartzman reaction in rabbits[51] and the interaction of fibroblasts and leukocytes *in vitro*[52]. The membrane effect is further reflected in the chemotactic or migratory properties of cells. Indomethacin decreases the motility of polymorphonuclear leukocytes induced by crystalline urate[53], the migration of bone-marrow derived monocytes to the inflamed site *in vivo*[54], and the infiltration of neutrophils in inflamed rat paw[55]. The effect of anti-inflammatory drugs on the membrane of intracellular granules was demonstrated with the aid of an integrated microdensitometry technique[56]. At a concentration of 5×10^{-5} mol/l indomethacin inhibits the histamine-induced rupture of lysosomes in human skin culture[57]. Unlike steroids, it has no effect on the histamine-induced increasing permeability of the mitochondria.

The stabilization of lysosomal membrane has received a great deal of attention as a potential antirheumatic approach. Recent *in vivo* studies[58,59] with chloroquine showed that daily doses of 120 mg/kg stabilize lysosomes in rat liver *vs.* the damaging effect of hyperoxia and neutral red. It also produces myeloid body formation in liver and heart tissue, presumably by reducing the membrane permeability and thus interfering with the formation of primary lysosomes. Other nonsteroidal anti-inflammatory agents have no pronounced effect on isolated lysosomes at low concentrations[60]. Some confusion in *in vitro* results[61,62] was probably caused by the sensitivity of some experiments to varying pH, temperature, media, and drug concentrations. Progress has been made in the development of artificial lysosome models, but the validity of studying lysosome rupture in an artificial system outside its cytoplasmic environment may require careful consideration.

Complement fixation is a recognized process in arthritic joints[63,64]. In addition to its roles in antigen-antibody reaction and hemolysis, it releases in a sequential manner anaphylatoxin, chemotactic factor and prostaglandins. Available anti-inflammatory agents are generally ineffective in controlling this important pathological process.

The anti-inflammatory effect of indomethacin was originally evaluated in the carrageenin foot-edema assay in rats. In searching for the primary mode of action, it was hypothesized recently that the observed reduction of foot-swelling by indomethacin may be attributable to the suppression of migration of monocytes to the inflamed site, thus preventing the subsequent activation of complement or enzymes, formation of prostaglandins, permeability increase, *etc.*[54].

Recently, *Vane* and his colleagues reported that indomethacin and aspirin inhibit the biosynthesis of prostaglandins from arachidonic acid in several tissue homogenates[160], human platelets[161], as well as isolated, perfused, intact spleen of the dog[162]. Prostaglandins have been implicated as mediators of inflammation in several experimental systems including cutaneous inflammation in man[163] and carrageenin foot-edema in rats[164].

The inhibition of their biosynthesis by these two drugs *in vitro* and *in vivo* at levels below their physiological concentrations thus appears to be an attractive mechanism of action[165]. As an extension of these studies we have found that the 5-fluoro analog of indomethacin is a competitive inhibitor ($K_i = 8 \times 10^{-6}$ mol/l) of arachidonic acid ($K_m = 2 \times 10^{-4}$ mol/l) in our *in vitro* system[166]. A large number of nonsteroidal anti-inflammatory agents such as phenylbutazone, indomethacin analogs *(2)*—*(5)*, phenylacetic acids *(11)* and *(12)*, ibuprofen *(19)*, alclofenac *(22)*, naproxen *(24)*, metiazinic acid *(26)*, flufenisal *(33)*, fenamates[*], nifluril *(38)*, azapropazone *(41)*, and several nonacidic compounds (*e.g.*, indoxole and thiabendazole), strongly inhibit the conversion of labeled arachidonic acid into prostaglandin E_2 at 0.1 to 10 μg/ml. The magnitude of *in vitro* activities are approximately parallel with the potency of these compounds in the carrageenin foot-edema assay.

The specificity of the prostaglandin synthetase assay was further demonstrated by the findings that slow-acting antirheumatic drugs, D-penicillamine and chloroquine, and many other drugs such as benemid, disodium cromoglycate, glyvenol, colchicine, *etc.*, are inactive at 10 μg/ml or higher.

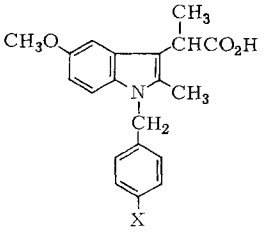
Of particular interest is the observation that the high degree of stereospecificity for the anti-inflammatory action of several pairs of α-methylarylacetic acids *in vivo* (see below) is also true for their inhibitory effect upon prostaglandin synthetase. In all cases examined, *e.g.*, *(3)*, *(4)*, and *(11)*, the dextrorotatory enantiomers are much more potent than the levorotatory ones. To our knowledge this is the first stereospecific correlation between an *in vitro* enzymatic effect and the *in vivo* activity of anti-inflammatory arylacetic acids.

The ability of nonsteroidal anti-inflammatory agents to inhibit prostaglandin biosynthesis has many implications[167]. The central issue seems to be the selective effects of these agents upon different tissues. Drug localization, sensitivity of various prostaglandin synthetases and the changing ratio of prostaglandins E and F may explain the safety and the primary actions of these agents *in vivo*. A better understanding of the basis for tissue specificity is also essential for the broader application of compounds related to these types of structures to other prostaglandin-mediated problems such as asthma, cholera, fertility control[168], *etc.*

[*] Fenamates is the name given to compounds such as mefenamic acid and flufenamic acid.

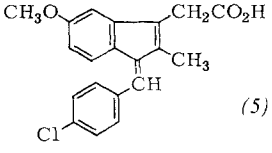
2.3. Indomethacin Analogs

In our study of indole derivatives, two dextrorotatory *N*-*p*-substituted α-(1-benzyl-5-methoxy-2-methyl-3-indolyl)propionic acids *(3)* and *(4)* were first investigated as clinical candidates. The demonstration of their clinical



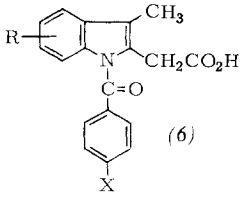
(3), X = Cl
(4), X = SCH_3
(4a), X = OCH_3

efficacy in man, albeit accompanied by gastrointestinal irritation at 1—2.5 g daily doses, established a reassuring correlation of their animal activity with clinical efficacy. Further study in this series led to the discovery of a more potent analog, indomethacin *(1)*[14]. Subsequently, the 5-dimethylamino analog *(2)*[65] and an indene isoster *(5)*[66] were found to be 1/3—1/2 as potent as indomethacin in animal assays, but with somewhat different metabolic and distribution characteristics[67,68]. Both analogs showed efficacy in clinical tests, but were less well tolerated. Other congeners of indomethacin are still under investigation.

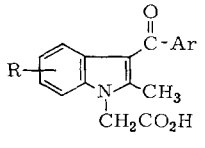


(5)

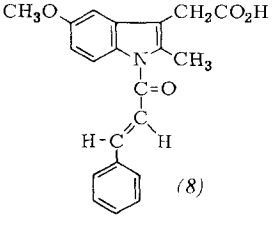
Meanwhile several analogs [*(6)*, *(7)*, *(8)*, and *(9)*] have been investigated by other laboratories. A position isomer *(6)* is described in a patent taken out by Geigy[69] and in some recent reviews, but no testing data are available. According to our previous studies some substituted indole-2-acetic acids appeared to be metastable and readily underwent thermal decarboxylation[70]. Another group of position isomers, the 3-aroyl-1-acetic acids *(7)*, was studied by us and independently at the firms Roussel[71], Geigy[72] and others. In general, they are less potent than analogs in the indomethacin series.



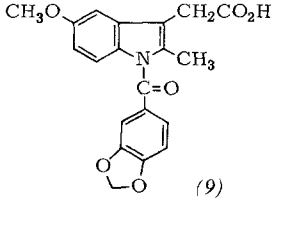
(6)



(7)



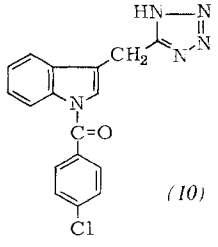
(8)



(9)

The Sumitomo laboratory in Japan has been very active in developing novel chemical processes for making indoles as well as in searching for newer analogs. The cinnamoyl analog *(8)* has a potency one-sixth that of indomethacin in the carrageenin edema assay and one third in some other assays[73]. The pharmacology of another Sumitomo compound, ID-955 *(9)*, the piperonylic acid analog, has also been described in detail[74]. It is about one-third as active as compound *(8)*.

The Bristol analog, Intrazole (BL-R 743) *(10)*, has a potency of 1/15—1/20th that of indomethacin[75]. Interestingly, the replacement of carboxyl by an acidic tetrazole moiety ($pK_a = 6$) circumvents the metabolic formation of



(10)

acyl glucuronide and thus prolongs its serum half-life[76]. Intrazole does not have the 2-methyl and 5-methoxy substituents which were found to be activity-enhancing in investigations of the indomethacin series. Intrazole appeared to be less irritating in the clinic but its overall assessment probably was less promising than expected.

The continued interest in developing new indomethacin analogs is presumably based on the assumption that better-tolerated, even though less potent, derivatives should have clinical utility. This is an attractive approach but is complicated by the poor correlation of animal data with clinical efficacy and by the uncertainty of relating acute animal toxicity to long-term safety in man. The ED_{50}[*] of indomethacin is 2.5 mg/kg in the carrageenin foot-edema assay but only 0.5 mg/kg in the adjuvant arthritis assay. In man, the average daily dose is about 1—1.5 mg/kg. Although indomethacin is 20—80 times more potent than phenylbutazone in the above two assays, in the clinic its potency advantage is only 3—4-fold.

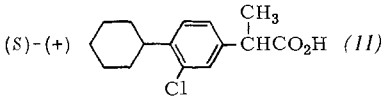
We have demonstrated previously that the toxicity and, to some extent, the metabolism of indomethacin are highly species specific[67]. In the selection of a new drug candidate any derivative which is less potent in animals but has higher plasma and tissue levels or other improved pharmacodynamic properties in man, may indeed be more effective in the clinic. However, the same metabolic differences may render its long-term tolerance in man even less predictable from toxic data of small animals. A remarkable instance of

[*] ED_{50} = Dosage required to produce 50% response in the animal assay.

species difference in tissue accumulation and the resulting chronic toxicity was described recently with metazamide[7]. (See Section 5.1.)

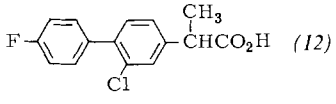
2.4. Phenyl Aliphatic Carboxylic Acids

Among many active phenylacetic acids, the most potent compound is probably (*S*)-(+)-3-chloro-4-cyclohexyl-α-methylphenyl acetic acid *(11)* with a potency of 20 times that of indomethacin in the carrageenin foot-edema assay[77,78]. Unfortunately, further development of *(11)*

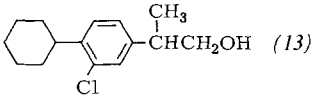


(11)

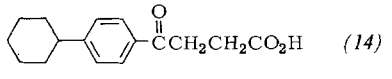
was discouraged by its narrow therapeutic ratio with respect to gastrointestinal irritation and renal papillary necrosis. No significant therapeutic advantage was obtained by replacing the cyclohexyl ring with 4'-fluorophenyl *(12)* or by reducing the acid *(11)* to its alcohol derivative



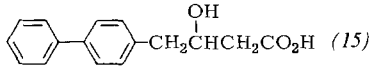
(12)



(13)[78]. Promising anti-inflammatory activities were also demonstrated by phenylbutyric acid derivatives such as *(14)*[78] and *(15)* (BDH 7538)[79,80] but no clinical data are available.



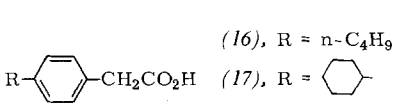
(14)



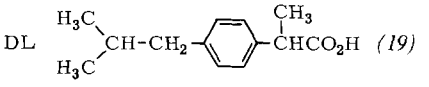
(15)

2.5. Development of Ibuprofen

The development of ibuprofen *(19)* (Brufen®) by Boots' laboratories dates back to their initial interest in *p*-alkylphenoxyacetic acids 15 years ago[13]. A total of 600 compounds have been examined. A notable feature in the Boots' study is their persistent attitude, undoubtedly for good reasons, in testing a series of candidates in the clinic. It was stated that[81] the first candidate, *p*-butylphenylacetic acid *(16)*, produced skin-rash in 50% of patients receiving doses of 2 g/day; the *p*-cyclohexyl analog *(17)* exhibited the same effect. Ibufenac *(18)* did not produce skin-rash and seemed less irritating to the G. I. tract than aspirin, but its clinical application was terminated by hepatotoxicity such as SGOT[*] elevation at high doses[82]. Finally, the α-methyl analog, ibuprofen *(19)*[83], was successfully developed as a mild and well tolerated antiarthritic agent at a daily dose of 0.8—1.6 g[84,85]. It is currently under evaluation by Upjohn laboratories in the U.S. (Further comments on ibuprofen's being a racemic mixture are included in Section 3.)



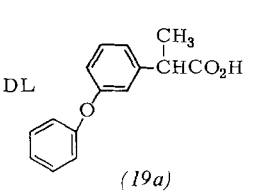
(16), R = n-C_4H_9
(17), R =
(18), R = i-C_4H_9



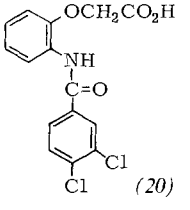
(19)

Fenoprofen[85a], DL-α-(3-phenoxyphenyl)propionic acid *(19a)*, is a *m*-substituted analog developed by the Lilly group. It is highly potent in the UV erythema assay in guinea pigs (ED_{50} = 0.5—1.0 mg/kg) but much less active in the rat foot-edema assay (ED_{50} ~ 50 mg/kg) and in febrile rats (at 25 mg/kg). The analgesic effect of (+)-propoxyphene was reported to be potentiated by fenoprofen and also by several other anti-inflammatory acids. The major metabolic conversion of *(19a)* is hydroxylation at the 4'-position. Its clinical trial is in progress.

An *o*-substituted phenoxyacetic acid with structure features resembling an open-chain analog of indomethacin is clamidoxic acid *(20)*[16].



(19a)



(20)

It is equivalent to phenylbutazone in acute anti-inflammatory assays and is now undergoing clinical evaluation.

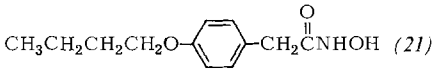
2.6. Bufexamac and Alclofenac

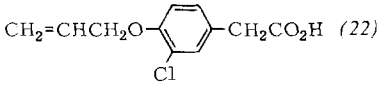
A generally assumed requirement for nonsteroid anti-inflammatory agents is that their mode of action should not be mediated by pituitary-adrenal stimulation and the release of endogenous cortico hormones. Whether a moderate degree of stimulation should always be avoided is controversial among some investigators. The hydroxamic derivative of *p*-butoxyphenylacetic acid, bufexamac *(21)* (Droxary®), represents such an example. Its anti-inflammatory effect in animals is, at least in part, attributable

[*] SGOT = Serum Glutamo-oxaloacetic Transaminase.

to adrenal stimulation[86]. In rheumatic patients it is used at a dose rate of 4 × 250 mg during the day and a 1 g suppository overnight[87]. Unlike most aryl acids it significantly decreases the abnormal sedimentation rate of erythrocyte in arthritic patients. It would be of interest to ascertain the long-term tolerance of this drug. The free acid of bufexamac is very weakly active in animal assays.

In our study of phenylacetic acids, a *m*-chloro substituent was found to be activity-enhancing[78]. In addition to the example of *(11)*, the 3-chloro derivatives of 4-isobutyl- and 4-cyclohexyl-phenylacetic acid are also more potent than their parent compounds. By combination of the 3-chloro- with the 4-allyloxy-substituents, *Buu-Hoi et al.* obtained alclofenac *(22)* (Mervan®)[88]. A marked species difference in the metabolism and toxicity was again demonstrated by


(21)

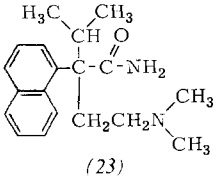

(22)

alclofenac[89]. Its LD_{50} is only 45 mg/kg in rats but 300 to 500 mg/kg in dogs and monkeys. The blood level, metabolism, and routes of excretion, *e. g.* urinary *vs.* biliary, also vary drastically with species. Compared with the metabolism of 4-alkylphenylacetic acids the presence of a *p*-allyloxy group apparently favors urinary excretion. Indications are that the allyloxy group is an active metabolic site leading to the formation of several metabolites.

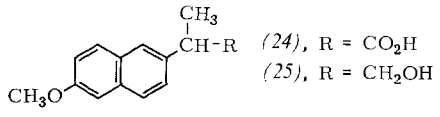
The activity of alclofenac is comparable to phenylbutazone in acute inflammatory assays[88]. However, in osteoarthritic patients it was used at 1.5 g to 3 g daily to match the efficacy of 300 mg phenylbutazone[90, 91]. The higher dosage required may be attributed to its low plasma level and short half-life in man.

2.7. Naphthylacetic Acid Derivatives

An α,α-disubstituted α-naphthylacetamide, naphthypramide *(23)* (DA-992), has been introduced as a mild analgesic anti-inflammatory agent with moderate muscle-relaxant activity as a useful adjunct[92, 93].


(23)

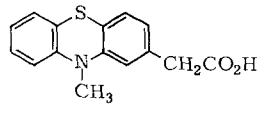
More recently (+)-α-(6-methoxy-2-naphthyl)propionic acid *(24)* (Naproxen) and its (−)-ethanol analog *(25)* (Naproxol) were found by the Syntex group to be potent


(24), R = CO_2H
(25), R = CH_2OH

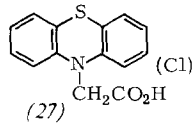
anti-inflammatory agents[94, 95]. Naproxen possesses an anti-edema activity of *ca.* 1/3 that of indomethacin with similar G. I. irritation properties. Both *(24)* and *(25)* were reported to be in clinical trial.

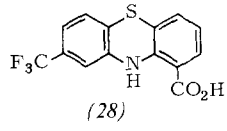
2.8. Metiazinic Acid

Considering phenothiazine as a fused-ring aromatic moiety, its acetic acid derivative, metiazinic acid *(26)* (Soripal®) was found by the Rhône-Poulenc group to be a clinically


(26)

useful drug[96]. Several years ago, in order to compare the optimal aryl moieties in CNS and antihistamine drugs with those in anti-inflammatory agents, we investigated a number of phenothiazinyl-*N*-carboxylic acids *(27)* and were discouraged by their weak anti-inflammatory activities. In


(27)


(28)

investigations by the Rhône-Poulenc's group, metiazinic acid was one of the first members of this series to be synthesized; the anti-inflammatory activity was not improved by the evaluation of some 300 analogs. It was tested in 6000 clinical cases over a period of 5 years. The daily doses were 3—6 capsules, each of 250 mg; several minor side-effects were observed[97, 98].

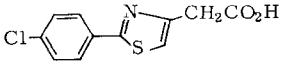
One may recall that the phenothiazine analog of flufenamic acid *(28)* was investigated by Smith, Kline and French a few years ago, but no clinical findings were reported[99].

2.9. Fenclozic Acid and Related Compounds

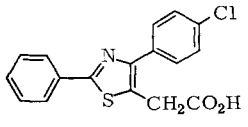
A less fortunate venture in the field of heteroarylacetic acids was I.C.I.'s fenclozic acid *(29)* (Myalex®)[100, 101]. Fenclozic acid showed early promise as a moderately active compound with a wide-range of tolerance. In short-term assays, such as the carrageenin foot-edema assay, fenclozic acid is comparable to phenylbutazone with an ED_{50} of *ca.* 90 mg/kg. It is four times more effective than phenylbutazone in the adjuvant arthritis assay, both against developing and established arthritis. In rats it was well tolerated at 70 mg/kg for 3 months. A species difference in serum half-life, in favor of man, was also noticed. In fact,

the half-life turned out to be longest in rheumatoid arthritis patients (46 hrs), almost twice that in normal volunteers[102,103]. It was excreted in the urine mainly as unchanged drug or ester conjugates. The clinical efficacy of 300—400 mg of fenclozic acid was comparable to 3.6 g aspirin[104]. However, further development of this drug was terminated by the occurrence of hepatotoxicity[105]. I.C.I.'s workers[106] found that the corresponding oxazole, isoxazole, pyridine, and pyrimidine analogs are less active.

It is of interest to note that the potency of fenclozic acid, on a weight basis, is higher in man than in animals. It is comparable to other arylacetic acids, *e.g.* ibuprofen, metiazinic acid and alclofenac, in animals, yet its effective clinical dose is only 1/4—1/5 times the others. Perhaps it is the pharmacodynamic advantage of fenclozic acid which enhances its potency and, unfortunately at the same time, toxicity in man.



(29)



(30)

A related compound [2-phenyl-4-(*p*-chlorophenyl)-5-thiazolyl]acetic acid *(30)* is undergoing clinical study by the Wyeth group in England[107].

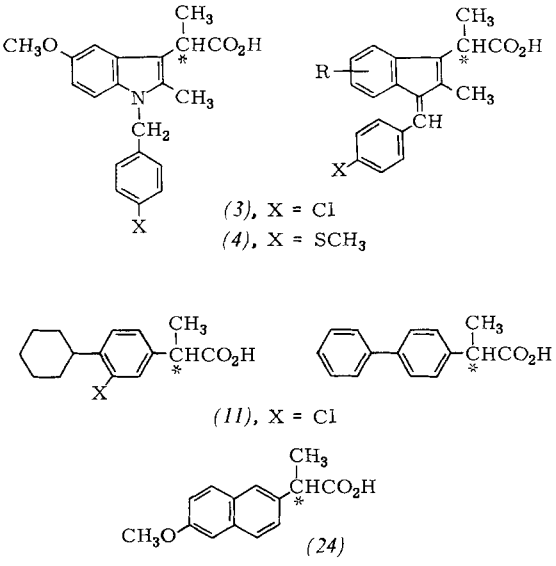
3. Stereospecificity of Arylacetic Acids

Generally speaking, arylacetic acids constitute a broad anti-inflammatory lead. As we have seen, moderate to good activities are readily found with many combinations of heteroaryl and substituted phenyl groups bearing an acetic acid side-chain. A partial dissociation of activity and toxicity, in terms of its tolerance in man, has been achieved by the fortuitous selection of some aryl moieties.

The object of the game is to find less toxic aryl moieties, but unfortunately not enough data are available to guide a rational approach. The preferred geometry of the aryl groups, their interaction with aromatic amino acids, such as tryptophan and tyrosine, in albumin or membrane proteins, their metabolic stability, their distribution and excretion characteristics *etc.*, have been examined as possible factors. During the past few years we have looked into some properties of the acetic acid side-chain, which is a constant feature of all arylacetic acids, particularly the stereochemistry of the α-methyl group.

3.1. Potency Correlation

In several series the activity of an arylacetic acid is enhanced several-fold by the introduction of an α-methyl group. In most cases, the dextrorotatory isomer, with (*S*) configuration, seems to possess higher, if not exclusive, activity *in vivo*[2]. A recent example is Naproxen *(24)* (see Scheme 1).



(3), X = Cl
(4), X = SCH_3

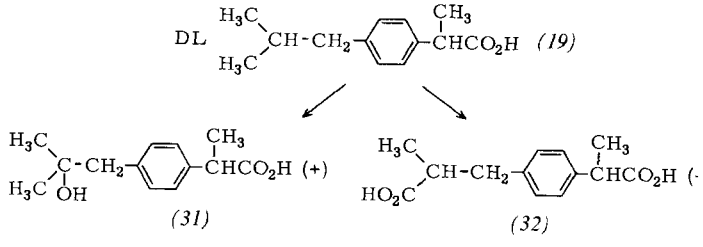
(11), X = Cl

(24)

Scheme 1. Examples of (*S*)-(+) isomers with higher activity than (*R*)-(−) isomers.

3.2. Preferential Metabolism

In the case of ibuprofen *(19)*, Boots' use the DL mixture; presumably similar activity was found with both optical isomers[83]. Interestingly, a partial analysis of the metabolic mixture showed that only dextrorotatory metabolites had been formed[108]. In metabolite *(31)* the only asymmetric center is present in the acetic acid side-chain. α-Alkylphenyl acetic acid generally gives a plain positive



(19)

(31) *(32)*

Scheme 2. Preferential metabolism of a racemic mixture of iboprufen.

ORD curve[109]. As the sign of rotation is not much affected by *p*-alkyl substitutions, one may assume that this metabolite has the same (*S*)-(+) configuration as the compounds in Scheme 1. With metabolite *(32)* assignment of absolute configuration is complicated by the presence of the second asymmetrical center in the molecule. The stereoselective metabolism of a racemic mixture has been observed in other cases[110]. Further characterization of metabolite *(32)* may shed some light on the specificity of side-chain oxidation of arylacetic acids.

3.3. Biochemical Comparisons

In order to see whether the observed difference in *in vivo* activity of optical enantiomers is really attributable to selective "receptor site" binding, their activities in several

in vitro biochemical systems were examined. With several pairs of substituted indolyl- and phenyl-α-methylacetic acids, no significant difference was observed in erythrocyte membrane stabilization[110], protein denaturation, and uncoupling of oxidative phosphorylation[112]. Both isomers showed inhibitor activity at 10^{-4}—10^{-5} mol/l, roughly parallel with the *in vivo* potency of the dextrorotatory enantiomer. So far, the only demonstration of stereospecificity is the inhibition of prostaglandin synthetase by dextrorotatory enantiomers (see Section 2.2).

3.4. Serum Albumin Binding

Most arylacetic acids have strong affinity for serum proteins, a property which has obvious pharmacodynamic, or even mechanistic, implications. We recently became interested in using the induced Cotton effect to study drug biopolymer interactions. Cotton effect denotes the anomalous change of optical rotation at the wavelength corresponding to the UV maximum of an asymmetrical molecule. A drug such as phenylbutazone is not asymmetric and shows no optical rotation. However,—as aptly described by *Chignall*[113,114]—when phenylbutazone is bound to serum albumin, the interaction between the ligand chromophore and an asymmetric locus at the binding site perturbs the chromophore in an asymmetric manner and induces optical activity. The rotatory dispersion curve of the mixture shows a Cotton effect near the UV maximum of phenylbutazone, this is referred to as an induced, or extrinsic, Cotton effect.

Chignall investigated the comparative binding of phenylbutazone analogs[114] and flufenamic acid analogs[40]. Each group shows three strong binding sites on human serum albumin. The molar ellipticities of drug-albumin complexes are enhanced by hydrophobic interactions and by rigidity of the complex. The change in ellipticity also provides a rapid method for estimating association constants[115]. The binding of drugs such as dicoumarol and warfarin to serum albumin quenches the native tryptophan fluorescence of the protein. The light energy absorbed by the tryptophan groups and nonradioactively transferred to bound warfarin is re-emitted by the drug as fluorescent light. The mean effective transfer distance between the two groups estimated in this way gives an indication of the receptor site structure[116].

Hypothetical "receptor sites" derived from structure activity relationships have often been postulated as working models by medicinal chemists. Until a real receptor site is actually isolated, as in the case of estradiol[117], or possibly, corticosteroids[118], the significance of postulated receptor contours can only be measured by their usefulness in suggesting new and active structure equivalents. For a drug like indomethacin, which possibly executes a multitude of primary actions, one would assume that the optimal structural features are the best fit for several similar but nonidentical binding sites. Since strong serum protein binding is a common characteristic for nonsteroid anti-inflammatory aryl acids, one might use serum albumin as a model to probe the "receptor site" interaction; thrombocyte and erythrocyte membrane preparations[119,120] may serve as other models.

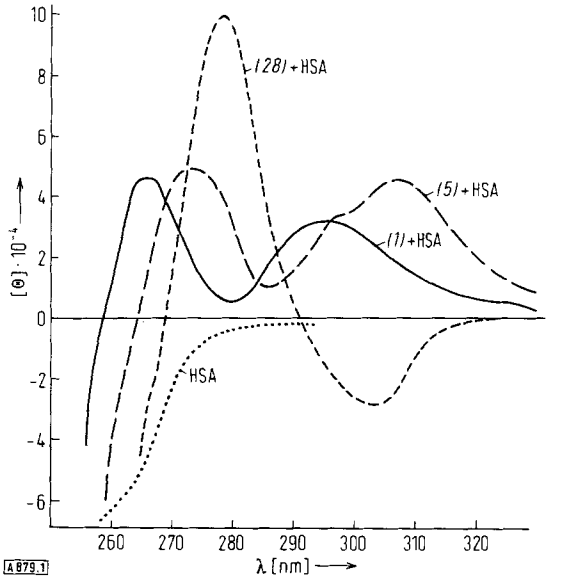


Fig. 1. CD spectra of indomethacin *(1)*, its indene isoster *(5)*, and flufenaminic acid *(28)* in the presence of human serum albumin; HSA = serum albumin alone (phosphate buffer pH 7.4).

Phenylacetic acid derivatives do not produce significant extrinsic Cotton effects in the presence of human serum albumin. The circular dichroic spectra of indomethacin and its indene analog are shown in Fig. 1[121]. The optical activities are in general less pronounced than that produced by flufenamic acid. We are particularly interested in the binding of their α-methyl analogs which have an asymmetric acid side-chain. As mentioned above the stereospecificity of the α-methyl side-chain in *in vivo* activity was not found in a number of *in vitro* assays. If albumin binding involves the acetic acid side-chain in a stereospecific manner one might detect the difference in binding in the circular dichroic spectra of those optical enantiomers. As shown in Fig. 2, the spectra of HSA plus an optical isomer do indeed vary according to the configuration of the α-carbon atom. The difference spectra in Fig. 3 seem to suggest two distinctive groups of binders. The influence of *p*-substituents

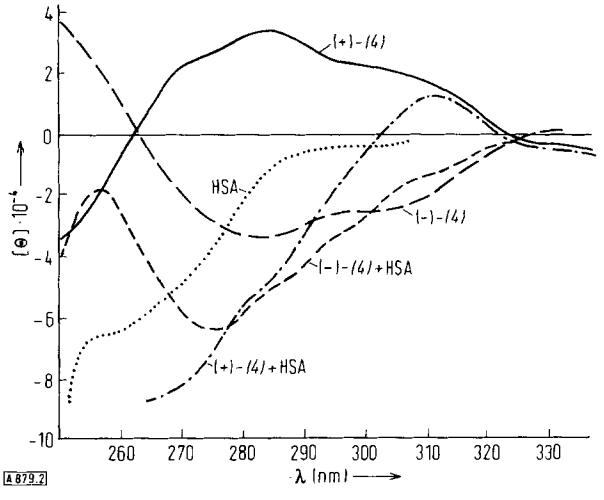


Fig. 2. CD spectra of the enantiomers of α-[1-(*p*-methylthiobenzyl)-5-methoxy-2-methyl-3-indolyl]propionic acid *(4)* with and without addition of human serum albumin (HSA).

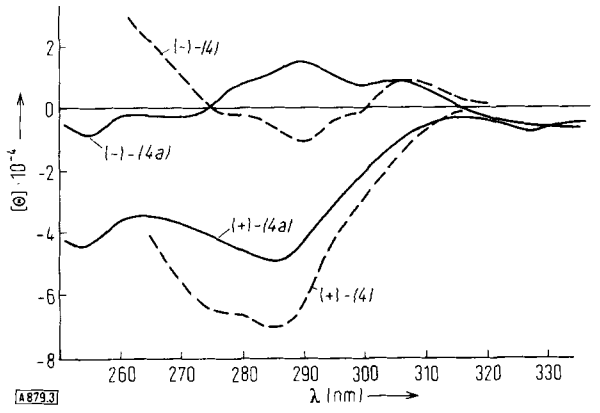


Fig. 3. Difference CD spectra of the enantiomers of α-[1-(*p*-methylthiobenzyl)-5-methoxy-2-methyl-3-indolyl]propionic acid *(4)* and the *p*-methoxy derivative *(4a)* with and without addition of human serum albumin (HSA): [Observed (compound + HSA)] — (spectrum of compound) — (spectrum of HSA).

on binding is also observable. As the theoretical implications of an asymmetric side-chain on the extrinsic Cotton effect of a chromophore have not been analyzed, more detailed interpretation of these spectra was not attempted. Further investigations to elucidate the number of binding sites for each group of enantiomers and the competition of common binding sites between enantiomers and among different analogs are in progress. The sensitivity of this technique to steric and electronic environment and the small amount of sample required provide us with a valuable tool for studying drug-biopolymer interaction in solution.

4. New Salicylate Derivatives

4.1. Objectives and Structure-Activity Relationship

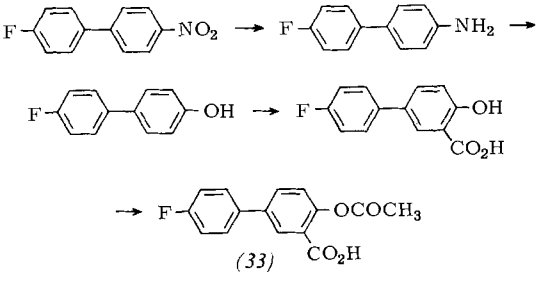
The search for a novel salicylate analog as a superior anti-arthritic drug has been an attractive yet highly elusive goal for many years. In general, the objectives are three-fold: (i) to increase potency, (ii) to reduce gastric irritation, and (iii) to provide a longer duration of action. While various sustained-release and antiacid formulations of aspirin have been developed in recent years to improve the last two properties, no single chemical derivative of salicylate has been uncovered as a superior aspirin analog. In our broad-based research on nonsteroidal anti-inflammatory agents a determined effort was launched several years ago to evaluate a large number of substituted salicylic acid derivatives by the granuloma-pellet and carrageenin foot-edema assays, both of which seemed to be responsive to the anti-inflammatory activity of nonsteroidal drugs such as phenylbutazone, indomethacin, and other experimental agents.

The structure-activity relationships established by previous studies of salicylates[13] have shown that replacement of the *O*-acetyl group by other acyl or alkyl groups and derivatization of the carboxyl group, although beneficial in certain aspects, are generally detrimental to the overall anti-inflammatory-analgesic-antipyretic profile of aspirin. Ring-substitution of salicyclic acid with chloro, hydroxy, methoxy, amino, alkyl groups *etc.*, either diminished activity or increased both potency and toxicity in a nonspecific manner. Similar conclusions were readily verified in our assays with more than 300 salicylates including many newly synthesized analogs.

With salicylates, the establishment of a definitive structure-activity relationship was complicated by the low order of activity of many analogs which were very sensitive to biological variations, and by the apparent lack of additive effects of different activity-enhancing groups. Obviously, with a small molecule like salicylic acid the overall physicochemical and metabolic properties become easily influenced by multiple substitutions. Advantages sometimes occurred in the case of *O*-acetylation of less hydrophobic salicylic analogs, presumably due to an improvement of absorption or distribution. Perhaps more significant was the apparent trend of hydrophobic substitutions, *e.g.* phenyl, 4'-chlorophenyl, and benzyloxy, at the 5-position to enhance the activity of salicylic acid. Interestingly, similar preference of 5-alkyl[122] and 5-halo[123] substituents was recently observed in the inhibition of several enzyme systems by salicylic acid derivatives.

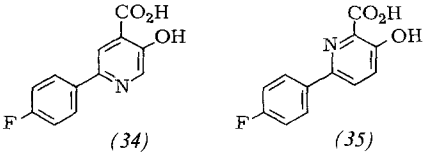
4.2. Synthesis of Flufenisal

The activity-enhancing effect of a *p*-fluorophenyl group in anti-inflammatory agents was well demonstrated by the potency of *p*-fluorophenylpyrazolo[3,2-*c*] steroids[124] and α-(4'-fluorobiphenyl)propionic acid *(12)* which were studied previously in our Laboratories. The 5-(4-fluorophenyl) derivative of aspirin, flufenisal *(33)*, was synthesized as shown in Scheme 3[125]:



Scheme 3. Synthesis of flufenisal *(33)*.

Other aryl and heteroaryl analogs substituted in position 5[126] as well as two aza isosters of flufenisal *(34)* and *(35)*[127] were also investigated.



4.3. Biological Properties of Flufenisal

Compared to aspirin, flufenisal *(33)* is 4—5 times more potent in the carrageenin foot-edema and cotton pellet

granuloma assays. In acute gastric hemorrhage test in the rat the ED_{50} for flufenisal was *ca.* 200 mg/kg, almost 15 times the ED_{50} of 14 mg/kg for aspirin. Its analgesia in the yeast-induced hyperesthesia assay was estimated as twice that of aspirin during the first 2—3 hours; but more interestingly, the duration of effect was much longer. Flufenisal is present in the plasma as its deacetyl derivative which is 98—99.5% bound to the plasma protein in equilibrium dialysis experiments. It produces a higher and more prolonged plasma level than aspirin in rats and in dogs. The longer duration of analgesic action has been confirmed in the clinic[128]. Single doses of 300 or 600 mg of flufenisal appeared equal in effectiveness to 600—1200 mg of aspirin in relieving episiotomy pain; further, the duration of action was double that of aspirin.

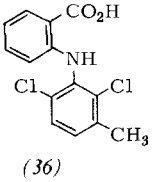
Aspirin has a spectrum of side-effects which are widely recognized but also accepted as reasonable risks by clinicians and patients alike[129]. An up-to-date pharmacological analysis of aspirin summarized its many actions in terms of depression of defensive reactions[130]. Some subtle biological properties, such as potential renal papillary necrosis[131] and *in vivo* acetylation of platelet membrane[132] and serum proteins, have attracted a certain amount of attention. The need to re-evaluate the safety of aspirin has also been suggested[129].

The difficulty in quantifying the anti-inflammatory effect of nonsteroids and aspirin-like compounds has been well documented in recent clinical literature. To improve the time-honored aspirin therapy by a new derivative may well require large-scale and long-term comparative studies. Nevertheless, with flufenisal we have both the encouragement and a new direction for further exploitation of this grand old lead in the arthritis field.

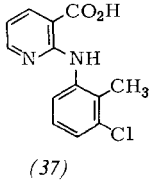
5. Other Chemical Compounds

5.1. Anti-inflammatory Agents

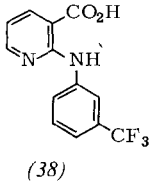
Several members of the fenamate family (mefenamic acid, flufenamic acid), such as meclofenamic acid *(36)* and Sch 10304 *(37)*, are still under clinical evaluation. The propensity of *N*-arylanthranilic acids to produce papillary necrosis in animals has been noted recently[133]. In clinical use, the aza analog of flufenaminic acid, Nifluril *(38)*, seems to be more irritating to the gastrointestinal tract than fenamates.



(36)

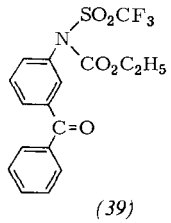


(37)

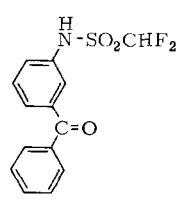


(38)

Two benzophenone derivatives[134], triflumidate *(39)* and diflumidone *(40)* bearing certain structural resemblance to fenamates, showed some promise as effective but less irritating anti-inflammatory agents. The fluorinated methanesulfonylamino groups constituted novel variations of the carboxy group in anti-inflammatory aryl acids.

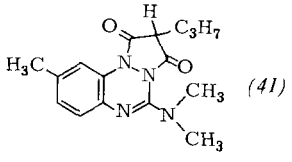


(39)



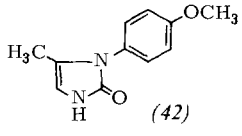
(40)

A new antiarthritic drug with a partial structure of phenylbutazone (or generally of 3,5-dioxopyrazolidines) is the azapropazon (MI 85, Apazone®) *(41)*[135]. This compound is generally comparable to phenylbutazone but is more active in the UV erythema assay. The daily dose for man is 0.6—1.2 g, *i.e.* about 2—4 times that for phenylbutazone[136].

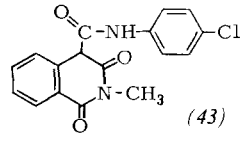


(41)

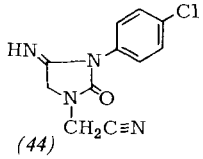
Several aryl lactam derivatives, *e.g.* metazamide *(42)*[6,137], tesikam *(43)*[138,139], nimazone *(44)*[140], and substituted pyridones *(45)*[141], showed activity in animals, apparently



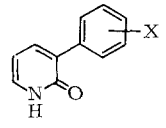
(42)



(43)



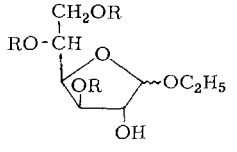
(44)



(45)

with activity-profiles different from aryl acids; however, their further development was curtailed by unexpected toxicities encountered in the clinic or in animals.

A novel carbohydrate derivative, tribenoside (Glyvenol®, Ciba 21401-Ba) *(46)*, was reported to be antiallergic, antiexudative, and capable of inhibiting antigen-antibody



(46), R = $CH_2C_6H_5$

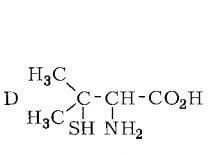
reaction and capillary stabilization[142]. It was not very effective in the treatment of rheumatoid arthritis patients[143].

5.2. Antirheumatic Agents

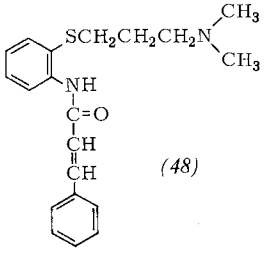
Some renewed interest in D-penicillamine *(47)*[144-147] and gold therapy has been noted among rheumatologists

in Europe and in the USA. Both agents have a slow onset, but sustained objective improvements in rheumatic patients are often observed after 3—6 months' treatment. Their clinical application is still somewhat limited by various side effects. Unfortunately, no animal assay is available to aid the development of a superior agent with similar clinical efficacy. The mode of action of D-penicillamine remains speculative. There is not enough evidence to decide whether any of its biochemical properties considered previously, *e.g.* increase of tissue sulfhydryl groups[148], dissociation of macroglobulins[149], metal chelation, pyridoxine antagonism, and inhibition of collagen biosynthesis, play a major role in its antirheumatic action[144].

Immunosuppressants, such as cytoxan[150] and imuran, have been used effectively in severe cases of rheumatoid arthritis, but with anticipated toxicities. The possible application of the less cytotoxic cinanserin *(48)*[151] was precluded by its hepatotoxicity. Contrary to the general



(47)



(48)

assumption, no direct correlation could be made between the clinical efficacy of cyclophosphamide and its depression of several immunological parameters such as rheumatoid factor, serum immunoglobulins, and *in vitro* lymphocyte response *etc.*[152]. The activity of immunosuppressive agents may be enhanced if potential antibody-forming cells are first stimulated by antigen. When administered with antigen the drug suppresses both the primary response and immunological memory. Specific tolerance induced in this way may last for several months[153]. It would be of great interest if the autoimmune component in rheumatoid arthritis could be suppressed by a similar strategy.

Recent interests in the immunological aspects of rheumatoid arthritis have focused attention on abnormal immunoglobulins, complement fixation, degradative enzymes, mediators of delayed hypersensitivity, and deranged metabolic activities of synovial cells in arthritic joints[3]. The current fervor in immunological research may suggest additional approaches to curtail the pathogenesis process of arthritis. Undoubtedly, a new series of non-cytotoxic and narrow-spectrum inhibitors or immunoregulants should emerge from many laboratories in the years to come. Their clinical applications, either alone or in conjunction with conventional anti-inflammatory therapy, may bring forth a new era of antirheumatic treatment.

6. Drug Combinations and Interactions

As indicated above, a major concern in the current search for new antiarthritic drugs is to minimize their side effects. The clinical efficacy of some drugs may be limited not by their intrinsic activity but by their low ceiling of tolerable dosage. A logical approach to circumvent the side effects commonly associated with broad-spectrum nonspecific anti-inflammatory drugs would be the development of a group of narrow-spectrum agents, each acting specifically at one of the many facets of the complex inflammatory process, such as lysosomal enzymes, inflammation mediators, *etc.* A "cocktail" mixture comprising several such inhibitors has been suggested as an ultimate treatment[154]. This futuristic approach of combination therapy is worthy of consideration as we become more proficient in delineating the pathogenesis of various arthritic disorders and in prescribing the optimal combination for individual cases. On the other hand, many adverse problems associated with drug interactions must be very carefully investigated. Perhaps a case in point is the growing awareness of the possible interaction between aspirin and other nonsteroid anti-inflammatory agents. Salicylate is often used concurrently with other drugs in the therapy of arthritis, either by design or unintentionally. In two independent animal studies[155, 156] no cumulative anti-inflammatory effect was observed with combinations of salicylate and other agents. A dramatic antagonism was observed in certain adjuvant arthritis protocol[156], the inhibitor actions of indomethacin, phenylbutazone, and others were markedly diminished by low doses of aspirin given in combination. The mechanism of this antagonism is not clear, although it is reminiscent of the observation that the anticoagulant effect of warfarin is potentiated by aspirin or phenylbutazone through interference with serum protein binding of warfarin[157, 158]. A profound influence of salicylate, but not phenylbutazone, on the metabolism distribution and excretion of indomethacin by rats has recently been demonstrated[159]. Possible factors involved are inhibition of intestinal absorption, alteration of tissue deposition, competitive glucuronide conjugation, and serum protein binding. Whether these laboratory observations are also true in the clinic remains to be verified.

7. Conclusion

In conclusion, the extensive chemical efforts on arylacetic acids, fenamates, and salicylates in recent years have gradually produced a small group of "second generation" clinical candidates of the usual anti-inflammatory-analgesic-antipyretic category. Nevertheless, better tolerated and more effective agents of this type are still needed. Progress towards the elucidation of mechanisms of action of known drugs and the understanding of their potential side effects, such as gastrointestinal irritation, hepatotoxicity, and papillary necrosis, should help in the selection of a safer antiarthritic candidate. It would be interesting to see whether some newer types of active structures under study in many laboratories will lead to the discovery of superior drugs having distinct biological profiles. From the pathogenesis point of view, immunological control seems to offer a new direction with many promising possibilities, but further knowledge and more convincing clinical verification of some concepts are still needed to establish a rational approach with a high degree

of selectivity. To regulate the dynamic network of the chronic inflammatory process, advances in membrane chemistry, immunotolerance, and host resistance, may offer fresh perspectives.

Received: December 3, 1971 [A 879 IE]
German version: Angew. Chem. *84*, 512 (1972)

---

[1] Adapted from a presentation at the Gordon Conference on Medicinal Chemistry, New Hampshire (USA), August 1970.

[2] *T. Y. Shen*, Annu. Rep. Med. Chem. *1967*, p. 215.

[3] Nineteenth Rheumatism Review in Arthritis and Rheum. *13*, Sept.-Oct. 1970.

[4] *R. H. Ferguson* and *J. W. Worthington*, Ann. Intern. Med. *73*, 109 (1970).

[5] Brit. Med. J. [4] 601 (1970).

[6] *F. D. Hart*, Practitioner *205*, 597 (1970).

[7] *M. Weiner* and *S. J. Piliero*, Annu. Rev. Pharmacol. *10*, 171 (1970).

[8] *J.-R. Boissier*, *J.-M. Lwoff*, and *F. Hertz*, Therapie *25*, 43 (1970).

[9] *R. Domenjoz*, Z. Rheumaforsch. *28*, Suppl. 1, 343 (1969).

[10] *A. Bertelli* and *J. C. Houck*: Inflammation Biochemistry and Drug Interaction. Williams and Wilkins, Baltimore and Excerpta Medica Foundation, Amsterdam 1969.

[11] *T. Y. Shen*, Annu. Rep. Med. Chem. *1968*, 215.

[12] *K. J. Doebel*, *M. L. Graeme*, *N. Gruenfeld*, *L. J. Iguarro*, *S. J. Piliero*, and *J. W. F. Wasley*, Annu. Rep. Med. Chem. *1969*, 207.

[13] *S. S. Adams* and *R. Cobb*, Progr. Med. Chem. *5*, 59 (1967).

[14] *T. Y. Shen*, *T. B. Windholz*, *A. Rosegay*, *B. E. Witzel*, *A. N. Wilson*, *J. D. Willet*, *W. J. Holtz*, *R. L. Ellis*, *A. R. Matzuk*, *S. L. Lucas*, *C. H. Stammer*, *F. W. Holly*, *L. H. Sarett*, *E. A. Risley*, *G. W. Nuss*, and *C. A. Winter*, J. Amer. Chem. Soc. *85*, 488 (1963).

[15] *C. A. Winter*, Fortschr. Arzneimittelforsch. *10*, 139 (1966).

[16] *D. J. Drain*, *M. J. Daly*, *B. Davy*, *M. Horlington*, *J. G. B. Howes*, *J. M. Scrution*, and *R. A. Selway*, J. Pharm. Pharmacol. *22*, 684 (1970).

[17] *T. Y. Shen*, unpublished observations.

[18] For more recent clinical appraisals see: a) *C. J. Smyth*, Ann. Intern. Med. *72*, 430 (1970); b) *E. C. Huskisson*, *R. T. Taylor*, *D. Burston*, *P. J. Chuter*, and *F. D. Hart*, Ann. Rheum. Dis. *29*, 393 (1970); c) Brit. Med. J. *1970*, No. 5720, p. 449.

[19] *I. F. Skidmore* and *M. W. Whitehouse*, J. Pharm. Pharmacol. *18*, 558 (1966); *A. Bertelli*, Biochem. Pharmacol. Suppl. 229 (1968).

[20] *J. H. Brown* and *S. H. Pollock*, Proc. Soc. Exp. Biol. Med. *135*, 792 (1970).

[21] *K. Fehr*, *J. LoSpalluto*, and *M. Ziff*, J. Immunology *105*, 973 (1970).

[22] *A. J. Anderson*, Biochem. J. *113*, 457 (1969).

[23] *E. D. Harris*, *D. R. DiBona*, and *S. M. Krane*, Clin. Res. *18*, 534 (1970).

[24] *A. Z. Eisen*, *E. A. Bauer*, and *J. J. Jeffrey*, J. Invest. Dermatol. *55*, 359 (1970).

[25] *P. D. Weston*, *A. J. Barrett*, and *J. T. Dingle*, Nature *222*, 285 (1969).

[26] *E. A. Bauer*, *A. Z. Eisen*, and *J. J. Jeffrey*, Biochim. Biophys. Acta *206*, 152 (1970).

[27] *I. F. Skidmore* and *M. W. Whitehouse*, Biochem. Pharmacol. *15*, 1965 (1966).

[28] *A. G. Radwan* and *G. B. West*, Brit. J. Pharmacol. Chemother. *33*, 193 (1968).

[29] *J. J. Petillo*, *A. Gulbenkian*, and *I. I. A. Tabachnick*, Biochem. Pharmacol. *18*, 1784 (1969).

[30] *R. W. Schayer*, Amer. J. Physiol. *198*, 1187 (1960).

[31] *M. I. D. Cawley* and *D. A. Willoughby*, Lancet *1956 II*, 24; *W. G. Spector* and *D. A. Willoughby*: The Pharmacology of Inflammation. Grune and Stratton, New York 1968, p. 81.

[32] *G. E. Davies*, *G. Holman*, *T. P. Johnston*, and *J. J. Lowe*, Brit. J. Pharmacol. Chemother. *28*, 212 (1966).

[33] *C. G. Van Arman* and *R. P. Carlson* in: Bradykinin and Related Kinins. Plenum Press, New York 1970, p. 525.

[34] *K. N. von Kaulla*, Thromb. Diath. Haemorrh. *18*, 301 (1967).

[35] *B. B. Vargaftig*, *E. P. De Miranda*, and *B. Lacoume*, Nature *222*, 883 (1969).

[36] *B. B. Vargaftig* and *N. Dao*, Pharmacol. Res. Commun. *2*, 149 (1970).

[37] *P. J. Piper* and *J. R. Vane*, Nature *223*, 29 (1969).

[38] *M. W. Whitehouse*, Fortschr. Arzneimittelforsch. *8*, 358 (1965).

[39] *H. J. Broehr* and *D. A. Kalbhen*, Arch. Int. Pharmacodyn. Ther. *176*, 380 (1968).

[40] *C. F. Chignell*, Mol. Pharmacol. *5*, 455 (1969).

[41] *D. A. Gerber*, *N. Cohen*, and *R. Giustra*, Biochem. Pharmacol. *16*, 115 (1967); *K. F. Swingle*, *L. W. Jaques*, *T. J. Grant*, and *D. C. Kuam*, *ibid. 19*, 2995 (1970).

[42] *E. M. Sellers* and *J. Koch-Weser*, Clin. Pharmacol. Ther. *11*, 524 (1970).

[43] *G. Müller* and *W. Zollinger* in *R. Heister* and *H. F. Hofmann*: Die Entzündung – Grundlagen und pharmakolische Beeinflussung. Urban und Schwarzenberg, München 1966, p. 376; *C. A. Winter*, Calif. Med. *110*, 175 (1969).

[44] *N. H. Grant*, *H. E. Alburn*, and *C. Kryzanauskas*, Biochem. Pharmacol. *19*, 715 (1970).

[45] *J. H. Brown*, *H. K. Mackey*, and *D. A. Riggilo*, Proc. Soc. Exp. Biol. Med. *125*, 837 (1967); *B. Catanese*, *R. Lisciani*, and *D. Piccinelli*, Biochem. Pharmacol. *18*, 1707 (1969).

[46] *D. A. Kalbhen*, *P. Gelderblom*, and *R. Domenjoz*, Pharmacology *3*, 353 (1970).

[47] *P. Gőrög* and *I. B. Kovács*, J. Pharm. Pharmacol. *22*, 86 (1970).

[48] *J. Peterson* and *M. B. Zucker*, Thromb. Diath. Haemorrh. *23*, 148 (1970).

[49] *J. R. O'Brien*, *W. Finch*, and *E. Clark*, J. Clin. Pathol. *23*, 522 (1970).

[50] *M. B. Zucker* and *J. Peterson*, J. Lab. Clin. Med. *76*, 66 (1970); *M. B. Zucker* and *J. Peterson*, Blood *34*, 536 (1969).

[51] *C. G. Van Arman* and *R. P. Carlson*, personal communication.

[52] *M. Yaron* and *C. W. Castor*, Arthritis Rheum. *12*, 365 (1969).

[53] *P. Phelps*, Arthritis Rheum. *12*, 189 (1969).

[54] *Di Rosa*, *J. M. Papadimitriou*, and *D. A. Willoughby*, unpublished.

[55] *C. G. Van Arman*, *D. L. Bokelman*, *E. A. Risley*, and *G. W. Nuss*, Fed. Proc. *30*, A 386 (1971).

[56] *J. Chayen*, *L. Bitensky*, *R. G. Butcher*, *L. W. Poulter*, and *G. S. Ubhi*, Brit. J. Dermatol. *82*, Suppl. 6, 62 (1970).

[57] *J. Chayen* and *L. Bitensky*, personal communication.

[58] *R. Abraham*, *R. Hendy*, and *P. Grasso*, Exp. Mol. Pathol. *9*, 212 (1968); *R. Abraham* and *R. Hendy*, *ibid. 12*, 148 (1970).

[59] *R. J. Hendy*, *R. Abraham*, and *P. Grasso*, J. Ultrastruct. Res. *29*, 485 (1969).

[60] *D. H. Harford* and *M. J. H. Smith*, J. Pharm. Pharmacol. *22*, 578 (1970); *D. A. Lewis*, *ibid. 22*, 909 (1970).

[61] *K. Tanaka* and *Y. Iizuka*, Biochem. Pharmacol. *17*, 2023 (1968).

[62] *J. Hyttel* and *A. Jørgensen*, Eur. J. Pharmacol. *11*, 383 (1970).

[63] *S. Ruddy* and *K. F. Austen*, Arthritis Rheum. *13*, 713 (1970).

[64] *N. J. Zvaifler*, Arthritis Rheum. *13*, 895 (1970).

[65] *T. Y. Shen*, *B. E. Witzel*, *A. Rosegay*, *R. E. Ellis*, and *L. H. Sarett*, Proceedings 2nd IUPAC Symposium on Pharmaceutical Chemistry, Münster, July 1968.

[66] *T. Y. Shen*, *R. E. Ellis*, *B. E. Witzel*, and *A. R. Matzuk*, Abstr. Pap., 152nd Meeting, Amer. Chem. Soc. New York, Sept. 1966, 3 P; *T. Y. Shen*, Top. Med. Chem. *1*, 48 (1967).

[67] *H. B. Hucker*, *A. G. Zacchei*, *S. V. Cox*, *D. A. Brodie*, and *N. H. Cantwell*, J. Pharmacol. Exp. Ther. *153*, 237 (1966); *D. W. Yesair*, *M. Callahan*, *L. Remington*, and *C. J. Kensler*, Biochem. Pharmacol. *19*, 1579 (1970).

[68] *H. B. Hucker*, *A. Hochberg*, *E. A. Hoffman*, and *B. O. Braunfeld*, Fed. Proc. *27*, 238 (1968).

[69] *K. Fitzi*, *R. Göschke*, and *R. Pfister*, Swiss Pat. 454858 and 455777 (1968), Geigy.

[70] *R. A. Firestone* and *T. Y. Shen*, unpublished observations.

[71] *A. Allais* and *M. Paturet*, French Pat. 5173 M (1967), Roussel-Uclaf.

[72] *K. J. Doebel* and *J. W. F. Wasley*, US-Pat. 3505354 (1970), Geigy.

[73] *H. Yamamoto* and *M. Nakao*, J. Med. Chem. *12*, 176 (1969).

[74] *H. Yamamoto*, *C. Saito*, *T. Okamoto*, *H. Awata*, *T. Inukai*, *A. Hirohashi*, and *Y. Yukawa*, Arzneim.-Forsch. *19*, 981 (1969).

[75] *P. F. Juby* and *T. W. Hudyma*, J. Med. Chem. *12*, 396 (1969).

[76] *J. S. Fleming*, *M. E. Bierwagen*, *M. Losada*, *J. A. L. Campbell*, *J. P. King*, and *M. H. Pindell*, Arch. Int. Pharmacodyn. *186*, 120 (1970).

[77] *T. Y. Shen*, Chim. Ther. 459 (1967).

[78] *C. P. Dorn*, *W. V. Ruyle*, *B. E. Witzel*, and *T. Y. Shen*, unpublished.

[79] *D. I. Barron*, *P. T. Bysouth*, *R. W. Clarke*, *A. R. Copley*, *O. Stephenson*, *D. K. Vallance*, and *A. M. Wild*, J. Med. Chem. *11*, 1139 (1968).

[80] *D. I. Barron*, *A. R. Copley*, and *D. K. Vallance*, Brit. J. Pharmacol. Chemother. *33*, 396 (1968).

[81] *J. S. Nicholson*, Lecture at Nonsteroidal Anti-Inflammatory Drugs Sympos. Chelsea College of Technology, London, Jan. 1970.

[82] *M. Thompson, P. Stephenson*, and *J. S. Percy*, Ann. Rheum. Dis. *23*, 397 (1964).

[83] *S. S. Adams, K. F. McCullough*, and *J. S. Nicholson*, Arch. Int. Pharmacodyn. *178*, 115 (1969).

[84] *M. K. Jasani, W. W. Downie*, and *B. M. Samuels*, Ann. Rheum. Dis. *27*, 457 (1968).

[85] *T. M. Chalmers*, Ann. Rheum. Dis. *28*, 513 (1969).

[85a] *R. C. Nickander, R. J. Kraay*, and *W. S. Marshall*, Fed. Proc. *30*, 563 (1971); *J. A. Miller, Jr.* and *T. A. Bromstrup*, *ibid. 30*, 564 (1971).

[86] *G. Lambelin, N. P. Buu-Hoi, H. Brouilhet, M. Gautier, G. C. Gillet, J. Roba*, and *S. Thiriaux*, Arzneim.-Forsch. *18*, 1404 (1968).

[87] *K. Pavelka* and *F. Wagenhauser*, Curr. Ther. Res. *12*, 69 (1970).

[88] *G. Lambelin, J. Roba, C. Gillet*, and *N. P. Buu-Hoi*, Arzneim.-Forsch. *20*, 610 (1970).

[89] *R. Roncucci, M.-J. Simon, G. Lambelin, C. Gillet, M. Staquet*, and *N. P. Buu-Hoi*, Arzneim.-Forsch. *20*, 569 (1970).

[90] *F. Lambotte*, Arzneim.-Forsch. *20*, 569 (1970); *C. Klemm, R. Fricke, M. Schattenkirschner, W. Treiber*, and *H. Mathies*, Z. Rheumaforsch. *30*, 17 (1971).

[91] *J. Van Hoek*, Curr. Ther. Res. *12*, 551 (1970).

[92] *B. Lumachi, E. Marazzi-Uberti, M. Gaetani*, and *G. Coppi*, Arch. Int. Pharmacodyn. *186*, 66 (1970).

[93] *E. Camarri, D. D'Alonzo*, and *L. Zaccherotti*, Curr. Ther. Res. *12*, 1 (1970).

[94] *I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis*, and *J. H. Fried*, J. Med. Chem. *13*, 203 (1970).

[95] *G. F. Thompson* and *J. M. Collins*, Abstr. 9th Nat. Meeting Amer. Pharm. Assoc. Acad. Pharm. Sci., Washington, D. C., Nov. 1970.

[96] *D. Farge, J. C. Guyonnet, C. Jeanmart*, and *L. Julous*, Arzneim.-Forsch. *19*, 1193 (1969).

[97] *A. M. Recordier, P. Acquaviva, J. Eisinger, D'Omezon*, and *H. Roux*, Marseille Med. *106*, 531 (1969).

[98] *G. Vignon, P. P. Boissel*, and *M. Cibert*, Rev. Rhum. *36*, 715 (1969).

[99] *B. M. Sutton* and *J. H. Birnie*, J. Med. Chem. *9*, 835 (1966).

[100] *W. Hepworth, B. B. Newbould, D. P. Platt*, and *G. J. Stacey*, Nature *221*, 582 (1969).

[101] *B. B. Newbould*, Brit. J. Pharmacol. *35*, 487 (1969).

[102] *T. M. Chalmers, J. E. F. Pohl*, and *D. S. Platt*, Ann. Rheum. Dis. *28*, 590 (1969).

[103] *D. M. Foulkes*, J. Pharmacol. Exp. Ther. *172*, 115 (1970).

[104] *T. M. Chalmers, J. H. Kellgren*, and *D. S. Platt*, Ann. Rheum. Dis. *28*, 595 (1969).

[105] Lancet *1970 I*, 662; *F. Dudley Hart, L. S. Bain, E. C. Huskisson, T. R. Littler*, and *R. T. Taylor*. Ann. Rheum. Dis. *29*, 684 (1970).

[106] *W. Hepworth*, Lecture at Nonsteroidal Anti-Inflammatory Drugs Symposium, Chelsea College of Technology, London, Jan. 1970.

[107] *K. Brown, J. F. Cavalla, D. Green*, and *A. B. Wilson*, Nature *219*, 164 (1968).

[108] *S. S. Adams, E. E. Cliffe, B. Lessel*, and *J. S. Nicholson*, J. Pharm. Sci. *56*, 1686 (1967).

[109] *G. Barth, W. Voelter, H. S. Mocher, E. Bunnenberg*, and *C. Djerassi*, J. Amer. Chem. Soc. *92*, 875 (1970).

[110] *D. R. Galpin, T. G. Cochran*, and *A. C. Huitric*, Biochem. Pharmacol. *18*, 979 (1969).

[111] *M. Hichens*, unpublished.

[112] *J. Peter*, private communication.

[113] *C. F. Chignell*, Life Sci. *7*, 1181 (1968).

[114] *C. F. Chignell*, Mol. Pharmacol. *5*, 244 (1969).

[115] *A. Rosen*, Biochem. Pharmacol. *19*, 2075 (1970).

[116] *C. F. Chignell*, Mol. Pharmacol. *6*, 1 (1970).

[117] *E. V. Jensen, T. Suzuki, T. Kawashima, W. E. Stumpf, P. W. Jungblut*, and *E. R. De Sombre*, Proc. Nat. Acad. Sci. USA *59*, 632 (1968).

[118] *B. P. Schaumburg*, Biochim. Biophys. Acta *214*, 520 (1970).

[119] *A. J. Barber* and *G. A. Jamieson*, J. Biol. Chem. *245*, 6357 (1970).

[120] *A. H. Maddy*, Seminars Hematol. *7*, 275 (1970).

[121] *K. H. Boswell, E. J. Maitheny*, and *T. Y. Shen*, unpublished.

[122] *A. McCoubrey, M. H. Smith*, and *A. C. Lane*, J. Pharm. Pharmacol. *22*, 333 (1970).

[123] *R. Karler, W. C. Petty*, and *T. S. Sulkowski*, Arch. Int. Pharmacodyn. Ther. *173*, 270 (1968).

[124] *J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann*, and *S. L. Steelman*, J. Amer. Chem. Soc. *85*, 236 (1963).

[125] *J. Hannah, W. V. Ruyle, K. Kelly, A. Matzuk, W. J. Holtz, B. E. Witzel, C. A. Winter, R. H. Silber*, and *T. Y. Shen*, Abstr. Pap. Joint Conference Chem. Inst. Canada and Amer. Chem. Soc. May 1970, Toronto, Canada, Medi. 18.

[126] *W. V. Ruyle, H. Jones, M. Fordice*, and *T. Y. Shen*, unpublished.

[127] *G. L. Walford, H. Jones*, and *T. Y. Shen*, J. Med. Chem. *14*, 339 (1971).

[128] *S. S. Bloomfield, T. P. Barden*, and *R. Hille*, Clin. Pharmacol. Ther. *11*, 747 (1970).

[129] *R. S. Farr* and *J. Allergy 45*, 321 (1970).

[130] *H. O. J. Collier*, Advan. Pharmacol. Chemother. *7*, 333 (1969).

[131] *L. F. Prescott*, Scot. Med. J. *14*, 83 (1969); *R. S. Mantra* and *P. Kincaid-Smith*, Brit. Med. J. *1970*, No. 3, p. 559.

[132] Brit. Med. J. *1969*, No. 5667, p. 371; *A. H. Youssef* and *P. Barkhan*, *ibid. 1969*, No. 5667, p. 394.

[133] *T. L. Hardy*, Brit. J. Exp. Pathol. *51*, 348 (1970).

[134] *K. T. McGurran, R. J. Trancik, K. F. Swingle, G. G. I. Moore*, and *J. F. Gerster*, J. Med. Chem. *13*, 137 (1970); *K. F. Swingle, R. R. Hamilton, J. E. Robertson, J. K. Harrington*, and *D. C. Kuam*, Pharmacologist *11*, 266 (1969); *K. F. Swingle, R. R. Hamilton, J. K. Harrington*, and *D. C. Kvam*, Arch. Int. Pharmacodyn. Ther. *189*, 129 (1971).

[135] *U. Jahn* and *R. W. Adrian*, Arzneim.-Forsch. *19*, 36 (1969).

[136] *W. Beckschäfer*, Arzneim.-Forsch. *19*, 52 (1969).

[137] *K. J. Doebel*, Int. Symp. Pharm. Chem., in Pure and Applied Chemistry *19*, 45 (1969).

[138] *S. B. Kadin* and *E. H. Wiseman*, Nature *222*, 275 (1969).

[139] *E. H. Wiseman, E. J. Gralla, J. Chiaini, J. R. Migliandi*, and *Y.-H. Chang*, J. Pharmacol. Exp. Ther. *172*, 138 (1970).

[140] J. Amer. Med. Ass. *204*, 814 (1968).

[141] *B. E. Witzel, P. Graham*, and *T. Y. Shen*, unpublished results.

[142] *M. Di-Rosa*, Arch. Int. Pharmacodyn. Ther. *173*, 162 (1968).

[143] *W. C. Dick, G. M. Cunningham, G. Nuki, M. K. Jasani*, and *K. Whaley*, Ann. Rheum. Dis. *28*, 187 (1969).

[144] *I. A. Jaffe*, Arthritis Rheum. *13*, 436 (1970).

[145] *J. G. Golding, J. V. Wilson*, and *A. T. Day*, Postgrad. Med. J. *46*, 599 (1970).

[146] *J. Zuckner, R. H. Ramsey, R. W. Dorner*, and *G. E. Gantner, Jr.*, Arthritis Rheum. *13*, 131 (1970).

[147] *D. Hagemann* and *R. Frankl*, Med. Welt *35*, 1920 (1969); *J. P. Camus, P. Guillien, J. Crouzet, A. Schaeffer*, and *J. A. Lievre*, Ann. Med. Intern. *121*, 237 (1970).

[148] *A. Lorber, C. C. Chang, D. Masuoka*, and *I. Meacham*, Biochem. Pharmacol. *19*, 1551 (1970).

[149] *G. Virella* and *M. F. Lopes-Virella*, Clin. Exp. Immunol. *7*, 85 (1970).

[150] New England J. Med. *283*, 883 (1970).

[151] *J. Krapcho, R. C. Millonig, C. F. Turk*, and *B. J. Amrein*, J. Med. Chem. *12*, 164 (1969).

[152] *F. P. Alepa, N. J. Zvaifler*, and *A. J. Sliwinski*, Arthritis Rheum. *13*, 754 (1970).

[153] *A. Many* and *R. S. Schwartz*, Clin. Exp. Immunol. *6*, 87 (1970).

[154] INFLO (Intramural Upjohn publication, News of Inflammation and Therapy) *3*, No. 2 (1970); *D. A. Willoughby*, private communication.

[155] *K. F. Swingle, T. J. Grant, L. W. Jaques*, and *D. C. Kuam*, J. Pharmacol. Exp. Ther. *172*, 423 (1970).

[156] J. Amer. Med. Ass. *214*, 39 (1970).

[157] *L. T. Sigell* and *H. C. Flessa*, J. Amer. Med. Ass. *214*, 2035 (1970).

[158] *M. G. MacDonald, D. S. Robinson, D. Sylvester*, and *J. J. Jaffe*, Clin. Pharmacol. Ther. *10*, 80 (1969).

[159] *D. W. Yesair, L. Remington, M. Callahan*, and *C. J. Kensler*, Biochem. Pharmacol. *19*, 1591 (1970).

[160] *J. R. Vane*, Nature *231*, 232 (1971).

[161] *J. B. Smith* and *A. L. Willis*, Nature *231*, 235 (1971).

[162] *S. H. Ferreira, S. Moncada*, and *J. R. Vane*, Nature *231*, 237 (1971).

[163] *M. W. Greaves, J. Sondergaard*, and *W. McDonald-Gibson*, Brit. Med. J. *1971*, No. 2, p. 258.

[164] *A. L. Willis*, Pharmacol. Res. Commun. *2*, 297 (1970); *A. J. Anderson, W. E. Brocklehurst*, and *A. L. Willis*, *ibid. 3*, 13 (1971).

[165] Brit. Med. J. *1971*, No. 5766, p. 61.

[166] *E. A. Ham, V. J. Cirillo, M. Zanetti, T. Y. Shen*, and *F. A. Kuehl, Jr.*, Proceedings of the Alza Conference on Prostaglandins in Cellular Biology and the Inflammatory Processes. 1972, in press.

[167] *H. O. J. Collier*, Nature *232*, 17 (1971).

[168] *J. G. Collier* and *R. J. Flower*, Lancet, *1971 II*, 852.

The Chemistry of Carbenoids and Other Thermolabile Organolithium Compounds[1]

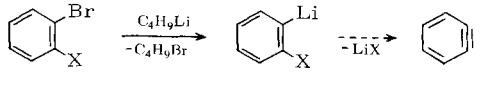
By Gert Köbrich[*]

Dedicated to Professor G. Wittig on the occasion of his 75th birthday

Organolithium compounds are thermally quite stable, despite their extremely high reactivity. Thermolability, *i.e.* the property of undergoing irreversible changes at low temperatures without the participation of molecules of a different kind, is associated with additional functional groups, which may be readily eliminated together with the metal cation, may cause intramolecular rearrangements, or may lead to intermolecular additions and substitutions involving several molecules of the same type. Thermolabile organolithium compounds have frequently been postulated or detected as intermediates of important reactions, and are therefore of theoretical and practical interest. If certain precautions are taken, it is occasionally possible (mainly at low temperatures) to prepare them intact, and hence to release them from the constraint of the fate assigned to them as short-lived intermediates. Investigations with this aim have for some time occupied a place of considerable importance in the chemistry of organometallic compounds.

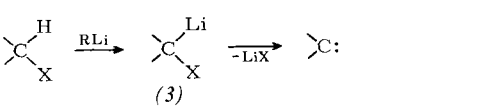
1. Introduction

A high tendency of an organometallic compound to decompose is not synonymous with a low formation tendency. On the contrary, because of their electron-attracting inductive and/or mesomeric effect, the functional groups that are responsible for the thermolability mostly increase the acidity of the neutral molecule from which the organometallic compound is derived. One consequence, to which too little attention was given in the past, is that the metal can often be introduced under very mild conditions. Early examples are *o*-fluorophenyllithium and *o*-chlorophenyllithium *(1)*, which are very unstable because of their tendency to form dehydrobenzene *(2)*, but which, according to *Gilman et al.*[2], can be prepared intact at -60 and $-90\,^{\circ}C$, respectively [eq. (1)].



X = F, Cl (1) (2) (1)

A large class of thermally unstable substances consists of the α-haloorganolithium compounds *(3)*, which, together with a number of other thermolabile compounds investigated by our research group, form the subject of the present progress report. They are intermediates of the α-elimination whose general formulation is given in eq. (2), and since they function as latent carbenes, they are known as carbenoids[**]. Perhaps the best evidence of their instability is the fact that they were postulated as intermediates by *Wittig et al.*[4] as early as 1941, but despite subsequent intensive studies in the field of carbene chemistry, apart from a few perfluoro compounds having atypical behavior, they were not detected directly until 1963.



(3) (2)

Though the following sections are intended as a continuation of earlier reviews[5], the material presented in these earlier publications is repeated with a shift of accent wherever this seems essential to the overall picture. The reader is also referred to two reviews by other authors, in which lithiated organic halogen compounds are treated as a part of the field[6].

2. Preparation of Carbenoids by Metalation

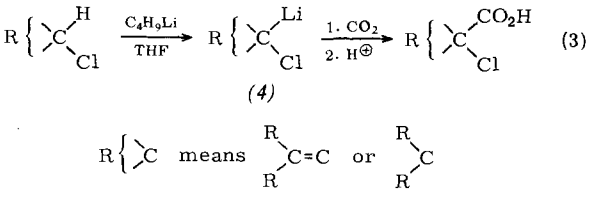
In a method discovered by our research group in 1963, many carbenoids can be very easily prepared without decomposition by low-temperature metalation[***] of the corre-

[*] Prof. Dr. G. Köbrich
Institut für Organische Chemie der Technischen Universität
3 Hannover, Schneiderberg 1 B (Germany)

[**] Whereas the adjective "carbenoid" is used to describe any carbene-like reaction, and was first used in this sense by *L. Friedman* and *H. Shechter* (J. Amer. Chem. Soc. *81*, 5512 (1959)), the noun "carbenoid" is used in different senses. *M. E. Volpin, Yu. D. Koreshov, V. G. Dulova,* and *D. N. Kursanov* (Tetrahedron *18*, 107 (1962)) used the term to denote intermediates in which the role of the bivalent carbon is taken over by another element, and which are now known as "carbene analogs" (see *O. M. Nefedov* and *M. N. Manakov*, Angew. Chem. *78*, 1039 (1966); Angew. Chem. internat. Edit., *5*, 1021 (1966)). According to *G. L. Closs* and *R. A. Moss* (J. Amer. Chem. Soc. *86*, 4042 (1964)), a carbenoid is a species that is responsible for electrophilic reactions instead of a carbene; in particular, this may be an α-haloorganolithium compound, but the term is used primarily to characterize a type of mechanistic behavior, while the structural assignment remains a matter of interpretation. In this progress report, as in our earlier publications, the term carbenoid is used without mechanistic implications to denote α-haloorganolithium compounds, and compounds in general that have a metal atom and a leaving group on the same carbon atom.

[***] The term "metalation" is used to denote the hydrogen-lithium exchange between an organic substrate and an organolithium compound (or a lithium amide).

sponding chlorinated hydrocarbons with *n*-butyllithium in tetrahydrofuran (THF) or THF-rich solvent mixtures (such as the Trapp mixture of THF, ether, and petroleum ether in a volume ratio of 4 : 1 : 1), and can then be characterized by suitable subsequent reactions, preferably by carboxylation [eq. (3)][7–10][*].



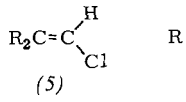
(3)

(4)

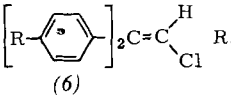
The optimum reaction temperature, which is normally between −70 and −120 °C, is limited at the lower end of the range by the rate of formation, and at the upper end by the tendency of the carbenoids *(4)* to decompose. Both of these factors are strongly and fairly predictably influenced by the hybridization of the carbon and by substituent effects.

The metalation proceeds on all sp^3-hybridized carbon atoms carrying at least two chlorine atoms[8, 10d, 10e, 11]; it fails with chloromethane[14]. In the case of olefins, where the hydrogen atoms are more acidic because of the sp^2-hybridized carbon atoms, activation by a single α-chlorine atom is sufficient[7, 9, 10]. However, chlorocyclopropanes (*e.g.* 7-chloronorcarane), whose C—H bonds are also assumed to be sp^2-hybridized[15], do not undergo metalation below −80 °C[16].

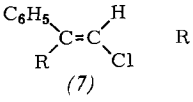
In addition to the hybridization, electronic and steric substituent effects are also active. They are particularly noticeable in the alkenes. Electron-attracting groups in the β position decrease the electron density at the α-carbon, and so increase its C—H acidity. Conversely, as the bulk of the β-substituent increases, the α-hydrogen is increasingly protected against attack by the metalating agent, and its removal is therefore slower. These patterns are evident from the relative rates of metalation of the chloroalkenes of the types *(5)* to *(7)* by *n*-butyllithium.



(5) R: $CH_3 < CH_2C_6H_5 < H < Cl$ [10c, 10f]

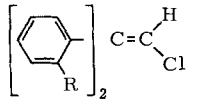


(6) R: $OCH_3 < CH_3 < H < C_6H_5 < Cl$ [10a, 10c, 10g]



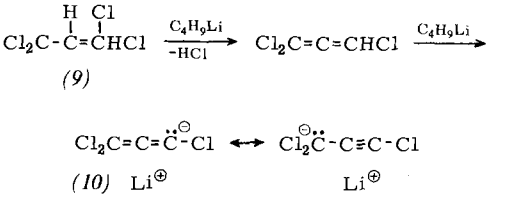
(7) R: $t\text{-}C_4H_9 < C_2H_5 < CH_3$ [17, 18]

The *o*-substituted β,β-diaryl compounds *(8)* are metalated more slowly than their *p*-isomers *(6)*[10a].



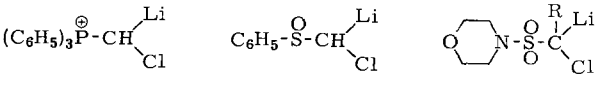
(8)

Trichloroallenyllithium *(10)* is obtained from the tetrachloropropene *(9)* with *n*-butyllithium (molar ratio 1 : 2)[19]. It presumably has an ion pair structure with resonance stabilization of the anion. The reaction therefore passes extremely rapidly through the stage of trichloroallene[19], which has been detected indirectly as an intermediate, and which can be intercepted under different conditions[20].



(9) *(10)*

Unlike the unstable chloromethyllithium[14], the carbenoids *(11)*[21], *(12)*[22], and *(13)*[23a] containing electron-attracting groups can be prepared at temperatures around −75 °C; the dimetalated compound *(14)* has recently been described[23b].



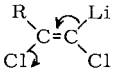
(11) *(12)* *(13)*, R = H, *(14)*, R = Li

Substituent effects that reduce the formation tendency of the carbenoids (electron pressure and steric crowding at the α-carbon atom) usually also increase their tendency to decompose. The range of temperatures that are suitable for their preparation is thus trimmed down both at the top and at the bottom end, and in unfavorable cases it shrinks to zero. (The halogen-metal exchange discussed in Section 3 is often helpful in such cases.) Conversely, sterically unhindered carbenoids with electron-attracting groups are obtainable over a wide range of temperatures, as can be shown for the compounds *(6)* to *(8)* and *(11)* to *(14)*.

[*] Our priority is shown by the sequence of publications. It was repeatedly stated in the review literature [12] that the α-halo*alkyl*lithium compounds were discovered simultaneously by several groups of workers. This statement is correct, roughly speaking, but it is only half the truth. It should be pointed out that the method that is nowadays regarded as the best for the preparation of α-halo*alkyl*lithium compounds, which we published in 1964 after careful optimization for dichloromethyllithium and trichloromethyllithium [8], was a direct application of the method discovered earlier by our group for the preparation of α-halo*alkenyl*lithium compounds, which we had reported in three short communications [7] before any other publication on the subject appeared. *Miller* and *Whalen* [13] independently prepared trichloromethyllithium and 2,2,2-trifluoro-1,1-dichloroethyllithium by bromo-lithium exchange with methyllithium in diethyl ether at −115 °C, but this method is laborious, and cannot be used as a general method because of the destabilizing action of ether on carbenoids. Also at about the same time, apparently independently and in ignorance of our previous publications, *Hoeg* and *Lusk*, in an unpublished manuscript, described the preparation of trichloromethyllithium and α,α-dichlorobenzyllithium by metalation of chloroform and of benzylidene chloride respectively in THF at −100 °C. Their results, in an expanded form, were published only in 1965 [11a]. 1¾ years after our first report, when we had already published all the main experimental results in a series of ten short communications [7—9, 28a, 28b].

Exceptions to this rule are found in carbenoids with additional functional groups that offer a decomposition path which is energetically particularly favorable, as is shown by the following examples.

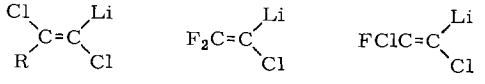
Trichloromethyllithium decomposes just above −90 °C, *i.e.* very much more readily than dichloromethyllithium[8, 24]. The reason for this is the ease of formation of the relatively "stable" dichlorocarbene (see Section 6.1).



$$\longrightarrow \text{R-C}\equiv\text{C-Cl} + \text{LiCl} \qquad (4)$$

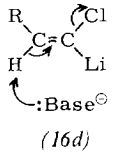
(15)

Compounds of the type *(15)* are readily formed, but decompose even below −100 °C. This is evidently due to a *trans*-β-elimination of lithium chloride in accordance with eq. (4)[10c]. The analogous *cis*-β-elimination takes place much less readily, as is shown by the comparatively high stability of *trans*-dichlorovinyllithium derivatives *(16a)*[10c, 19]. The *trans*-elimination in accordance with eq. (4) is slowed down by a second halogen in the β position (presumably as a result of electron attraction); trichlorovinyllithium *(16a)*, R = Cl, therefore decomposes only slowly at −120 °C, and can be isolated in good yields[10c]; the fluoro compounds *(16b)* and *(16c)* are even more stable[25].



(16a) *(16b)* *(16c)*

Metalated chloroolefins *(16d)* having a β-hydrogen atom undergo dehydrohalogenation in accordance with eq. (5) [E2cb mechanism] in the presence of strong bases, and are therefore also very unstable[10c, 26].



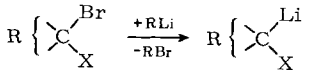
$$\longrightarrow \text{R-C}\equiv\text{C-Li} + \text{HBase} + \text{Cl}^{\ominus} \qquad (5)$$

(16d)

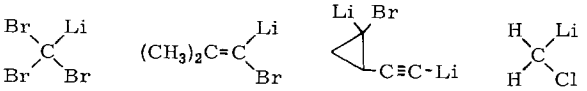
3. Thermolabile Organolithium Compounds by Halogen-Metal Exchange

Metalation has certain limitations as a path for the formation of carbenoids. Substrates such as chloromethane, 7-chloronorcarane, and 1-chloro-2-methyl-1-propene do not undergo lithiation at the low temperature required. While these reactions would be thermodynamically possible, since they would lead, in the sense of an acid-base formulation, from a stronger to a weaker acid-base pair, they are not ionic reactions in practice, but reactions of predominantly covalent species in a solvent of moderate polarity which contributes little to the stability of strongly polar transition states. The proton transfer therefore requires relatively high activation energies[*]. The limit to which the metalation is subject is therefore kinetic in origin, and not thermodynamic.

A solution is often provided by halogen-metal exchange, in which a halogen takes over the role of the hydrogen. With bromine and iodine, and less frequently with chlorine,



the exchange proceeds several orders of magnitude faster than the corresponding hydrogen-lithium exchange[4]. The reaction, which was discovered more than 30 years ago by *Wittig* and *Gilman*, and of which frequent use has been made[6], is therefore excellently suited for the preparation of thermolabile organolithium compounds. This can be illustrated by the preparation of tribromomethyllithium *(17a)* (from tetrabromomethane)[27] and of 1-bromo-2,2-dimethylvinyllithium *(17b)* (from the geminal dibromide)[28], which are obtained in 90% yield at −100 °C. The similarly prepared dilithiated cyclopropane *(18)* is stable even at −60 °C[29]. Chloromethyllithium *(19)*, which is very unstable even below −100 °C, was detected directly for the first time by Br—Li exchange on bromochloromethane[14].

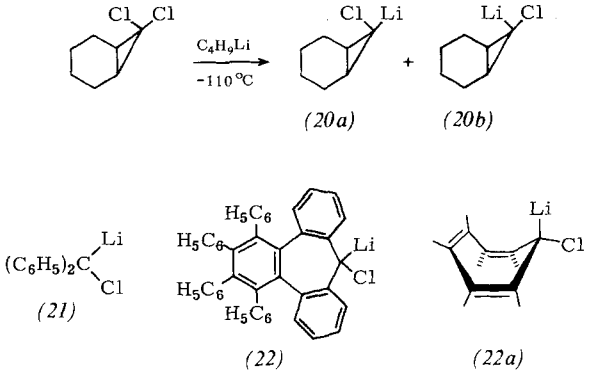


(17a) *(17b)* *(18)* *(19)*

The chloro-lithium exchange can often be used as an alternative to metalation. Trichloromethyllithium is obtainable from tetrachloromethane[11a], and β,β-diaryl-α-chlorovinyllithium compounds can be prepared from the readily available geminal dichlorides[10g]. Even the chloro-lithium exchange occasionally leads to the desired result when metalation fails. Thus the reaction of 7,7-dichloronorcarane with *n*-butyllithium at −110 °C yields a mixture of the stereoisomeric carbenoids *(20a)* and *(20b)*[16]. Diphenylchloromethyllithium *(21)* can be prepared from the corresponding dichloride, but not by metalation of diphenylchloromethane[11a]. In the carbenoid *(22)*, the fixed conformer with quasi-axial metal [formula *(22a)*] is favored, presumably owing to the better overlap of the metal-bonding electron pair with the adjacent aromatic π systems. It is obtained from the corresponding dichloride *(22)*, Cl instead of Li, by chloro-lithium exchange or from the monochloride *(22a)*, H instead of Li, by metalation[30]. The monochloride with axial chlorine undergoes a chloro-lithium exchange under the same conditions to give the halogen-free lithium compound *(22a)*, H instead of Cl.

However, the halogen-metal exchange is not merely a faster variant of metalation. As a very fast reaction under

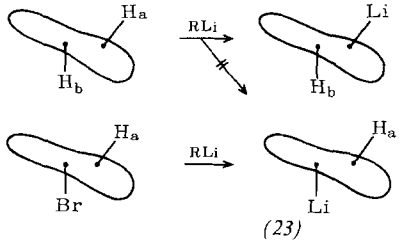
[*] The fact that the activation energies of many metalations are nevertheless very low is due to the extremely large basicity difference between the reacting and the resulting organolithium compound.



(20a) (20b)

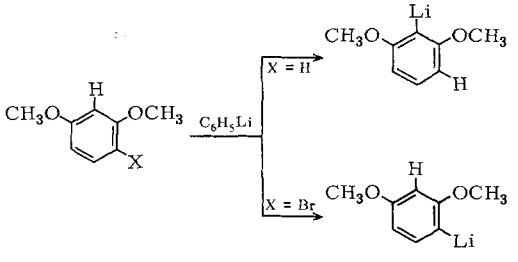
(21) (22) (22a)

conditions in which the product formation is kinetically controlled, it offers much more. Most organic molecules contain several differently bound hydrogen atoms, and are therefore polybasic acids from the standpoint of the acid-base theory. On metalation, only one of the hydrogen atoms (H_a), *i.e.* that having the highest kinetic acidity, is generally removed, while a less acidic C—H bond (H_b) remains intact. The halogen-metal exchange, because of its greater velocity, often allows the lithiation of a less acidic position, and so gives a new organolithium compound *(23)* that cannot be obtained by metalation.

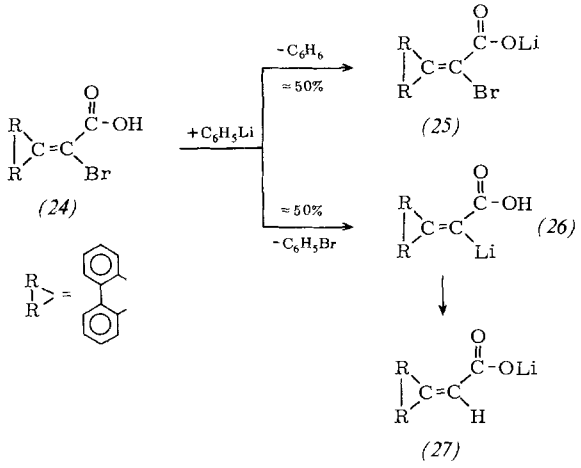


(23)

The first example was found on the discovery of the halogen-metal exchange[49a].

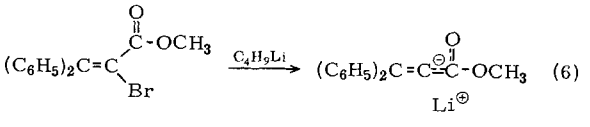


An extreme case is met in the reaction of fluorenylidene-bromoacetic acid *(24)* with phenyllithium in THF at −70 °C. On subsequent treatment with acid, 50% of the substrate is recovered, together with the bromine-free acid *(27)* and bromobenzene in a yield of about 50% each. The expected removal of the acidic proton by the strong base to form the α-bromocarboxylate *(25)* is thus accompanied in an almost equal measure by a bromo-lithium exchange to form the α-metalated carboxylic acid *(26)*, which then rearranges to give the thermodynamically stable halogen-free carboxylate *(27)*[31]. The bromo-lithium exchange thus competes successfully with the deprotonation of the carboxyl group in a position whose C—H acidity should be about 15—20 orders of magnitude lower than the acidity of the carboxyl group.

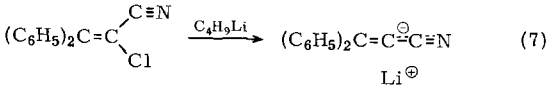


(24) (25) (26) (27)

The halogen-metal exchange also allows the preparation of functional organolithium compounds in cases where metalation would have practically no chance because of other fast reactions. In the reactions indicated in eqs. (6) and (7), the halogen-metal exchange prevails against the addition of the organolithium compound to the double bond (Michael addition) or to the functional group. The resulting α-lithiated acrylic acid derivatives are stable at low temperatures, and can thus be subjected to further transformations as desired. Their deep yellow [*(28)*] and green colors [*(29)*] point to ion-pair structures with resonance-stabilized anions[31].

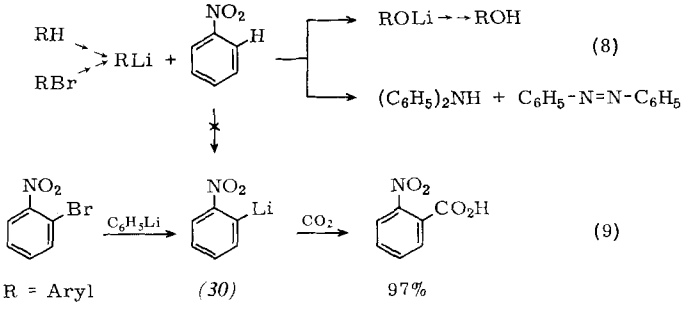


(28), 94%



(29), 75%

A similar situation is found for aromatic nitro compounds. The *o*-position in nitrobenzene is unquestionably much more acidic than that of most other benzene derivatives, and should therefore be very readily metalated with organolithium compounds. However, this is prevented by the redox reactions at the nitro group, which are very fast even at −100 °C in THF, and by which the aromatic nitro compound is converted *e.g.* into azobenzene and diphenyl-



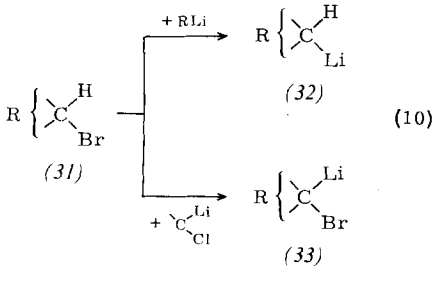
R = Aryl (30) 97%

amine, while the aryllithium used is converted quantitatively into the corresponding lithium phenoxide[32, 33]. The reaction is thus suitable for the preparation of phenols from aromatic compounds, particularly from bromo compounds, in accordance with eq. (8), but not for the preparation of lithiated aromatic nitro compounds.

However, the fast redox reactions at the nitro group can be beaten by the even faster bromo-lithium exchange. Thus the reaction of *o*-nitrobromobenzene with phenyllithium in THF at $-100\,^{\circ}C$ leads almost quantitatively to *o*-nitrophenyllithium *(30)* [eq. (9)]. This interesting, black-red compound is stable only below $-100\,^{\circ}C$[34]. Many other lithiated aromatic mononitro, dinitro, and trinitro compounds are obtainable in the same way[32–34].

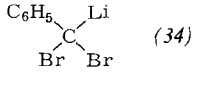
4. Carbenoids as Metalating Reagents

Because of the high reaction rates of bromo-lithium and iodo-lithium exchanges, the reaction of substrates *(31)* having hydrogen and bromine (or iodine) on the same carbon atom with common organolithium compounds proceeds predominantly by halogen-metal exchange to the product *(32)* containing less halogen, so that the metalated compounds *(33)* cannot be obtained in this way[35]. This gap can be filled by the use of sufficiently basic carbenoids as metalating reagents. The metalation of dibromomethane and of benzylidene bromide with dichloromethyllithium is the only method known at present for the preparation of dibromomethyllithium and α,α-dibromobenzyllithium

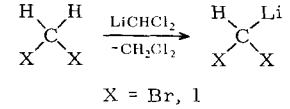


(31) *(32)* *(33)* (10)

(34) in good yields[35a]. Similarly, diiodomethyllithium can be obtained from diiodomethane in accordance with eq. (11) (an alternative method in this case is iodo-lithium exchange between triiodomethane and phenyllithium)[36]. Tribromomethane can be metalated with dichloromethyllithium[35a] (but also with nitrogen bases in THF/hexamethylphosphoramide mixtures[37]), though the bromo-lithium exchange gives better yields here as well as in the preparation of α-bromovinyllithium compounds, which can also be obtained by the above method [eq. (12)].

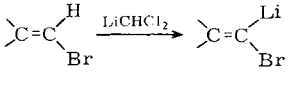


(34)



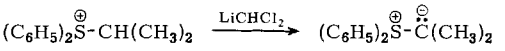
(11)

X = Br, I



(12)

Dichloromethyllithium is very suitable for the preparation of the sulfonium ylide *(35)*, which reacts with carbonyl compounds to form oxiranes[38].



(35)

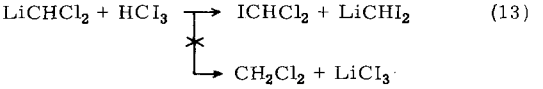
Why does dichloromethyllithium direct the reactions of eq. (10) toward the thermodynamically more stable base *(33)*?[*] The main reason is probably that no compound more strongly basic than the organolithium compound used can be formed. A bromo-lithium exchange on dibromomethane is possible with butyllithium, but not with dichloromethyllithium, since the resulting bromomethyllithium is a weaker base than butyllithium, but a stronger base than dichloromethyllithium. As is shown by these and other findings, the influence of the halogen on basicity as deduced by *Hine*[3a] from the investigation of the haloform anions in protonic media is also valid for the corresponding and other organolithium compounds in aprotic solvents.

The basicity increases

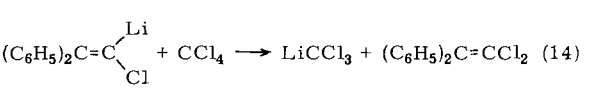
a) as the number of halogen atoms on the metalated carbon atom increases and

b) in the order Cl, Br, I for a given number of halogen atoms.

Of the alternatives indicated in eq. (10), the halogen-metal exchange can logically also become the principal reaction with carbenoids, provided that the product formed is a weaker base than the carbenoid used. For example, the reaction of iodoform with dichloromethyllithium proceeds exclusively by iodo-lithium exchange[36] [eq. (13)], and the carbenoid *(36)* reacts with tetrachloromethane to give trichloromethyllithium [eq. (14)][39].



(13)



(36) (14)

5. Solvent Effects

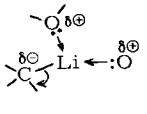
Reactions of organolithium compounds are strongly influenced by the solvent. They are usually faster in polar media, such as THF or 1,2-dimethoxyethane, than in less polar media. The deciding factor is evidently the donor-

[*] The terms "stable" and "unstable" used here in connection with base strengths should not be confused with thermal stability or instability. Thus trichloromethyllithium (or the trichloromethyl anion) is thermally less stable than dichloromethyllithium (or the dichloromethyl anion), but is the thermodynamically more stable base (owing to the additional halogen).

acceptor relationship between the metal and the oxygen of the solvent, which increases the polarity of the C—Li bond, and hence the carbanion character of the organometallic compound [formula *(37)*]. It should be remembered, however, that in a reaction yielding a new organolithium compound, the resulting compound is also subject to this solvent effect. Thus polar media accelerate not only the formation reactions but also the subsequent reactions if the nucleophilicity of the metalated carbon is decisive in the latter.

The fact that carbenoids, as described earlier, can often be prepared in high yields in THF is due to their relatively fast formation and above all to the remarkable retardation of their decomposition in this solvent[9b]. The stabilization effect differs in magnitude from one carbenoid to another. Thus trichloromethyllithium can also be obtained in diethyl ether[13], but it decomposes in this solvent at lower temperatures than in THF[9c]. Other compounds, such as dichloromethyllithium or the carbenoid *(36)*, which are stable in THF at −80 °C, decompose instantaneously in ether under otherwise identical conditions[9,10].

Carbenoids usually decompose by electrophilic reactions with replacement of the α-halogen. If the removal of the halogen is assumed to be facilitated in accordance with formula *(38)* by attraction of electrons from the halogen to the metal atom, the strength of the attraction, and hence the tendency to decompose, should decrease with increasing solvation of the metal by donor molecules, as observed[9b]. It is possible that other factors play a part, such as the degree of association of the carbenoids, which is unknown at present; however, the following recent findings support our assumption that the solvation of the lithium atom is of decisive importance. Trichloromethyllithium

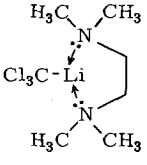


(37)

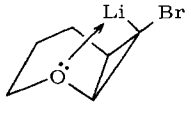


(38)

reacts with *N,N,N',N'*-tetramethylethylenediamine to form a complex *(39)* that is stable even in hexane at −90 °C[40]. The carbenoid *(40)* can be prepared in ether at (and above) −78 °C. It is much more stable than the carbocyclic analog *(20)*, presumably because of the intramolecular solvation by the ring oxygen. In addition to *(40)*, the *exo*-Li isomer can be detected in THF[41a].



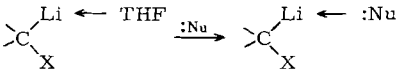
(39)



(40)

The influence of the metal on the solvent-dependence of the stability of carbenoids is also instructive. It should be weaker for the higher alkali metals than for lithium, because of the less pronounced Lewis acid character of the former. A number of dihalomethyl and trihalomethyl derivatives of sodium and of potassium, which have recently been prepared by metalation of the corresponding halogenated hydrocarbons with alkali metal bis(trimethylsilyl)-amides[41b], are in fact no more stable in THF than in ether. The relative low tendency in particular of the sodium compounds to decompose (*e.g.* tribromomethylsodium decomposes only at −77 °C[41b], whereas tribromomethyllithium decomposes at −100 °C[27]) is probably also partly due to the low attraction acting on the neighboring halogen atom in accordance with *(38)*. Conversely, the solvent effect is very pronounced in the case of magnesium carbenoids; thus dibromomethylmagnesium chloride, which decomposes rapidly in THF at −45 °C, is protected against decomposition by hexamethylphosphoramide (HMPT)[41c].

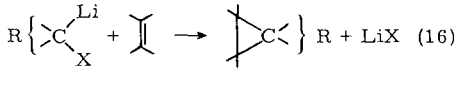
Other workers have argued that a nucleophilic compound that reacts with the carbenoid (*e.g.* an olefin) is first fixed to the lithium atom with displacement of a solvating molecule (as had been discussed earlier[5a]), and that the slower reaction in THF is simply due to the greater difficulty of displacement of the strongly attached THF molecule [eq. (15)]. This is refuted by the fact that the *intramolecular* Fritsch-Buttenberg-Wiechell rearrangement, in which this argument is inapplicable, exhibits the same solvent effect[9c,10a].



(15)

6. Electrophilic Reactions of Carbenoids

It is convenient to divide the reactions of carbenoids into nucleophilic reactions, which take place on the C—Li bond and are typical of conventional organolithium compounds, and electrophilic reactions, in which at least one α-halogen atom is eliminated, usually together with the metal atom. Electrophilic reactions, the best-known of which is carbene transfer to olefins [eq. (16)], can mostly be carried out without prior preparation of the carbenoid, though this is occasionally advantageous[42]. The *in-situ* production of the carbenoid in the presence of the nucleophilic reagent is generally sufficient. The following discussion will be concerned only with reactions in which the preparation of the carbenoid is either necessary or allows one to draw important mechanistic conclusions.



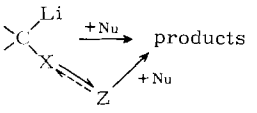
(16)

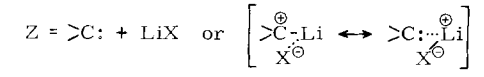
6.1. Mechanisms

The following mechanistic alternatives are fundamentally conceivable for the reaction of a carbenoid with a nucleophile Nu (*e.g.* an olefin) (cf. the scheme):

a) The nucleophile reacts with the carbenoid, without the intervention of an intermediate, to form the product.

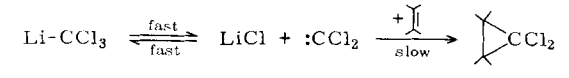
b) The nucleophile reacts with an intermediate "Z", which is previously formed (reversibly or irreversibly) from the carbenoid.





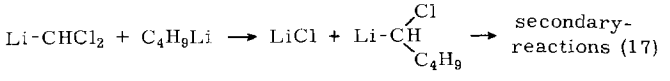
The intermediate "Z" may be either a free (but solvated) carbene or a species having an ionized C-halogen bond, in which the lithium halide remains bonded to the α-carbon atom *via* the metal atom (complexed carbene, carbene complex). The numerous types of behavior lead to the conclusion that a variety of mechanisms is operative. The direct reaction of carbenoids with olefins to form cyclopropanes (similar to that of Simmons-Smith reagents[43]) was first suggested by *Closs et al.*[44]. As another alternative, we[9c,10e] have considered the carbene complex with an ionized C-halogen bond, which was later also discussed by other authors[11a,45].

In view of numerous indications to the contrary, it seemed doubtful until recently whether carbene intermediates do in fact occur in reactions of lithiated organic chloro and bromo compounds. According to recent experiments by *Skell* and *Cholod*[40] and results from our research group[46], the competition constants found in the dichlorocarbene transfer from trichloromethyllithium to pairs of olefins at −70 °C are practically the same as those found when other dichlorocarbene sources are used. It may therefore be concluded that dichlorocarbene occurs as intermediate in all dichlorocyclopropanations, including those with trichloromethyllithium. Since olefins nevertheless accelerate the decomposition of trichloromethyllithium[46], a relatively rapid equilibrium is probably established between trichloromethyllithium and dichlorocarbene at −70 °C, from which the dichlorocarbene is slowly removed by the olefin.



Trichloromethyllithium thus behaves in the same way as the trichloromethyl anion in aqueous medium[3a]. Another carbenoid that establishes an equilibrium with its carbene in aprotic media is tris(phenylthio)methyllithium[47].

The other extreme case, *i. e.* an attack by the nucleophile on the carbenoid, is probable in particular with strong nucleophiles. The chloro-*n*-butyl exchange between dichloromethyllithium and *n*-butyllithium [eq. (17)] presumably follows this (S_N2-like) mechanism, since it takes place under conditions where dichloromethyllithium is thermally stable in the absence of butyllithium and does not react with weaker nucleophiles[10d].

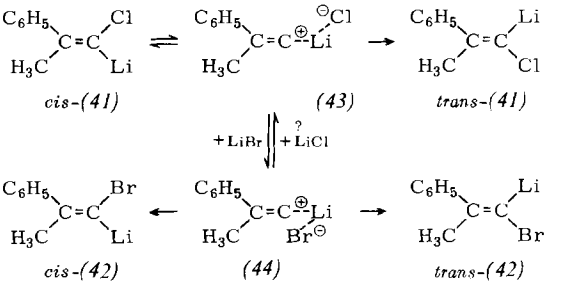


The types outlined above are probably the extreme cases of a continuous scale of reaction possibilities. However, it is not easy to determine the path that will be followed in a particular case, since there are no general criteria for differentiating between the reaction of a carbenoid and that of a carbene complex, and since the results of the competition method regarding the occurrence of intermediates are not beyond question.

There is so far only one discrete piece of stereochemical evidence for the existence of carbene complexes. The carbenoid *cis-(41)* rearranges irreversibly into the *trans*-isomer at −85 °C, and in the presence of lithium bromide it undergoes a Cl—Br exchange leading to the two bromocarbenoid isomers *(42)*[17]. Under the same conditions, the compound does not enter into reactions such as would be expected for a carbene intermediate (*e. g.* the dimerizing α-elimination or cyclopropanation with olefins); the only further reaction is the Fritsch-Buttenberg-Wiechell rearrangement to give phenylpropyne, which is known to involve no carbene intermediate.

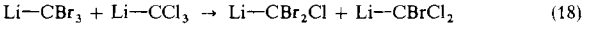
Substituent effects argue against a halogen exchange by the addition-elimination mechanism in the carbenoid, which is unlikely *a priori*. Finally, isomerization by carbanion inversion is unlikely, since halogen-free vinyllithium compounds are configurationally stable at low temperatures[48a] and an α-halogen atom, according to recent calculations, should raise the inversion barrier rather than lower it[48b].

The experimental facts are therefore best fitted by the assumption of a carbene complex intermediate *(43)*.

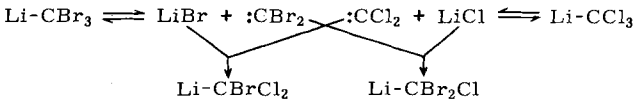


6.2. Ligand Exchange on Carbenoids

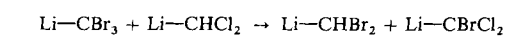
To conclude this mechanistic outline, we shall discuss a ligand exchange between tribromomethyllithium and other carbenoids, whose mechanism has not yet been conclusively established. When suspensions of tribromomethyllithium and trichloromethyllithium are mixed at −100 °C, bromodichloromethyllithium and dibromochloromethyllithium are formed [eq. (18)][27].



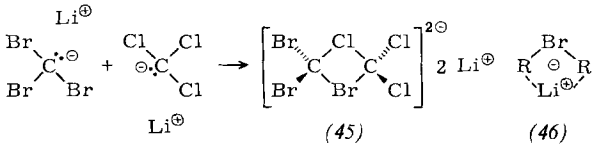
One would naturally expect such an exchange if the carbenoids used were in equilibrium with the corresponding carbenes and lithium halides.



However, the reaction[27] observed under the same conditions with dichloromethyllithium:

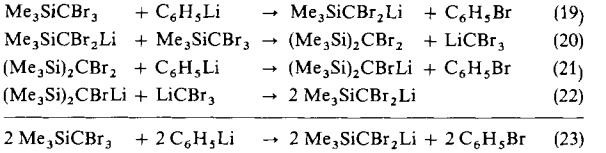


would be difficult to explain in this way, and certainly could not be explained without several intermediates. Moreover, none of the carbenoids exhibits any notable tendency to decompose in THF at −100 °C. Above all, tribromomethyllithium does not undergo halogen exchange with added lithium chloride under these conditions, nor does trichloromethyllithium in the presence of lithium bromide. A possible explanation is a direct reaction *via* a dinuclear complex *(45)* involving halogen bridges (the cations are to be regarded as lying above and below the plane of the paper). This complex is reminiscent of the complex *(46)* that was proposed for the halogen-metal exchange[49b], and the ligand exchange could in fact be regarded as a double halogen-metal exchange.



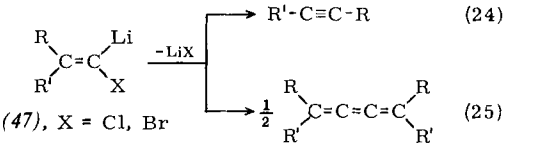
(45) *(46)*

A similar ligand exchange occurs in the commutation reaction between tribromomethyllithium and bis(trimethylsilyl)bromomethyllithium [eq. (22)], and proves to be the key to the understanding of the following apparently simple but in reality rather complicated reaction[50]. Trimethylsilyltribromomethane reacts with an equimolar quantity of phenyllithium to give trimethylsilyldibromomethyllithium (which can be characterized *e.g.* with trimethylchlorosilane as bis(trimethylsilyl)dibromomethane) in high yield [eq. (19)]. With the normal reaction procedure (slow addition of phenyllithium to the substrate), however, the carbenoid formed in accordance with eq. (19) rapidly reacts with the remaining substrate to form bis(trimethylsilyl)dibromomethane and tribromomethyllithium [eq. (20)]. Further phenyllithium converts the disilyl compound in accordance with eq. (21) into bis(trimethylsilyl)bromomethyllithium, which undergoes the commutation mentioned above [eq. (22)] with the tribromomethyllithium formed in eq. (20)[50a]. Strangely, therefore, trimethylsilyldibromomethyllithium can be satisfactorily prepared in this way only because the secondary reactions (all of which have been confirmed by control experiments) finally lead back to the same carbenoid *via* the commutation [eq. (23)].



6.3. Dimerizing α-Elimination and the Fritsch-Buttenberg-Wiechell Rearrangement

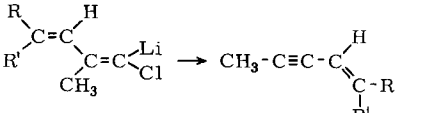
Olefinic carbenoids *(47)* have available two preparatively important decomposition paths, *i.e.* the Fritsch-Buttenberg-Wiechell (FBW) rearrangement to form disubstituted acetylenes [eq. (24)] and dimerizing α-elimination to form butatrienes [eq. (25)][51].



(47), X = Cl, Br (24) (25)

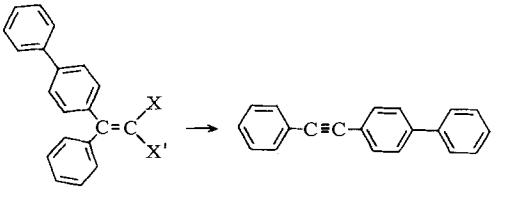
The dimerizing α-elimination (which, as a formal dimerization of a carbene, is the most general thermolysis reaction of carbenoids) is observed for compounds *(47)* having two β-alkyl residues (R,R′ = CH_3, $CH_2C_6H_5$)[10f,28c]; to obtain good yields, the carbenoid must be prepared before the thermolysis.

The FBW rearrangement, which also proceeds in high yields without prior preparation of the carbenoid, takes place under mild conditions whenever at least one of the β substituents has available a π system conjugated with the metalated olefin, *i.e.* with aryl[51] and alkenyl groups[18]. The migration of the alkenyl group proceeds stereospecifically with retention of configuration within the detection limits[18].



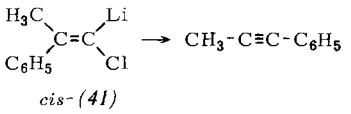
R = H, R′ = C_6H_5
R = C_6H_5, R′ = H

When two β substituents are capable of rearranging, the migration of the substituent *trans* to the α halogen[52] (*trans* migration) predominates; for example, 97% migration of the biphenylyl residue occurs in the case of the compound *(48)*, and 95% migration of the phenyl group (contrary to earlier reports[10g]) in the case of the isomer *(49)* (±2% in each case)[53].



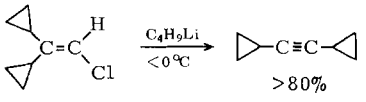
(48), X = Li, X′ = Cl
(49), X = Cl, X′ = Li

If the group *trans* to the halogen cannot rearrange while the *cis* substituent can, *cis* migration prevails. This was first observed for *cis-(41)*[17a], which decomposes at lower temperatures than the *trans* isomer, presumably on steric grounds.



cis-(41)

It was uncertain for a long time whether the nonstereospecific part of the FBW rearrangement in β,β-diarylated carbenoids is also due to a "true" *cis* migration, or whether the *cis* migration is simulated by partial isomerization of the carbenoid with subsequent *trans* migration. The results of recent investigations favor the *cis* migration[53]. On the one hand, the FBW rearrangement of β,β-diarylated carbenoids is suppressed in favor of dimerizing α-elimination when the aryl residues are linked by short bridges, since the rearrangement would then lead to a highly strained cycloalkyne. On the other hand, FBW rearrangement can be forced in β,β-dialkylated haloolefins under drastic conditions[51]. The rearrangement proceeds particularly smoothly with "vinyl-like"[115] cyclopropyl groups[54].

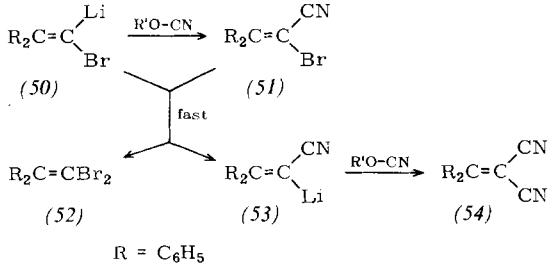


7. Nucleophilic Reactions of the Carbenoids

For nucleophilic reactions, the preparation of the carbenoids before their reaction with the electrophilic reagent is necessary or at least advantageous, since the organometallic compound used for the preparation of the carbenoid would otherwise compete with the latter for the electrophile. Examples of the addition to carbon dioxide and carbonyl compounds and of halogenation, cyanation, and alkylation were given earlier[5]. The nucleophilic reactions of the carbenoids also include the lithiation of halogenated hydrocarbons by metalation or halogen-metal exchange (Section 4). Some reactions that make use of special, preparatively useful properties of carbenoids are discussed below.

7.1. Multiple Functionalization

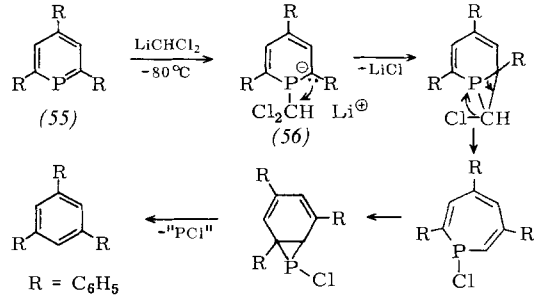
The replacement of the lithium by a functional group may activate the α-halogen (particularly Br or I) so strongly that the resulting compound undergoes a halogen-metal exchange with unreacted carbenoid. Thus the cyanation of the carbenoid *(50)* leads not to *(51)* but to an equimolar mixture of *(52)* and the dicyano compound *(54)* (the latter reacts further with *(50)* and *(53)* in Michael additions)[31].



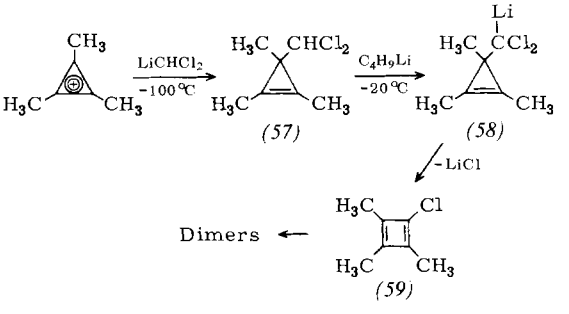
Such transmetalations can occur in particular between a reaction product of a carbenoid and an excess of the organolithium compound used to prepare the carbenoid, and can thus simulate the occurrence of a dilithium intermediate[31].

7.2. Reaction with Electrophilic Aromatic Systems

2,4,6-Triphenylphosphabenzene *(55)* reacts with dichloromethyllithium at −80 °C to form a deep red adduct *(56)*, whose thermal decomposition (presumably *via* the interesting intermediates indicated below) leads to *sym*-triphenylbenzene[55].

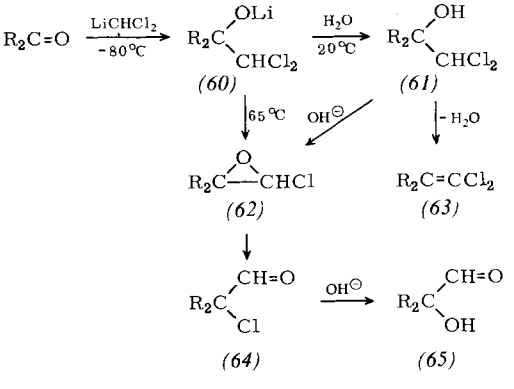


The alkylation of dichloromethyllithium with trimethylcyclopropenylium salt yields the cyclopropane *(57)*, whose metalation and subsequent carbenoid decomposition leads in 85% yield to four structurally isomeric dimers of chlorotrimethylcyclobutadiene *(59)*[56].



7.3. Reactions of Dichloromethylalkoxides

The alcohols *(61)* obtained from carbonyl compounds and dichloromethyllithium can, for R = aryl, be dehydrated in high yields to 1,1-dichloroolefins *(63)*[10g, 21b]. The overall

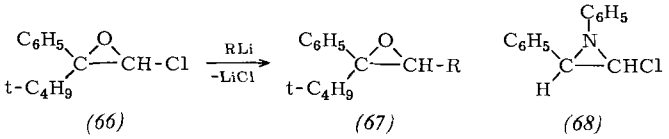


reaction provides a simple method for the dichloroolefination of diaryl ketones.

If the alkoxides *(60)* are heated for a short time at 65 °C before being hydrolyzed, they rearrange with elimination of lithium chloride into α-chloro aldehydes *(64)*, which can be readily converted into α-hydroxy aldehydes *(65)* by treatment with alkali[57]. The sequence leading from the carbonyl compound to *(65)* is a nucleophilic formylation; dichloromethyllithium is found to be a masked formyl anion[58].

According to *Kirrmann et al.*, the rearrangement of the alkoxides *(60)* into α-chloro aldehydes *(64)* proceeds *via* the unstable chlorooxiranes *(62)*, some of which can be obtained from the alcohols *(61)* by treatment with alkali under carefully chosen conditions[59].

The alkoxide from *tert*-butyl phenyl ketone and dichloromethyllithium, *i.e.* lithium 1,1-dichloro-3,3-dimethyl-2-phenyl-2-butoxide, is converted into the chlorooxirane *(66)* even below room temperature[57] (the chloroaziridine *(68)* is presumably formed in a similar manner from benzylideneaniline[60]). The chlorine atom of *(66)* is smoothly exchanged with organolithium compounds to give the trisubstituted oxiranes *(67)*[57]. The overall reaction is a carbene transfer (:CHR) to the carbonyl group by three nucleophilic addition and substitution steps. With bromomethyllithium produced *in situ*, carbonyl compounds are converted into oxiranes by methylene transfer[60b].



(66) *(67)* *(68)*

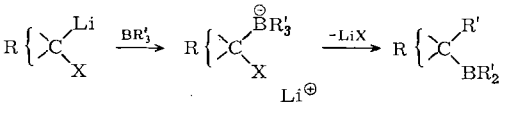
7.4. Reaction of Carbenoids with Metal Compounds

Like other organolithium compounds, carbenoids react smoothly with salts of less electropositive metals to give new organometallic compounds[5]. A simple example is the reaction of dichloromethyllithium with zinc chloride or mercury(II) chloride to form bis(dichloromethyl)zinc and bis(dichloromethyl)mercury, respectively[8,10d].

$$2\,Li{-}CHCl_2 + MCl_2 \xrightarrow[-2\,LiCl]{} M(CHCl_2)_2 \qquad M = Zn, Hg$$

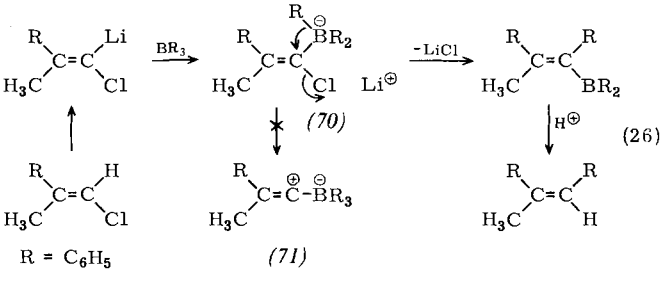
7.4.1. Rearrangement of α-Chloro Borates

Triphenylborane combines with carbenoids to form ate-complexes *(69)*. Because of the α-halogen, these complexes are thermolabile and decompose with elimination of lithium chloride and phenyl rearrangement to form boranes[61]:



R' = C_6H_5 *(69)*

The stereochemistry has been elucidated from the reaction sequence shown in eq. (26). It proceeds with an overall yield of 65% and is a rare example of a nucleophilic substitution on olefinic carbon (replacement of chlorine by phenyl) with *inversion of configuration*; the stereoselectivity is 98% (the *cis*-isomeric substrate gives the *trans*-stilbene derivative with the same selectivity and in a yield of 73%)[61].



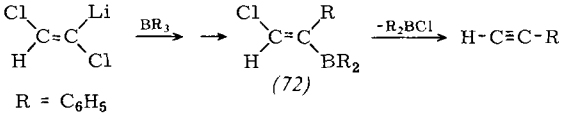
(26)

R = C_6H_5 *(70)* *(71)*

The inversion takes place in the rearrangement step [formula *(70)*], since all the other steps are electrophilic reactions at the olefinic carbon, for which *retention of configuration* is typical. The results conclusively rule out the conceivable "inverse ylide" *(71)* as an intermediate[*].

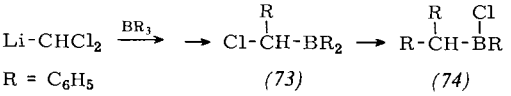
The ate-complex formed from α-lithiofuran and trialkylboranes is assumed to undergo a similar inversion to give 1,2-oxabora-4-cyclohexenes[63].

If the carbenoid contains several halogen atoms, the rearrangement may be followed by further reactions. Thus the reaction of *trans*-dichlorovinyllithium with triphenylborane leads, probably by a *trans*-β-elimination in the rearranged borane *(72)*, to phenylacetylene as the main product[61].



R = C_6H_5 *(72)*

The primary rearrangement product *(73)* formed from dichloromethyllithium and triphenylborane undergoes a second phenyl rearrangement to form the borane *(74)*, as can be deduced from alkaline oxidation to 62% benzhydrol and 10% benzophenone[61].



R = C_6H_5 *(73)* *(74)*

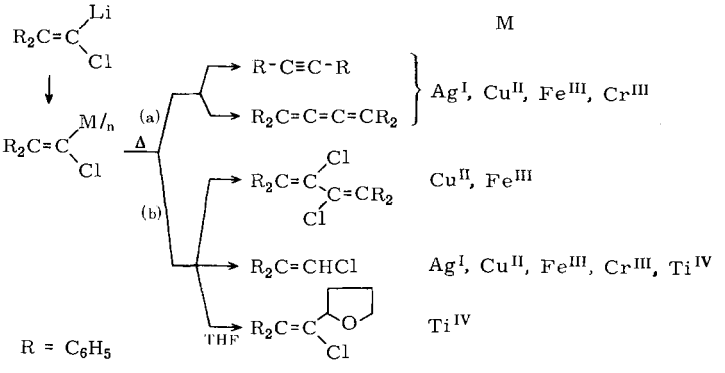
With trichloromethyllithium as the substrate, the third ligand from the boron can also be transferred to the α-carbon atom, so that alkaline oxidation leads to the tertiary alcohol (37% of tri-*n*-butylmethanol from tri-*n*-butylborane)[64].

[*] "Inverse" because of the reversed charge distribution on the α-carbon atom and the hetero atom in relation to that in conventional ylides, cf. Ref. [62].

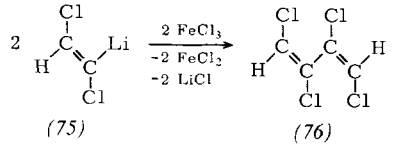
7.4.2. Reactions of Thermolabile Transition Metal Carbenoids

The organometallic compounds formed from Li carbenoids with transition metal salts by metal-metal exchange are mostly thermolabile. Their reactions depend on the nature and quantity of the metal salt and on the nature of the organic residue. Depending on the fate of the α-halogen, it is possible to distinguish two fundamental modes of reaction, which are illustrated for 1-chloro-2,2-diphenylvinyllithium[65, 66a].

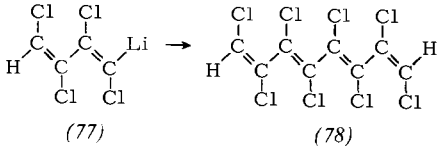
The halogen is either removed together with the metal, with formation of carbenoid products [path (a)], or it remains in the molecule, and radicaloid secondary reactions are observed [path (b)].



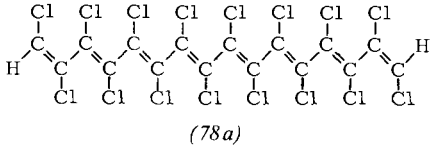
A system that has proved to be particularly interesting is that of *trans*-dichlorovinyllithium *(75)* with iron(III) chloride, which allows the stereospecific synthesis of polychloropolyenes and polychloropolyenynes[66, 67]. 1 mole of *(75)* couples with 1—2 moles of $FeCl_3$ to give tetrachlorobutadiene *(76)* in good yields. The metalation product *(77)* of *(76)* similarly gives octachlorooctatetraene *(78)*, from which a hexadecachlorohexadecaoctaene *(78a)* can be prepared in a similar manner[66].



(75) *(76)*



(77) *(78)*



(78a)

The lithium carbenoids and their analogs with σ-bonded iron, which can be detected at low temperatures[67b], function as intermediates of an *oxidative* coupling, which can be represented by the following overall formulation:

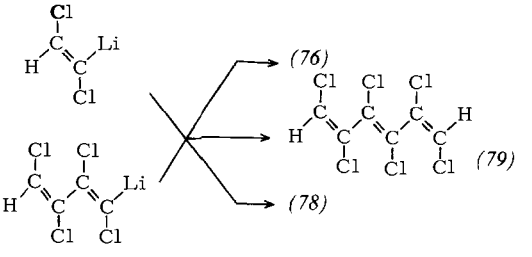
$$2\ H{-}[CCl]_n{-}H \xrightarrow{-2H} H{-}[CCl]_{2n}{-}H \qquad n = 2, 4, 8$$

The only notable side reaction is the regeneration of the substrate by saturation of the intermediate organometallic compounds with H from the solvent. It is very probable that no free vinyl radicals occur here or in the coupling[67b].

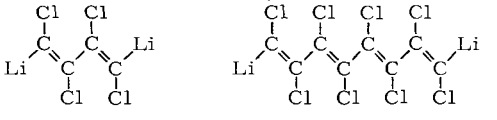
Two variants of the oxidative coupling allow the synthesis of intermediate members of the polyene series. In *mixed oxidative coupling* in accordance with:

$$H{-}[CCl]_m{-}H + H{-}[CCl]_n{-}H \xrightarrow{-2H} H{-}[CCl]_{m+n}{-}H$$

carbenoids with different chain lengths are allowed to react simultaneously with $FeCl_3$. In this way *(75)* and *(77)* give hexachlorohexatriene *(79)* besides *(76)* and *(78)*.



The *oxidative oligomerization* is based on the smooth formation of α,ω-dimetalated compounds such as *(80)* and *(81)*, which can be coupled at both ends. Mixtures of monometalated and dimetalated substrates *(77)* and *(80)* therefore



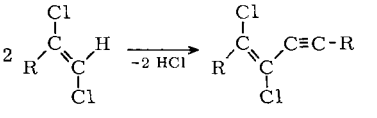
(80) *(81)*

give not only the dimers but also trimers, tetramers, and higher oligomers, whose relative yields depend on the ratio of the monometalated to the dimetalated species[66].

$$\underset{(77)}{H{-}[CCl]_4{-}Li} + (x-2)\,\underset{(80)}{Li{-}[CCl]_4{-}Li} + \underset{(77)}{Li{-}[CCl]_4{-}H} \rightarrow$$

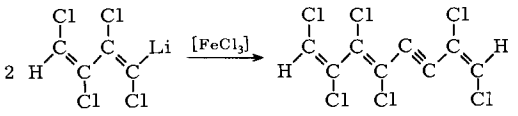
$$\rightarrow H{-}[CCl]_{4x}{-}H \qquad x = 2, 3, 4 \ldots$$

If less than the equimolar quantity of iron(III) salt is used for the coupling (optimum 1/4—1/3 mole of $FeCl_3$ per mole of carbenoid), the reaction surprisingly leads to polychloropolyenynes[67a] in accordance with the overall equation (27).



(27)

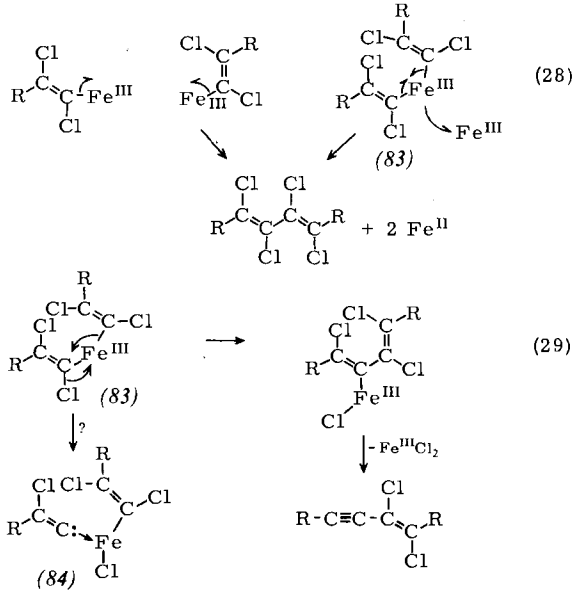
This novel reaction, whose final result is a dehydrohalogenation, and which can therefore be described as an *eliminative coupling*[67b], also proceeds stereospecifically, and the main product obtained *e.g.* from *(77)* is 1,3,7-octatrien-5-yne *(82)*[67].



(77) *(82)*

According to the experiments carried out so far, the product always contains only *one* triple bond, which is located at one of the formerly metalated carbon atoms. It is formed during the coupling, and not by subsequent dechlorination of the polyene. In complete contrast with the oxidative coupling, the iron salt has a purely catalytic function in eliminative coupling, *i.e.* it is found in its original oxidation state at the end of the reaction[67a].

To explain the reactions, it is assumed that the intermediate organoiron compounds having the partial structure *(83)* preferentially undergo oxidative coupling in the presence of sufficient quantities of iron salt (or of some other oxidizing agent) [eq. (28)], but otherwise undergo a rearrangement (possibly *via* carbene-iron complexes *(84)*) with subsequent β-elimination [eq. (29)].



(28)

(29)

As can be seen especially from the last section, the chemistry of carbenoids, which is closely interwoven with the chemistry of other thermolabile organometallic compounds, is full of surprises and mechanistic problems, but also of preparative possibilities whose further investigation presents an attractive task.

My work in this field has been carried out at the Institute of Organic Chemistry at the University of Heidelberg. I am grateful to many persons at this Institute who have contributed in numerous ways to the success of this work, and above all to those named in the references as my co-workers. I am also grateful to the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, the Bundesministerium für Wissenschaftliche Forschung, the Wirtschaftsministerium des Landes Baden-Württemberg, and numerous companies, particularly the Badische Anilin- und Soda-Fabrik, Ludwigshafen, for the promotion of the studies by material and financial support.

Received: July 30, 1971; supplemented: April 19, 1972 [A 882 IE]
German version: Angew. Chem. *84*, 557 (1972)
Translated by Express Translation Service, London

[1] Stable Carbenoids, Part 47.—Part 46: Ref. [36].

[2] *H. Gilman* and *R. D. Gorsich*, J. Amer. Chem. Soc. *77*, 3919 (1955); *78*, 2217 (1956); *H. Gilman* and *T. S. Soddy*, J. Org. Chem. *22*, 1715 (1957).

[3] a) *J. Hine:* Divalent Carbon. Ronald Press, New York 1964; b) *W. Kirmse:* Carbene Chemistry. 2nd Edit. Academic Press, New York 1971; Carbene, Carbenoide und Carbenanaloge. Verlag Chemie, Weinheim 1969.

[4] *G. Wittig* and *H. Witt*, Ber. dtsch. chem. Ges. *74*, 1474 (1941); *G. Wittig* and *G. Harborth*, *ibid. 77—79*, 306, 315 (1944).

[5] a) *G. Köbrich et al.*, Angew. Chem. *79*, 15 (1967); Angew. Chem. internat. Edit. *6*, 41 (1967); b) *G. Köbrich*, Bull. Soc. Chim. France *1969*, 2712.

[6] *U. Schöllkopf* in *Houben-Weyl-Müller:* Methoden der organischen Chemie. Vol. 13/1, Georg Thieme-Verlag, Stuttgart 1970, pp. 93 ff.; b) *T. Chivers*, Organometal. Chem. Rev. *A 6*, 1 (1970).

[7] *G. Köbrich* and *H. Trapp*, Z. Naturforsch. *18b*, 1125 (1963); *G. Köbrich*, *H. Trapp*, and *I. Hornke*, Tetrahedron Lett. *1964*, 1131; *G. Köbrich* and *K. Flory*, *ibid. 1964*, 1137.

[8] *G. Köbrich*, *K. Flory*, and *W. Drischel*, Angew. Chem. *76*, 536 (1964); Angew. Chem. internat. Edit. *3*, 513 (1964).

[9] a) *G. Köbrich* and *W. Drischel*, Angew. Chem. *77*, 95 (1965); Angew. Chem. internat. Edit. *4*, 74 (1965); b) *G. Köbrich*, *H. R. Merkle*, and *H. Trapp*, Tetrahedron Lett. *1965*, 969; c) *G. Köbrich*, *K. Flory*, and *H. R. Merkle*, *ibid. 1965*, 973; d) *G. Köbrich*, *K. Flory*, *H. R. Merkle*, and *H. Trapp*, Angew. Chem. *77*, 590 (1965); Angew. Chem. internat. Edit. *4*, 594 (1965).

[10] a) *G. Köbrich* and *H. Trapp*, Chem. Ber. *99*, 670, 680 (1966); b) *G. Köbrich*, *H. Trapp*, *K. Flory*, and *W. Drischel*, *ibid. 99*, 689 (1966); c) *G. Köbrich* and *K. Flory*, *ibid. 99*, 1773 (1966); d) *G. Köbrich* and *H. R. Merkle*, *ibid. 99*, 1782 (1966); e) *G. Köbrich*, *K. Flory*, and *R. H. Fischer*, *ibid. 99*, 1793 (1966); f) *G. Köbrich* and *W. Drischel*, Tetrahedron *22*, 2621 (1966); g) *G. Köbrich*, *H. Trapp*, and *I. Hornke*, Chem. Ber. *100*, 961 (1967).

[11] a) *D. F. Hoeg*, *D. I. Lusk*, and *A. L. Crumbliss*, J. Amer. Chem. Soc. *87*, 4147 (1965); b) *D. Seyferth* and *F. M. Armbrecht*, J. Organometal. Chem. *16*, 249 (1969).

[12] *D. Seyferth*, Annu. Surv. Organometal. Chem. *1*, 8 (1965); *2*, 11 (1966); see also [11b].

[13] *W. T. Miller* and *D. M. Whalen*, J. Amer. Chem. Soc. *86*, 2089 (1964).

[14] *G. Köbrich* and *R. H. Fischer*, Tetrahedron *24*, 4343 (1968).

[15] *W. A. Bernett*, J. Chem. Educ. *44*, 17 (1967); *M. Charton* in *S. Patai:* The Chemistry of Alkenes. Vol. 2. Interscience, London 1970. pp. 511 ff.

[16] *G. Köbrich* and *W. Goyert*, Tetrahedron *24*, 4327 (1968).

[17] *G. Köbrich* and *F. Ansari*, Chem. Ber. *100*, 2011 (1967).

[18] *W. Werner*, unpublished experiments, Heidelberg.

[19] *G. Köbrich* and *E. Wagner*, Angew. Chem. *80*, 481 (1968); Angew. Chem. internat. Edit. *7*, 470 (1968); Chem. Ber. *103*, 2515 (1970).

[20] *A. Roedig* and *N. Detzer*, Angew. Chem. *80*, 482 (1968); Angew. Chem. internat. Edit. *7*, 471 (1968).

[21] a) *G. Wittig* and *M. Schlosser*, Chem. Ber. *94*, 1373 (1961); b) *G. Köbrich*, *H. Trapp*, *K. Flory*, and *W. Drischel*, *ibid. 99*, 689 (1966).

[22] *E. J. Corey* and *T. Durst*, J. Amer. Chem. Soc. *88*, 5656 (1966); *90*, 5548 (1968); *T. Durst*, *ibid. 91*, 1034 (1969); Tetrahedron Lett. *1970*, 2369.

[23] a) *W. E. Truce* and *L. W. Christensen*, Tetrahedron Lett. *1969*, 3075; b) Chem. Commun. *1971*, 588.

[24] *M. Baumann*, Diplomarbeit, Universität Heidelberg 1970.

[25] *F. G. Drakesmith, R. D. Richardson, O. J. Stewart,* and *P. Tarrant,* J. Org. Chem. *33,* 286 (1968).

[26] *M. Schlosser* and *V. Ladenberger,* Chem. Ber. *100,* 3877, 3893 (1967); Tetrahedron Lett. *1964,* 1945.

[27] *R. H. Fischer* and *G. Köbrich,* Chem. Ber. *101,* 3230 (1968).

[28] a) *G. Köbrich, W. E. Breckoff, H. Heinemann,* and *A. Akthar,* J. Organometal. Chem. *3,* 492 (1965); b) *G. Köbrich* and *H. Heinemann,* Angew. Chem. *77,* 590 (1965); Angew. Chem. internat. Edit. *4,* 594 (1965); c) *G. Köbrich, H. Heinemann,* and *W. Zündorf,* Tetrahedron *23,* 565 (1967).

[29] *L. Vo-Quang* and *P. Cadiot,* Bull. Soc. Chim. France *1965,* 1521.

[30] a) *W. Tochtermann, H.-O. Horstmann, C. Degel,* and *D. Krauss,* Tetrahedron Lett. *1970,* 4719; b) *W. Tochtermann,* personal communication.

[31] *G. Köbrich, H. Trapp,* and *A. Akhtar,* Chem. Ber. *101,* 2644 (1968).

[32] *P. Buck* and *G. Köbrich,* Tetrahedron Lett. *1967,* 1563; *G. Köbrich* and *P. Buck,* Chem. Ber. *103,* 1412 (1970).

[33] *P. Buck,* Angew. Chem. *81,* 136 (1969); Angew. Chem. internat. Edit. *8,* 120 (1969).

[34] *G. Köbrich* and *P. Buck,* Angew. Chem. *78,* 1062 (1966); Angew. Chem. internat. Edit. *5,* 1044 (1966); *P. Buck* and *G. Köbrich,* Angew. Chem. *79,* 986 (1967); Angew. Chem. internat. Edit. *6,* 966 (1967); Chem. Ber. *103,* 1420 (1970).

[35] a) *G. Köbrich* and *R. H. Fischer,* Chem. Ber. *101,* 3208 (1968); b) *G. Köbrich* and *I. Stöber, ibid. 103,* 2744 (1970).

[36] *G. Köbrich* and *R. v. Nagel,* Chem.-Ztg. *94,* 984 (1970).

[37] *B. Castro* and *J. Villiéras,* C. R. Acad. Sci. *264,* 1609 (1967).

[38] *E. J. Corey, M. Jautelat,* and *W. Oppolzer,* Tetrahedron Lett. *1967,* 2325.

[39] *G. Köbrich* and *R. H. Fischer,* Chem. Ber. *101,* 3219 (1968).

[40] *P. S. Skell* and *M. S. Cholod,* J. Amer. Chem. Soc. *91,* 6035, 7131 (1969).

[41] a) *K. G. Taylor* and *W. E. Hobbs,* Tetrahedron Lett. *1968,* 1221; *K. G. Taylor, W. E. Hobbs,* and *M. Saquet,* J. Org. Chem. *36,* 369 (1971); b) *B. Martel* and *J. M. Hiriart,* Tetrahedron Lett. *1971,* 2737; c) *J. Villieras,* Bull. Soc. Chim. France *1967,* 1520.

[42] See, *e. g., R. Breslow* and *L. J. Altman,* J. Amer. Chem. Soc. *88,* 504 (1966).

[43] *H. E. Simmons* and *R. D. Smith,* J. Amer. Chem. Soc. *80,* 5323 (1958); *E. P. Blanchard* and *H. E. Simmons, ibid. 86,* 1337 (1964); *H. E. Simmons, E. P. Blanchard,* and *R. D. Smith, ibid. 86,* 1347 (1964); *G. Wittig* and *F. Wingler,* Liebigs Ann. Chem. *656,* 18 (1962); Chem. Ber. *97,* 2139, 2146 (1964).

[44] *G. L. Closs* and *L. E. Closs,* Angew. Chem. *74,* 431 (1962); Angew. Chem. internat. Edit. *1,* 334 (1962); *G. L. Closs* and *J. J. Coyle,* J. Amer. Chem. Soc. *84,* 4350 (1962); *87,* 4270 (1965); *G. L. Closs* and *R. A. Moss, ibid. 86,* 4042 (1964).

[45] *W. R. Moore* and *W. R. Moser,* J. Amer. Chem. Soc. *92,* 5469 (1970).

[46] *G. Köbrich, H. Büttner,* and *E. Wagner,* Angew. Chem. *82,* 177 (1970); Angew. Chem. internat. Edit. *9,* 169 (1970).

[47] *D. Seebach* and *A. K. Beck,* J. Amer. Chem. Soc. *91,* 1540 (1969); *D. Seebach,* Angew. Chem. *79,* 468, 469 (1967); Angew. Chem. Internat. Edit. *6,* 442, 443 (1967); Chem. Ber. *105,* 487 (1972).

[48] a) *E. A. Braude,* Progr. Org. Chem. *3,* 191 (1955); *D. Y. Curtin* and *J. W. Crump,* J. Amer. Chem. Soc. *80,* 1922 (1958), and further literature cited therein; b) *G. Szeimies,* Tetrahedron Lett. *1970,* 1949; *S. I. Miller* and *W. G. Lee,* J. Amer. Chem. Soc. *81,* 6316 (1959).

[49] a) *G. Wittig* and *U. Pockels,* Ber. dtsch. chem. Ges. *72,* 89 (1939); b) *G. Wittig* and *U. Schöllkopf,* Tetrahedron *3,* 91 (1958).

[50] a) *G. Köbrich* and *R. v. Nagel,* Tetrahedron Lett. *1970,* 4693; b) *R. v. Nagel* and *G. Köbrich, ibid. 1970,* 4697; c) The reaction was also studied by *D. Seyferth, R. L. Lambert,* and *E. M. Hanson,* J. Organometal. Chem. *24,* 647 (1970), who failed to observe the commutation corresponding to eq. (22).

[51] For reviews, see *G. Köbrich* and *P. Buck* in *H. G. Viehe:* Chemistry of Acetylenes. Marcel Dekker, New York 1969, p. 99; *G. Köbrich,* Angew. Chem. *77,* 75 (1965); Angew. Chem. internat. Edit. *4,* 49 (1965).

[52] *A. A. Bothner-By,* J. Amer. Chem. Soc. *77,* 3293 (1955); *C. Y. Curtin, E. W. Flynn,* and *R. F. Nystrom, ibid. 80,* 4599 (1958).

[53] *G. Köbrich, G. Reitz,* and *U. Schumacher,* Chem. Ber. *105,* 1674 (1972); *G. Reitz,* Diplomarbeit, Universität Heidelberg 1969.

[54] *G. Köbrich* and *D. Merkel,* Angew. Chem. *82,* 257 (1970); Angew. Chem. internat. Edit. *9,* 243 (1970); Chem. Ber. *105,* 1683 (1972).

[55] *G. Märkl* and *A. Merz,* Tetrahedron Lett. *1971,* 1269.

[56] *G. L. Closs* and *V. N. M. Rao,* J. Amer. Chem. Soc. *88,* 4116 (1966).

[57] *G. Köbrich* and *W. Werner,* Tetrahedron Lett. *1969,* 2181.

[58] For reviews of nucleophilic acylations, see *D. Seebach,* Angew. Chem. *81,* 690 (1969); Angew. Chem. internat. Edit. *8,* 639 (1969); Synthesis *1969,* 17.

[59] *A. Kirrmann, P. Duhamel,* and *R. Nouri-Bimorghi,* Liebigs Ann. Chem. *691,* 33 (1966); review: *R. N. McDonald* and *B. S. Thyagarajan:* Mechanisms of Molecular Migrations. Interscience, New York 1971, pp. 67ff.

[60] a) *J. A. Deyrup* and *R. B. Greenwald,* Tetrahedron Lett. *1965,* 321; b) *G. Cainelli, A. U. Ronchi, F. Bertini, P. Grasselli,* and *G. Zubiani,* Tetrahedron *27,* 6109 (1971).

[61] *G. Köbrich* and *H. R. Merkle,* Chem. Ber. *100,* 3371 (1967); Angew. Chem. *79,* 50 (1967); Angew. Chem. internat. Edit. *6,* 74 (1967).

[62] *G. Wittig, L. Gonsior,* and *H. Vogel,* Liebigs Ann. Chem. *688,* 1 (1965); *H. Jäger* and *G. Hesse,* Chem. Ber. *95,* 345 (1962).

[63] *A. Suzuki, N. Miyaura,* and *M. Itoh,* Tetrahedron *27,* 2775 (1971).

[64] *H. C. Brown, B. A. Carlson,* and *R. H. Prager,* J. Amer. Chem. Soc. *93,* 2070 (1971).

[65] *G. Köbrich, H. Fröhlich,* and *W. Drischel,* J. Organometal. Chem. *6,* 194 (1966); *H. Fröhlich,* Dissertation, Universität Heidelberg 1964; *M. Fariborz,* Diplomarbeit, Universität Heidelberg 1968.

[66] a) *G. Köbrich* and *H. Büttner,* Tetrahedron *25,* 883 (1969); b) *G. Köbrich* and *H. Büttner,* Naturwissenschaften *54,* 491 (1967).

[67] a) *G. Köbrich* and *H. Büttner,* Tetrahedron *25,* 2223 (1969); b) J. Organometal. Chem. *18,* 117 (1969).

Intermolecular Interactions: van der Waals Molecules[**]

By George E. Ewing[*]

Recent experiments using electron diffraction techniques, optical and infrared spectroscopy and mass spectroscopy have provided convincing evidence for the existence of bound states of gaseous Ar_2, $(H_2)_2$, $(O_2)_2$, $(NO)_2$ and other simple dimers. The bond strength of these van der Waals molecules is hundreds of times weaker than ordinary chemical bonds. These experimental studies yield information on the structure and stability of van der Waals molecules and can provide new insight into weak intermolecular interactions.

1. Introduction

The study of intermolecular interactions has always been an active area of research and reviews of the general subject appear each year[1-4]. One of the main purposes of experimental and theoretical work in this area is to characterize the shape of the intermolecular potential function. This goal has been approached by using measurements of bulk properties of matter, *e. g.*, virial coefficient and transport data of gases and various physical properties of solids and liquids to evaluate parameters of intermolecular potential functions. Theoretical work and particularly molecular beam scattering experiments have been valuable in determining, on the molecular level, properties of the intermolecular interactions.

Recently a few experiments have been described in which molecules bound by these weak intermolecular interactions have been studied. The measured properties of such van der Waals molecules, which provide a particularly direct approach to the study of intermolecular interactions, is the subject of this review.

Since theoretical studies of intermolecular interactions have been discussed elsewhere only those investigations which emphasize van der Waals molecules will be outlined here in the section entitled, "Theoretical Background" (see Section 2). In the other sections, experimental results will be described. Rather than mentioning in a cursory fashion all the work done in these areas several examples will be presented in detail to give the reader an insight into the new approaches possible in the study of van der Waals molecules. The discussion will be primarily restricted to studies of small van der Waals molecules bound by weak intermolecular interactions between atoms (*e.g.*, Ar_2, RbKr), or diatomic molecules (*e.g.*, $(H_2)_2$, $(HCl)_2$, $(NO)_2$). These weak intermolecular interactions include dispersion forces, hydrogen bonding and electric multipole interactions and lead to van der Waals bond strengths hundreds of times less than those usually associated with ordinary chemical bonding.

[*] Prof. Dr. G. E. Ewing
Department of Chemistry
Indiana University
Bloomington, Indiana 47401 (USA)

[**] This work (Contribution No. 2049) was supported by a grant from the National Science Foundation GP 27269.

2. Theoretical Background

It is particularly important to begin by defining what is meant by a van der Waals molecule. In the interaction of molecules in the gas phase it is possible to distinguish three types of binary encounters: collision pairs, metastable dimers, and bound dimers[5-7]. This is illustrated in Fig. 1 for atoms where the potential energy of interaction, $v(r)$, depends only on their separation, r. If the pair has angular momentum, indicated by the rotational quantum number L, then a centrifugal potential is added to give an effective potential

$$V_{eff} = V(r) + \frac{h^2}{8\pi^2\mu} \cdot \frac{L(L+1)}{r^2}$$

where μ is the reduced mass of the atoms and h is Planck's constant. The effect of the centrifugal potential is always positive and repulsive since when the pair is rotating centrifugal forces are in opposition to any attractive van

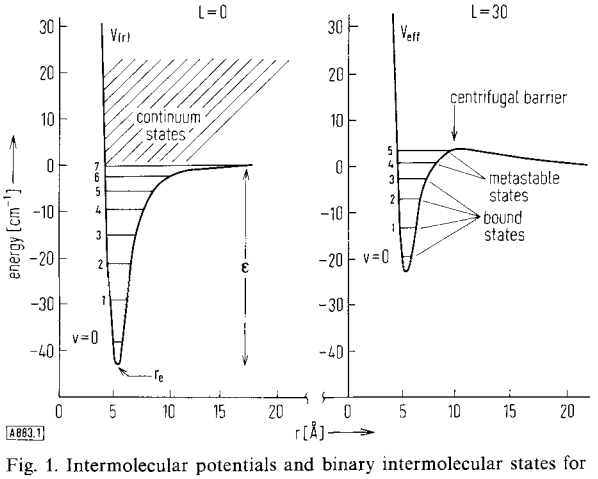


Fig. 1. Intermolecular potentials and binary intermolecular states for atoms.
The left side of the figure represents the binary pair interaction with no angular momentum (L = 0). The minimum of the potential curve occurs at a distance of r_e and the well depth is given by ε. The continuum states correspond to head-on collisions of the atoms. Below the dissociation limit bound states of the non-rotating van der Waals molecule exist.
On the right side of the figure the binary pair has angular momentum (*e. g.* L = 30). The atoms undergo glancing collisions above the centrifugal barrier. Below the barrier there are discrete levels for the rotating van der Waals molecules. (Data for RbAr are taken from Ref. [14]. The energy levels for L = 0 were estimated using a Morse potential, see Ref. [15].)

der Waals forces. Interacting atoms with no angular momentum ($L=0$; $V_{eff}=V(r)$) are described in Fig. 1.

Two atoms which reside in one of the vibration levels indicated by the quantum number v in the potential well below the dissociation limit are bound dimers. Atoms in the continuum of states above the dissociation limit are collision pairs.

If the interacting atoms are rotating then $L\neq 0$, and the effective potential exhibits a hump or barrier (centrifugal barrier). Dimers in the region below the dissociation limit are bound; dimers in the region above the dissociation limit but below the barrier of the effective potential curve are metastable. From the point of view of classical mechanics these dimers would be stable but quantum mechanically they can "leak" or "tunnel" through the potential barrier.

Formation of bound states without angular momentum, *i. e.* when $L=0$, can occur only when two approaching atoms in the continuum collide in the presence of another atom or molecule. This third body removes excess kinetic energy so the colliding pair can drop into one of the descrete levels in the intermolecular potential well. For $L\neq 0$ a third body is also needed if the pair has kinetic energy above the centrifugal barrier. However, if the colliding pair approach each other below the barrier, but above the dissociation limit, it is possible that tunneling can occur to form a dimer if the energy matches one of the metastable levels. Finally in the region immediately above the centrifugal barrier "resonances" can occur which physically correspond to multiple orbiting of the collision pair followed by dissociation.

Extension of the above definitions to intermolecular interactions of diatomic or polyatomic molecules in which the potential energy depends also on their relative orientations is analogous although exceedingly complicated.

For the purposes of this review van der Waals molecules will refer only to metastable and bound dimers. Molecules residing in the continuum above the potential barrier or —in the case of $L=0$—above the dissociation limit, will be called collision pairs.

There are a variety of potential functions which can be used to represent intermolecular interactions. In the experimental investigations of van der Waals molecules to be discussed here the analysis of data can often be made on the basis of angularly independent potential functions. If the system is complex and depends on the relative orientation of the constituents of the van der Waals molecule the analysis usually cannot be carried out far enough to specify angular dependence of the intermolecular potential.

A particularly useful angularly independent description of intermolecular interactions is the Lennard-Jones (6—12) potential,

$$V(r)=\varepsilon\left[\left(\frac{r_e}{r}\right)^{12}-2\left(\frac{r_e}{r}\right)^{6}\right] \tag{1}$$

where ε is the well depth and r_e is the value of the interparticle distance at the bottom of the well.

Table 1. Lennard-Jones (6—12)-parameters for some typical van der Waals interactions (after Ref. [8]).

System	ε/k [°K]	$R\varepsilon/k$ [cal/mole]	ε/hc [cm^{-1}]	r_e [Å]
He—He	10.22	20.31	7.10	2.869
H_2—H_2	37.00	73.53	25.72	3.287
Ar—Ar	119.8	238.1	83.27	3.822
Xe—Xe	221	439	154	4.602
N_2—N_2	95.05	188.9	66.07	4.151
O_2—O_2	117.5	233.5	81.67	4.02
NO—NO	131	260	91.05	3.56
Cl_2—Cl_2	357	709	248	4.619
I_2—I_2	550	1093	382	5.592
HCl—HCl	360	715	250	3.710
HI—HI	324	644	225	4.628

Values of the Lennard-Jones parameters for a number of molecules are given in Table 1. These values have not been determined from studies of van der Waals molecules but from an analysis of thermodynamic data. Non-spherical molecules are included even though they cannot be strictly treated by the angularly independent Lennard-Jones potential. However, as we shall see from the experiments to be discussed, angularly dependent interactions are very important for some of these molecules—particularly at low temperatures. A Lennard-Jones (6—10) potential is sometimes used, since it simplifies mathematical treatment. A variety of other intermolecular potentials have also been suggested[8].

A particularly useful function for analyzing spectroscopic data is the Morse potential[9],

$$V(r)=\varepsilon[(1-e^{-\beta(r-r_e)})^2-1] \tag{2}$$

which contains three parameters, r_e, β, and ε. The Hamiltonian containing this potential can be solved analytically by quantum mechanics. The resulting vibrational energy levels (in cm^{-1}) of the Morse potential (for $L=0$) are given by

$$G(v)=\omega_e(v+\tfrac{1}{2})-\omega_e x_e(v+\tfrac{1}{2})^2 \tag{3}$$

$$\omega_e=\frac{\beta}{\pi c}\sqrt{\frac{\varepsilon}{2\mu}};\qquad x_e=\frac{hc}{4\varepsilon}\omega_e$$

The vibration levels are measured from the bottom of the well. Thus if $G(v)$ is determined for several vibrational quantum levels the parameters ε and β can be evaluated. Using a value of r_e from other data enables the entire potential function to be evaluated from spectroscopic data.

There have been a number of theoretical determinations of the energy levels of van der Waals molecules. *Cashion*[10] has calculated numerical solutions of the radial Schrödinger equation for the vibrational and rotational energy levels using the Lennard-Jones (6—12) potential. The formula derived by this author is expressed by the coefficients Y_{ij}

$$T(v,L)=\sum_{i,j}Y_{ij}(v+\tfrac{1}{2})^i L^j(L+1)^j \tag{4}$$

where $T(v,L)$ is the energy of a level in the vibration and rotational quantum states v and L respectively. Each of the 18 Y_{ij} coefficients calculated is given in terms of the ε and r_e Lennard-Jones parameters. A desk calculator or

small computer can then be used to evaluate quantum levels with great precision. Despite the usefulness of these formulas and the ease with which precise energy values may be evaluated it must not be forgotten that a van der Waals molecule which obeys a Lennard-Jones (6—12) potential is a hypothetical molecule.

Cashion also gives the number of bound and metastable states for a few van der Waals molecules. For $(O_2)_2$ the (L=0)-state has seven bound vibrational levels. Since the centrifugal barrier effectively reduces the depth of the potential well (see Fig. 1) higher L states have fewer vibrational levels. The total number of bound v and L states for $(O_2)_2$ is 140. The total number of levels range from 1 for $(He)_2$, 2 for $(H_2)_2$, 171 for $(Ar)_2$ to over 10000 for $(I_2)_2$. The estimate for $(He)_2$ is particularly interesting since the existence of a bound state of this dimer depends critically on the values of ε and r_e selected for the calculation.

Estimates of bound state energy levels have been made by others. The Morse potential can be adjusted to describe gas phase intermolecular interactions, and the vibrational states follow from Eq. 3[10-12]. Perturbation, variational, and WBK calculations have also provided bound state energy levels[6, 13-15].

A knowledge of the van der Waals molecule energy level distributions enables the equilibrium constant, K, for the dimerization $A+A \rightleftarrows A_2$ to be calculated[15, 16]. It may be expressed in terms of the partition functions for monomer Q_A and dimer Q_A as follows:

$$K = \frac{[A_2]}{[A]^2} = \frac{(Q_{A_2}/V)}{(Q_A/V)^2} e^{+\varepsilon/kT} \quad (5)$$

where [ ] indicates concentration in moles/liter. If A represents a $^1S_0$ atom then only the translational energy contributes to the partition function:

$$Q_A = \frac{(2\pi m_A kT)^{3/2}}{h^3} V$$

with m_A the mass of A and V the volume of the system. The dimer partition function A_2 is

$$Q_{A_2} = \frac{(4\pi m_A kT)^{3/2}}{h^3} V \cdot \sum_{v,L} e^{-E(v,L)/kT}$$

where the sum over van der Waals bound levels must take account of nuclear spin symmetry. There are a number of simplications that can be used in evaluating K, particularly in summing terms of the dimer partition function. It is also important to notice whether a distinction between metastable and bound dimers is made in determining $[A_2]$.

Stogryn and *Hirschfelder*[6] who review earlier estimates use a classical partition function yet calculate metastable and bound dimer concentrations separately. These results are interesting to examine since they give an idea of the small concentrations of dimers present even under conditions which favor their formation. For example, consider argon at a temperature of 120°K which is equal to the well depth ε/k. At a concentration $[Ar]=1/22.4$ mole/liter (this would equal a pressure of 1 atm at STP) only 0.35% of the argon atoms are bound dimers while 0.16% are metastably dimerized. Concentration of van der Waals molecules have been calculated for alkali metal-rare gas pairs[14-15] and many other simple systems[11, 12, 17].

The lifetime of metastables has been estimated by the WKB method for a number of systems which are assumed to obey an angularly-independent intermolecular potential[6, 14]. For Ar_2 the mean lifetime of metastable states ranges from 10^{-11} s to well over 10^{10} s[6]. Since the mean time between collisions at one atmosphere and room temperature is of the order of 10^{-9} to 10^{-10} s most metastable molecules will probably be dissociated by collisions rather than by leaking through the centrifugal barrier. For the example in Figure 1 (L=30 for RbAr) *Baylis* has estimated a lifetime of 9×10^4 s for the v=4 level[14]; however, for v=5, which is near the top of the barrier, the lifetime is only 3×10^{-10} s.

Most of the discussion above applies to van der Waals molecules formed by the dimerization of atoms. In the case of dimers involving molecules (*e.g.*, HCl·Ar, $(N_2)_2$, $(O_2)_2$) it is often assumed that an angularly independent potential can be used to describe the interaction; this is probably a poor approximation in many cases. As we shall see, successful analysis of spectra of van der Waals data has been possible only in limiting cases: When both molecules of the dimer (*e.g.*, $(H_2)_2$) are freely rotating, angular dependent terms in the intermolecular potential are neglible. At the other extreme (*e.g.*, $(NO)_2$), molecules within the dimer have a locked geometry determined by very large angular-dependent potential terms. Between these two limiting cases the investigation of van der Waals molecules is exceedingly complicated.

One of the purposes of this Section has been to draw attention to some of the unique properties of van der Waals molecules. The extreme weakness of van der Waals bonds implies their exhibiting a number of properties which distinguish them from ordinary molecules.

The dissociation energy of a typical dimer is a few hundred cal/mol (see Table I) which is hundreds of times smaller than that of an ordinary chemical bond. Even at low temperatures where the kinetic energy becomes comparable to the well depth, less than 1% of the gas will be dimeric at pressures of 1 atm. Lowering the temperature further will of course increase the dimer concentration provided the monomer density does not change. However, below the gas condensation point the pressure decreases rapidly, so that the concentration of dimer, which depends quadratically on monomer density ($[A_2]=K[A]^2$), will also drop very significantly. These facts suggest that non-equilibrium techniques ought to be employed for the generation of van der Waals molecules. Since rotational kinetic energy is comparable to the intermolecular well depth, the concentration of metastable dimers is nearly the same as bound dimers.

Ordinary molecules are usually studied in their ground vibrational states because upper levels are not significantly populated. On the other hand, all the vibrational levels will be occupied in an investigation of van der Waals molecules because of their small spacings. As can be imagined, all these properties peculiar to van der Waals molecules make their experimental study particularly challenging. This explains, in part, why information on these interesting molecules has only recently become available.

3. Electron Diffraction

A direct and particularly exciting approach to the study of van der Waals molecules has been reported by *Audit, Rouault,* and *Farges*[18–21]. The authors describe the use of electron diffraction from molecular beams. Compressed gas is allowed to expand through a nozzle and the supersonic jet so produced is thereby adiabatically cooled (see Fig. 2). A skimmer and collimator placed in front of the nozzle reduces the jet to a molecular beam, and an electron beam directed perpendicularly produces an electron diffraction scattering pattern onto a photographic plate below. The condensation state of the final molecular beam depends on the initial pressure and temperature of the gas and on the geometry of the nozzle and collimator system. At room temperature and pressures of 50 atmospheres effective beam temperatures down to 35°K can be realized. Depending on the initial conditions, the molecular beam will contain monomers, dimers, polymers or particles of liquid or solid.

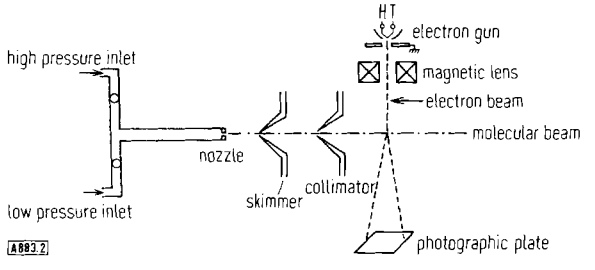


Fig. 2. Schematic diagram of a supersonic molecular beam electron diffractometer. Gases are expanded through a nozzle to produce an adiabatically cooled supersonic jet which is then collimated into a molecular beam which contains van der Waals molecules. An electron beam crossed into the molecular beam produces a diffraction pattern onto a photographic plate [18—21].

The diffraction pattern provides a means for determining the composition of the molecular beam: The smooth structureless pattern observed at low pressure is characteristic of scattering from atoms. At the highest pressures a complex scattering pattern corresponds to interference of the electron beam by an ordered array of atoms. From this pattern the crystal structure and lattice parameters for solid particles can be obtained. In regions of intermediate pressures a simpler diffraction pattern is observed which is produced by interference of atoms in van der Waals molecules. The scattering pattern on the photographic plate can be readily reduced to an interference function $G(s)$. The predicted form it takes for dimers is

$$G(s) = 2 + 2\frac{\sin sr}{sr} \tag{6}$$

where $s=(4\pi/\lambda)\sin\theta/2$ is called the scattering vector modulus; λ is the wavelength of the electron beam and θ the scattering angle[21]. The interference function is particularly simple for scattering from dimers because only a single characteristic distance, the bond length r, determines the interference of the electron beam. The dimer bond length may then be easily determined by fitting the experimental data to eq. (6).

Properly chosen initial gas conditions will produce a molecular beam containing about 50% van der Waals molecules. The interference function calculated for Ar_2 from Eqn. (6) is shown in Fig. 3[21]. The interatomic distance obtained is $r=3.93\pm.06$ Å. This is somewhat longer than the Lennard-Jones value of $r_e=3.82$ Å (cf. Table I); however, the distance measured in the electron diffraction experiment is averaged over the vibrational states of Ar_2 which are all significantly populated even at low temperatures. The expected values for the first vibrational levels, $<r>_v$, as given by *Cashion*[22] are $<r>_0=3.89$ Å, $<r>_1=4.08$ Å and $<r>_2=4.31$ Å. A comparison of these distances with the results of electron diffraction is therefore entirely consistent.

In addition to the positions of the maxima in the interference pattern the decay of the pattern also contains information on the properties of the van der Waals molecule. Since each vibrational state of the molecule produces a slightly different interference spacing the decay of the pattern becomes a measure of the distribution of bond lengths. Including this effect the interference function becomes

$$G(s) = 2 + 2e^{-l^2s^2/2}\frac{\sin sr}{sr}$$

where l is the mean vibrational displacement.

The intense scattering pattern observed for Xe_2 enabled the determination[21] of l. A value of $l=0.11$ Å was obtained for bond length $r=4.41\pm.03$ Å. The large value

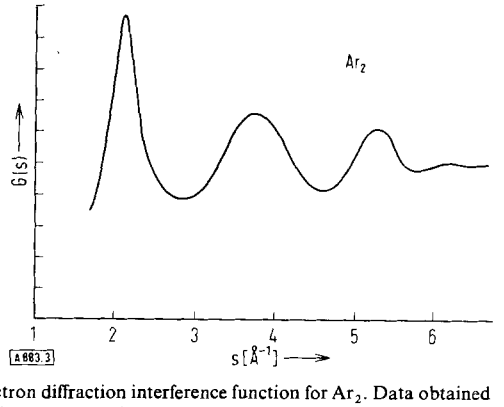


Fig. 3. Electron diffraction interference function for Ar_2. Data obtained from the electron scattering pattern of Ar_2 van der Waals molecules contained in a supersonic molecular beam [21].

of l is consistent with the anharmonicity of the intermolecular potential well and the population of many vibrational levels in the sample studied. Since the mean vibrational displacement depends on temperature and the shape of the potential function, a measurement of l at a known temperature would enable the van der Waals interaction to be characterized. Unfortunately, the effective vibrational temperature of these molecular beams is uncertain so l can only be used to test the feasibility of the Lennard-Jones parameters.

The application of supersonic jets and electron diffraction techniques to the study of polyatomic van der Waals molecules appears promising. Studies with CO_2 suggest that the molecular beams produced contain $(CO_2)_2$[23]. Since this system is more complex than dimers of the rare gases, analysis of the data is not yet complete. In the near future structural information on this and other polyatomic van der Waals molecules will undoubtably be available and, from the determined geometry, the angular dependence of intermolecular interactions can then be inferred. A recent review by *Bonham*[24] of electron diffraction studies of dimers and polymers of strongly hydrogen bonded molecules, which are somewhat outside the scope of the present review, is recommended. Future electron diffraction studies may provide some of the most valuable information on polyatomic van der Waals molecules.

4. Spectroscopy

One of the most dramatic examples of the usefulness of spectroscopy to the study of van der Waals molecules has been the recent investigation of Ar_2 by *Tanaka* and *Yoshino*[25]. The ground state of argon is $3p^6 — {}^1S_0$. On excitation a p electron is promoted to a higher unfilled atomic orbital. Absorption of low pressure gaseous argon at room temperature to these states occurs in the vacuum UV region and gives the usual atomic line absorption profiles. However, at liquid nitrogen temperatures the gaseous argon absorption reveals fine structure which has been convincingly assigned to vibration transitions of bound Ar_2 van der Waals molecules. In the longest wavelength region (System I, Fig. 4) the molecular absorption is described by a ${}^3\Sigma_u^+ \leftarrow {}^1\Sigma_g^+$ transition. The upper dimer state correlates to one atom being in its lowest excited state $3p^5 4s^1 — {}^3P_2^0$, while the other atom is in its ground state. The ground state dimer is bound by the dispersion forces of two ground state argon atoms. Absorption of a dimer with one ${}^1S_0$- and one ${}^3P_1^0$-atom is labeled as System II.

Fig. 4 shows the experimental data for these systems. On the long wavelength side of each of the atomic resonance lines, the vibrational bandheads of the dimer are plainly evident. For these systems transitions from $v''=0$ to $v''=4$ vibrational levels of the ground state dimer to several vibrational levels of the excited states are observed. The separation between the ground ($v''=0$) and first excited vibrational state ($v''=1$) of Ar_2 was determined as 25.5 cm^{-1}, and evidence from other observed band systems suggested six bound vibrational states for the potential with $L=0$. From the spectroscopically determined vibrational spacings, and an assumed equilibrium distance, the potential curve for Ar_2 is constructed using a Morse potential. The derived dissociation energy $\varepsilon = 91.6$ cm^{-1} (262 cal/mol) is within 10% of that determined from physical measurements (cf. Table I). *Bruch* and *McGee*[26] point out that the extrapolated value of ε obtained from the spectroscopic data depends significantly on the assumed functional form of the potential and can give results that vary by as much as 10%.

The band head positions determined from spectroscopic data do not correspond to a potential $L=0$. When an analysis of the rotational contour of the dimer bands is available, we can expect a more precise determination of

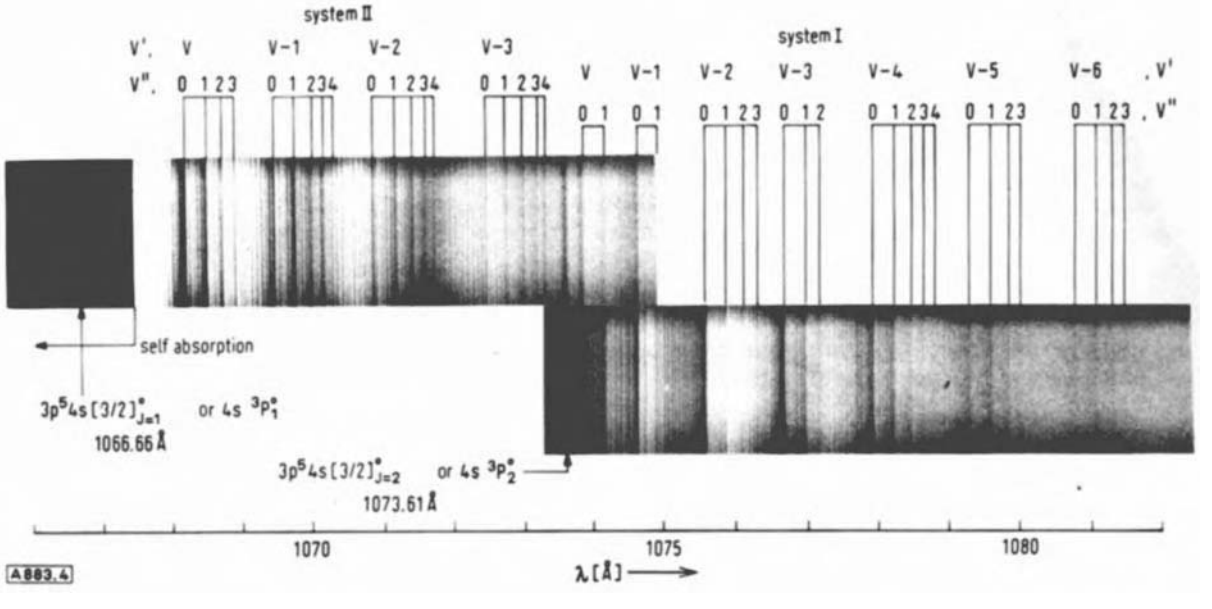


Fig. 4. The absorption spectrum of Ar_2. The absorption cell containing argon was cooled by liquid nitrogen. The argon pressures were 10 to 20 torr for the top and bottom exposures, respectively. The regions of strong absorption near 1066.66 Å and 1073.61 Å represent transitions of atomic argon. On the long-wavelength side of these atomic transitions are bandheads of the vibrational transitions of Ar_2 [25].

the intermolecular potential. Vacuum UV studies of Xe_2 and other rare gas dimers[27] will undoubtedly provide a rich source of information on these van der Waals molecules.

Optical absorption and emission studies of other diatomic van der Waals molecules have not yielded unambiguous information on intermolecular interactions. Diffuse band systems, which suggest collision pair transitions, have been reported for Hg_2, Cd_2, and Zn_2, and other homonuclear molecules[28]. Some fine structure has been observed in absorption studies of HgAr and a detailed analysis has provided evidence that the absorbing species are bound states based on energy level calculations on an assumed form of an intermolecular potential[29]. Structuring observed in other spectroscopic studies of Hg with foreign gases has been reported but has not been analyzed in detail[30]. Many studies of the emission and absorption spectra of alkali metal-foreign gas mixtures have been reported and are reviewed elsewhere[31-34]. Satallite bands both to the high and low frequency side of the alkali metal transitions depend on the foreign gas, pressure, and temperature in a complex way. Interpretation of this data is still controversial and while some of the features may involve transitions of van der Waals molecules[35-36], it is evident that much of the absorption arises from collision pairs[37].

Further experimental and theoretical work will be required before the spectroscopy of alkali metal—foreign gas mixtures is fully understood.

Optical pumping experiments have provided evidence for van der Waals molecules in alkali metal-rare gas pairs[38]. In these studies the hyperfine levels in the alkali metal are split by a magnetic field and are optically pumped to obtain a nonequilibrium population distribution; the relaxation of these states to equilibrium is then measured. Relaxation can occur during collisions with another atom, usually a rare gas.

In experiments with Rb—Kr two relaxation times were distinguished[39-40]. One, τ_2, of the order of 10^{-12} s, reasonably corresponds to the duration of a kinetic collision; the second, τ_1, of the order of 10^{-8} s, is identified with the lifetime of a metastable or bound state van der Waals molecule. Since, however, the Rb—Kr molecule is very likely destroyed on each collision with another atom, the time measured is actually the time between collisions. This is made apparent since τ_1 becomes shorter as a foreign gas such as He is added to the system.

It is difficult to predict what new information about the intermolecular potential will become available from optical pumping experiments. Nevertheless it does appear to be a useful technique for measuring lifetimes of van der Waals molecules containing an alkali metal.

A particularly valuable spectroscopic approach to the investigation of van der Waals molecules has been the use of collision induced absorption studies pioneered by *H. L. Welsh et al.*[41]. Homonuclear molecules such as H_2, N_2, O_2, *etc.*, possess no dipole moments and therefore have no allowed electric dipole infrared absorption. However, when one of these molecules comes into close contact with another molecule or atom its quadrupole moment can induce a dipole moment in the neighbor. In addition, overlapping electron clouds can become distorted and produce a dipole moment in the interacting pair of molecules. These induced dipoles are modulated as the molecule pair vibrates and rotates, and infrared absorption is then possible.

The theory of this absorption has been explored by *van Kranendonk*[42]. These effects are small and path lengths of 10—100 m are required for measurable absorption in gases at pressures of about 1 atmosphere.

The appearance of the absorption depends on the nature of the molecule pair interaction. For collision pairs, transitions originate from the continuum of states above the dissociation limit of the intermolecular potential (see Fig. 1) and a broad diffuse absorption results. Transitions from bound van der Waals molecules originate from descrete levels and sharp absorption profiles are expected (cf. Fig. 1).

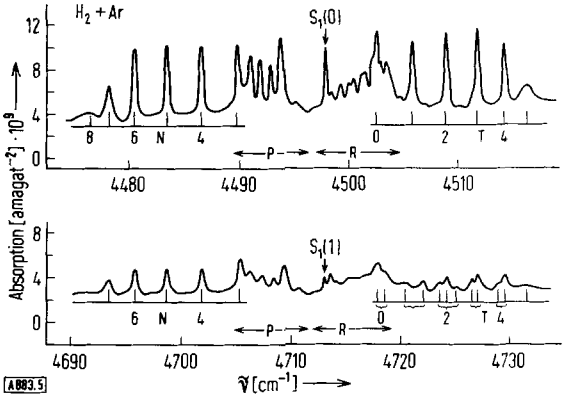


Fig. 5. Infrared spectrum of the H_2—Ar. The absorbing path length is 165 m. The total gas density is between 1—2 amagats (an amagat is the gas density at 1 atm pressure and 0 °C) [46].

Watanabe and *Welsh*[43] have obtained spectroscopic evidence for the $(H_2)_2$ van der Waals molecule which has a dissociation energy of only 10 cal/mol[44]. A somewhat stabler complex is formed between H_2 and foreign gases[45-47]. As example, a portion of the H_2—Ar spectrum[46] is shown in Fig. 5. The absorption is in the fundamental vibrational region of H_2 with the rotational transitions $J=0\rightarrow J'=2$ ($S_1(0)$) and $J=1\rightarrow J'=3$ ($S_1(1)$).

The transition originates from the ground vibrational state of H_2 and goes to the first excited vibrational state (indicated by the single prime). In the absence of Ar the only spectrum in the regions shown would be the two sharp features under the arrows of Fig. 5. These absorptions arise because of exceedingly weak electric quadrupole transitions which are possible in H_2. There is a broad underlying continuum which represents induced absorption by collisions of H_2 and Ar. The wealth of fine structure observed arises from absorption by bound states of H_2—Ar.

Since the binding energy of this complex is exceedingly small and H_2 is a light molecule and zero point vibration

is a significant fraction of the intermolecular potential well depth, only the v=0 bound state is involved in the absorption apparent in Fig. 5. The rotational quantum number J identifies the internal rotation of H_2 and L characterizes the end-over-end rotation of H_2—Ar. The selection rules permit transitions with $\Delta L = +1$ and $+3$, *i.e.* R and T branches respectively as well as $\Delta L = -1$ and -3, *i.e.* P and N branches respectively (Fig. 5). Having made these assignments the rotational constants can be used to find the intermolecular distance for H_2—Ar in its (v=0) state ($r = 3.94$ Å). The observed energy levels T(v,L) may also be used to evaluate Y_{lj} of eq. (4). Since *Cashion*[10] has given these Y_{lj} coefficients in terms of ε and r_e of the Lennard-Jones (6—12)-potential, spectroscopic data provide a direct evaluation of these parameters.

Most of the features shown represent bound→bound transitions of H_2—Ar, *i.e.* the absorptions are characteristically sharp. However, for transitions to high L states the absorptions become noticeably broad (*e.g.* compare T(5) with T(4) in the upper portion of Fig. 5). As the complex rotates faster, the well of the effective potential becomes shallower (see Fig. 1) and the (v=0) state comes closer to the top of the centrifugal barrier. "Tunneling" through the barrier can then occur rapidly with the result that the lifetime of the H_2—Ar van der Waals molecule is reduced and the level becomes broadened. These diffuse bands are the evidence of bound→metastable transitions.

The features discussed so far are consistent with the model that H_2 is freely rotating in the van der Waals molecule. This is to be expected if the intermolecular potential is isotropic. Evidence for anisotropic interactions in H_2—Ar appears in the lower portion of Figure 5. Splittings are apparent in the T branch features as a result of coupling between J and L. This coupling arises because of the weak anisotropic interaction between the rotation of H_2 in the complex and the end-over-end rotation of the complex.

This wealth of spectroscopic information is not only provided by the complex H_2—Ar but also by other H_2- and D_2—rare gas complexes[43,45-47]. Analysis of this data provides information on both ε and r_e for an assumed intermolecular potential function. A careful comparison of these spectra with the energy states calculated for various trial potentials can also provide a good test of acceptable functional forms of intermolecular interactions[48]. Although a quantitative explanation of the splitting of van der Waals rotational states is not yet available, further theoretical work will undoubtedly provide valuable information on anisotropic interactions. The spectroscopic findings of *Welsh et al.* probably provide the most detailed information available on intermolecular interactions for any polyatomic van der Waals molecule.

The coupling between internal rotation and end-over-end rotation of the complex is much more evident in H_2—CO or H_2—N_2 than in H_2—rare gas complexes[46,47]. In H_2—N_2 for example, spectroscopic features corresponding to ΔL changes are diffuse in comparison to the sharp features shown in Fig. 5 for H_2—Ar.

It is suggested[47] that the internal rotation of N_2 couples with the end-over-end rotation of the complex and a complicated splitting in energy levels results which cannot be completely resolved. Furthermore, transfer of rotational energy of N_2 to end-over-end rotation of the complex results in dissociation by centrifugal forces; this broadens the levels and shows up as the observed diffuse absorption. Evidence for this type of dissociation of van der Waals molecules through transfer of internal rotational energy is also supported by mass spectroscopic experiments (cf. Section 5).

Analysis of the infrared spectrum of $(NO)_2$[49] suggests that this dimer structure is nearly rigid. Figure 6 shows the spectrum of nitric oxide in the region of fundamental vibration of NO. Spectrum A is of the gas at room temperature and shows the usual vibration-rotation fine structure of NO. However, at low temperatures a new feature centered at 1790 cm^{-1} appears. This absorption depends quadratically on NO density, as would be expected if it is due to $(NO)_2$. The band shape of this feature resembles an unresolved vibration-rotation absorption of a near symmetric top. An analysis of this band shape and other observed absorption characteristics suggests that the dimer has a *cis* configuration with a van der Waals bond

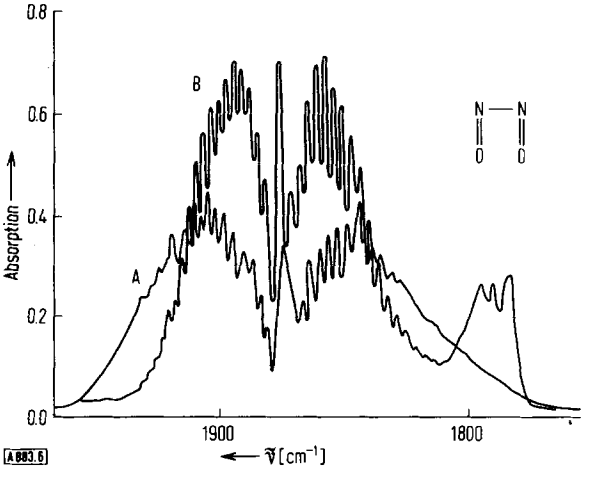


Fig. 6. IR spectrum of $(NO)_2$. Nitric oxide pressure 480 torr at 298 °K (A), and 270 torr at 123 °K (B). Path length is 6 cm. Curve (A) shows only the usual vibration-rotation absorption of NO near room temperature. However when the temperature is lowered, absorption due to $(NO)_2$ appears near 1780 cm^{-1} (curve B) [49].

length of 2.2±.2 Å and an NNO angle of *ca.* 90°. This molecule contains $3N-6=6$ vibrational modes. Two appear at high frequency (1860 and 1790 cm^{-1}) and belong to the in-phase and out-of-phase stretching of two coupled NO molecules. The other absorptions (~100 cm^{-1}) represent low frequency stretching, bending and torsional motions against the weak van der Waals bond. Since these low lying vibrational states will be populated even at low temperature, their occupation considerably complicates the observed spectrum and thus makes a more precise determination of $(NO)_2$ geometry impossible.

A study of the temperature dependence of the dimer absorption enables an estimation of the energy of dissociation of the dimer; it is found to be $\Delta E = 2450$ cal/mol. Unfortunately, ΔE is not directly related to ε as eq. 5 suggests.

The equilibrium constant K can only be calculated from ΔE and ε if estimates of the partition functions are available[50]. A comparison of the geometric data obtained from spectroscopic measurements and the relatively large energy of dissociation with the values listed in Table I shows considerable disagreement. This points to the inadequacy of forcing a fit of a Lennard-Jones intermolecular potential from thermodynamic data for some molecular systems. The descrepancy arises because the values presented in Table I were derived from gaseous measurements at room temperature. Molecules which collide at room temperature approach each other at random orientations, so in this case fitting the intermolecular interaction with the isotropic Lennard-Jones potential is acceptable. However at low temperatures angularly dependent interactions of bound states and colliding pairs become relatively more important and favor those orientations which increase the intermolecular attraction. The effective potential well depth becomes deeper and the intermolecular distance at the bottom of the well becomes shorter.

A careful examination of the low temperature properties of a gas reveals the existence of dimers and leads to energies of formation which are in good agreement with spectroscopic data[51-53].

The low temperature behavior of NO is significantly different from say O_2 or N_2 and suggests, as do theoretical studies, that the bonding in $(NO)_2$ is considerably stronger than that expected from dispersion forces[54].

In the search for the $(O_2)_2$ van der Waals molecule with induced IR absorption at low temperature we have found evidence for a somewhat rigid dimer but the data do not permit a structure determination[55]. The dissociation energy of $(O_2)_2$ is consistent with the value given in Table I. IR spectroscopic evidence for bound states of $(N_2)_2$ has been searched for but not found[56].

The formation energies of $(HCl)_2$, HCl—Ar, and other van der Waals molecules involving combinations of hydrogen halides and rare gases have been determined by IR spectroscopic investigations[57-60]. The interactions in $(HF)_2$ are particularly important to investigate since they represent the simplest examples of hydrogen bonding[61,62]. In such investigations sharp absorption features of the bound dimers can be detected between the intense vibration-rotation features of the uncomplexed hydrogen halides. The temperature dependence of these features provides a means of determining the heats of dissociation of these van der Waals molecules. A typical value is $\Delta H =$ 2140 cal/mol for $(HCl)_2$[58]. A difficulty met with in analyzing these data is that some dimer absorptions are obscured by intense monomer absorptions.

While a general theory for the coupling process in van der Waals molecules has already been developed, analysis of the observed spectroscopic features has not provided a complete picture of the geometry or nature of the angularly dependent forces in these interesting species[63].

Billingsley and *Callear*[64] have reported on the far ultraviolet absorption of gaseous $(NO)_2$ and obtained a dissociation energy in agreement with the IR results[49]. Attempts to study other van der Waals molecules by the examination of electronic transitions have usually not been too successful. One problem is that the allowed transitions of non-complexed molecules overwhelm the absorptions of the less plentiful van der Waals molecules. One way of circumventing this difficulty is to examine spectroscopic transitions which are forbidden in the monomer but are induced in the dimer by the presence of another component. Studies on $(O_2)_2$[65-68], $(Br_2)_2$[69] and $(I_2)_2$[70] have followed this procedure. An example is the examination of the forbidden oxygen-($^1\Delta_g \leftarrow {}^3\Sigma_g^-$) transition[67]. The absorption depends quadratically on the O_2 pressure. Since the selection rules are relaxed when one O_2 molecule is interacting with another, the observed band is due to $(O_2)_2$. If the temperature of the gaseous oxygen is lowered then the absorption increases, since more molecular aggregates are formed by the attractive intermolecular potential. However, it is still unclear whether the absorption by $(O_2)_2$ is due to collision pairs or van der Waals molecules. The absorption profile is broad and no fine structure which could positively identify van der Waals molecules have been detected. This of course does not mean that bound states of $(O_2)_2$ do not exist, for theory[6,10], as well as infrared[55] and mass spectroscopic evidence, to be discussed later, support their existence. As mentioned earlier, collision pairs yield broad absorptions. However, a complex overlapping spectral pattern originating from van der Waals molecules may also appear diffuse with insufficient spectroscopic resolution. Thus the low temperature electronic absorption of gaseous oxygen undoubtedly contains contributions from bound dimers although these spectroscopic data do not prove their presence.

Spectroscopic studies of $(Br_2)_2$ and $(I_2)_2$ have also revealed broad structureless absorption bands[69,70]. Moreover, the absorption by a given density of gaseous Br_2 or I_2, increases as the temperature is lowered, thus suggesting the formation of more dimers. However, the attractive intermolecular potential makes the collision of a pair of molecules more likely at lower temperatures as well as increasing the concentration of bound states. As in the case of $(O_2)_2$ the observed broad absorption profiles do not allow distinction between the concentration of collision pairs and van der Waals molecules.

Since equilibrium conditions do not favor high concentrations of van der Waals molecules, other experimental approaches have been considered for spectroscopic studies. For example, matrix isolation studies have been carried out on $(HCl)_2$[71] and $(NO)_2$[72]. The difficulty with this technique is that intermolecular forces of the surrounding matrix are comparable to the bonds of the van der Waals molecule and significant structural differences between the gas phase and matrix isolated molecule can be expected. Rotational motion is hindered by the matrix so band shapes do not yield structural information. Finally, since matrix isolation is under nonequilibrium conditions, heats of formation cannot be obtained from this type of experiment. Nevertheless, matrix isolation has provided valuable information for some of the stronger van der Waals molecules. The vibrational frequencies of $(H_2O)_2$ have been obtained only by this technique[73]. It

was also established that the van der Waals bonding of $(NO)_2$ was through N—N[72].

Supersonic molecular beams attain very low temperatures yet the total molecular concentrations are too low for the usual spectroscopic absorption experiments. The use of microwave absorption spectroscopy together with mass spectroscopic detection of the beam will probably prove a promising technique in the near future[74].

5. Mass Spectroscopy

Recent experiments using mass spectroscopy have proved particularly valuable in determining the properties of simple van der Waals molecules. As a source for the dimers, *Leckenby* and *Robbins*[75] used a gas reservoir with a small orifice. Since the mean free path of the escaping gas was comparable with the orifice diameter there was no adiabatic cooling of the gas as in the supersonic molecular beam experiments discussed previously. Provision was made for heating or cooling the sample gas, so that the monomer-dimer equilibrium properties in the reservoir could then be directly examined at various temperatures.

There are many experimental difficulties in making quantitative measurements on dimers with the aid of mass spectroscopy. Great care must be taken to dinstinguish between real dimers which originate from the equilibrium properties of the gas in the reservoir and dimers produced from ion-atom reactions in the mass spectrometer. Careful design of the sample source together with efficient pumping, which maintains the molecular beam, reduce the importance of ion-atom reactions. The low values of dimer concentration makes quantitiative detection difficult. Furthermore, uncertainties of ionization cross sections of dimers makes absolute measurements somewhat unreliable.

Leckenby and *Robbins*[75] have investigated dimers of CO_2, N_2O, N_2, O_2, Ar and Xe. They find, as expected, that the dimer concentration depends quadratically on the gas pressure. The temperature variation of $(Ar)_2$, for example, is shown in Figure 7. It compares favorably with the calculations of *Stogryn* and *Hirschfelder*[6]. Their calculated concentrations for bound states are indicated by the curve labeled "theor. (b.)" and bound and metastable states are shown by "theor. (b.m.)". Since the time of flight from reservoir to detector is of the order of 10^{-5} to 10^{-6} s, metastables contribute significantly to the dimers detected by mass spectroscopy. Although absolute measurements of dimers is uncertain by possibly a factor of 2 the relative concentrations at various temperatures provide a means of determining the energy of formation.

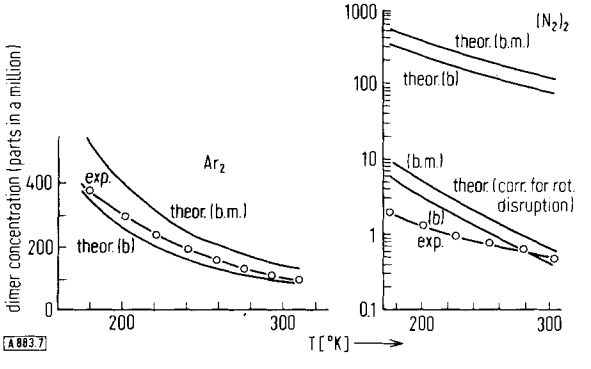


Fig. 7. Mass spectrometrically determined [75] and calculated [6] concentration of Ar_2 and $(N_2)_2$ as a function of temperature.

While the agreement between mass spectroscopic determination of rare gas dimer concentrations and the theory of *Stogryn* and *Hirschfelder* is satisfactory, there is a dramatic descrepancy when polyatomic van der Waals molecules are studied. For example, the measured concentrations of $(N_2)_2$ or $(O_2)_2$ are two orders of magnitude lower than the theoretical predictions. *Leckenby* and *Robbins* have proposed a simple and convincing model to account for this descrepancy. It is to be recalled that only a few collisions are required for the transfer of rotational-translational energy in gases[76]. Since a van der Waals molecule is in a state of perpetual collision this efficient transfer can be expected to occur between the rotation of the individual molecules in the dimer (*e.g.* N_2 in $(N_2)_2$) and the end-over-end rotation of the dimer. If the combined rotational energy of the two molecules in the dimer exceeds the van der Waals binding energy then after a short time there is the chance that all the rotational energy will be eventually transferred into the end-over-end rotation of the dimer and the resulting centrifugal forces will cause dissociation. Calculations based on this simple model give reasonable agreement with measured dimer concentrations for polyatomic van der Waals molecules. In Figure 7 the concentration of $(N_2)_2$ corrected for rotational disruption is compared to the measured concentration. Evidence for this type of metastable van der Waals molecule. which can occur only for polyatomic dimers, was observed in the infrared spectra of H_2—N_2 and H_2—CO (cf. Section 4).

Other groups[77-80] have studied van der Waals molecules with the aid of supersonic molecular beams produced from high pressure gas reservoirs. Since adiabatic cooling can produce very low temperatures, higher polymers as well as dimers are generated. For example, in a study by *Milne* and *Greene*[81] on argon clusters, species from $(Ar)_2^+$ to $(Ar)_{20}^+$ could be detected.

The advantage of high-pressure sources (up to 5 atm was used) is that cluster concentrations are higher. While this is interesting for the study of nucleation phenomena, quantitative conclusions on equilibrium properties are uncertain. If the size of the orifice is greater than the mean free path of the gas, no adiabatic cooling results. In this case information on the monomer-dimer equilibrium is utilizable. The results of *Milne* and *Greene* for dimers of Ar, N_2 and O_2 are in substantial agreement with those of *Leckenby* and *Robbins*.

6. Conclusions

It is apparent from the examples discussed above that electron diffraction, optical and infrared spectroscopic, and mass spectroscopic studies of van der Waals molecules provide a wealth of detailed information about intermolecular interactions. It is to be expected that such

experiments will, in the near future, not only afford quantitative details about the isotropic interactions between atoms but also about the anisotropic interactions between small molecules.

Received: May 10, 1971 [A 883 IE]
German version: Angew. Chem. *84*, 570 (1972)

[1] *A. D. Buckingham* and *B. D. Utting*, Annu. Rev. Phys. Chem. *21*, 287 (1970).

[2] *C. Schlier*, Annu. Rev. Phys. Chem. *20*, 191 (1969).

[3] *H. Margenau* and *N. R. Kestner*: Theory of Intermolecular Forces. Pergamon Press, Oxford 1969.

[4] *J. O. Hirschfelder*: Intermolecular Forces (Advan. Chem. Phys. *12*). Interscience, New York 1967.

[5] *T. L. Hill*, J. Chem. Phys. *23*, 617 (1955).

[6] *D. E. Stogryn* and *J. O. Hirschfelder*, J. Chem. Phys. *31*, 1531 (1959); *33*, 942 (1960).

[7] *N. R. Davidson*: Statistical Mechanics. McGraw-Hill, New York 1962.

[8] *J. O. Hirschfelder, C. F. Curtiss*, and *R. B. Bird*: The Molecular Theory of Gases and Liquids. Wiley, New York 1954.

[9] *G. Herzberg*: Molecular Spectra and Molecular Structure. Van Nostrand, New York 1954.

[10] *J. K. Cashion*, J. Chem. Phys. *48*, 94 (1968).

[11] *N. Bernardes* and *H. Primakoff*, J. Chem. Phys. *30*, 691 (1959).

[12] *E. Buluggiu* and *C. Foglia*, Chem. Phys. Lett. *1*, 82 (1967).

[13] *J. E. Kilpatrick* and *M. F. Kilpatrick*, J. Chem. Phys. *19*, 930 (1951).

[14] *W. E. Baylis*, Phys. Rev. *A 1*, 990 (1970).

[15] *G. D. Mahan* and *M. Lapp*, Phys. Rev. *179*, 19 (1969).

[16] *T. L. Hill*: Statistical Mechanics. McGraw-Hill, New York 1956.

[17] *S. G. Reed, Jr.*, J. Chem. Phys. *20*, 208 (1952).

[18] *P. Audit* and *M. Rouault*, C. R. Acad. Sci. Paris *265 B*, 1100 (1967).

[19] *P. Audit* and *M. Rouault*, Entropie *18*, 22 (1967).

[20] *B. Raoult, J. Farges*, and *M. Rouault*, C. R. Acad. Sci. Paris *267 B*, 942 (1968).

[21] *P. Audit*, J. Phys. (Paris) *30*, 192 (1969).

[22] *J. K. Cashion*, quoted in Ref. [21].

[23] *A. Jaegle, A. Duguet*, and *M. Rouault*, C. R. Acad. Sci. Paris *267 B*, 1081 (1968).

[24] *R. A. Bonham* and *R. L. Hilderbrandt*, Annu. Rev. Phys. Chem. *2*, 279 (1971).

[25] *Y. Tanaka* and *K. Yoshino*, J. Chem. Phys. *53*, 2012 (1970).

[26] *L. W. Bruch* and *I. J. McGee*, J. Chem. Phys. *53*, 4710 (1970).

[27] *Shardanand*, Phys. Rev. *160*, 67 (1967); J. Quant. Spectry. Rad. Trans. *8*, 1373 (1968).

[28] *W. Finkelnburg* and *Th. Peters* in *S. Flügge*: Handbuch der Physik, Vol. 28. Springer-Verlag, Berlin 1957.

[29] *A. Michels, H. de Kluiver*, and *C. A. ten Seldam*, Physica *25*, 1321 (1959).

[30] See for example: *H. E. Gunning, S. Penzes, H. S. Sandhu*, and *O. P. Strausz*, J. Amer. Chem. Soc. *91*, 7684 (1969) and literature cited therein.

[31] *S. Y. Chen* and *M. Takeo*, Rev. Mod. Phys. *29*, 20 (1957).

[32] *J. F. Kielkopf* and *J. A. Gwinn*, J. Chem. Phys. *48*, 5570 (1968).

[33] *S. Y. Chen* and *C. W. Fountain*, J. Quant. Spectry. Rad. Trans. *4*, 471 (1964).

[34] *J. A. Gwinn, P. M. Thomas*, and *J. F. Kielkopf*, J. Chem. Phys. *48*, 568 (1968).

[35] *L. Klein* and *H. Margenau*, J. Chem. Phys. *30*, 1556 (1959).

[36] *R. Herman* and *L. Herman*, J. Quant. Spectry. Rad. Trans. *4*, 487 (1964).

[37] *O. Jefimenko*, J. Chem. Phys. *39*, 2457 (1963).

[38] *C. C. Bouchiat* and *M. A. Bouchiat*, Phys. Rev. *A 2*, 1274 (1970).

[39] *M. Aymar, M. A. Bouchiat*, and *J. Brossel*, Phys. Lett. *24 A*, 753 (1967).

[40] *M. A. Bouchiat, J. Brossel*, and *L. Pottier*, Phys. Rev. Lett. *19*, 817 (1967).

[41] *E. J. Allin, A. D. May, B. P. Stoicheff*, and *H. L. Welsh*, Appl. Opt. *6*, 1597 (1967).

[42] *J. van Kranendonk*, Physica *24*, 347 (1958).

[43] *A. Watanabe* and *H. L. Welsh*, Phys. Rev. Lett. *13*, 810 (1964); Can. J. Phys. *43*, 818 (1965); *45*, 2859 (1967).

[44] This value of 10 cal/mol is the difference in energy between the lowest bound energy level of $(H_2)_2$ and the interaction potential dissociation limit. The depth of the well is 74 cal/mol. The difference is due to the large zero point vibration of the light H_2 molecules.

[45] *A. Kudian, H. L. Welsh*, and *A. Watanabe*, J. Chem. Phys. *43*, 3397 (1965); *A. Kudian* and *H. L. Welsh*, Can. J. Phys. *49*, 230 (1971).

[46] *A. R. W. McKellar* and *H. L. Welsh*, J. Chem. Phys. *55*, 595 (1971).

[47] *A. Kudian, H. L. Welsh*, and *A. Watanabe*, J. Chem. Phys. *47*, 1553 (1967).

[48] *R. G. Gordon* and *J. K. Cashion*, J. Chem. Phys. *44*, 1190 (1966); *J. K. Cashion, ibid. 45*, 1656 (1966).

[49] *C. E. Dinerman* and *G. E. Ewing*, J. Chem. Phys. *53*, 626 (1970); *54*, 3660 (1971).

[50] *T. A. Milne* and *F. T. Greene*, J. Chem. Phys. *47*, 3684 (1967).

[51] *R. L. Scott*, Mol. Phys. *11*, 399 (1966).

[52] *E. A. Guggenheim*, Mol. Phys. *10*, 401 (1966).

[53] *E. A. Guggenheim*, Mol. Phys. *11*, 403 (1966).

[54] *B. M. Gimarc*, J. Amer. Chem. Soc. *92*, 266 (1970).

[55] *C. Long* and *G. Ewing*, Chem. Phys. Lett. *9*, 225 (1971).

[56] *De T. Sheng*, Thesis, Indiana University, Bloomington 1971.

[57] *D. H. Rank, B. S. Rao*, and *T. A. Wiggins*, J. Chem. Phys. *37*, 2511 (1962).

[58] *D. H. Rank, P. Sitaram, W. A. Glickman*, and *T. A. Wiggins*, J. Chem. Phys. *39*, 2673 (1963).

[59] *D. H. Rank, W. A. Glickman*, and *T. A. Wiggins*, J. Chem. Phys. *43*, 1304 (1965).

[60] *Vu-Haï* and *B. Vodar*, Z. Elektrochem., Ber. Bunsenges. Phys. Chem. *64*, 756 (1960).

[61] *D. F. Smith*, J. Mol. Spectrosc. *3*, 473 (1959).

[62] *W. F. Herget, N. M. Gailar, R. J. Lovell*, and *A. H. Nielsen*, J. Opt. Soc. Am. *50*, 1264 (1960).

[63] *S. Bratož* and *M. L. Martin*, J. Chem. Phys. *42*, 1051 (1965).

[64] *J. Billingsley* and *A. B. Callear*, Trans. Faraday Soc. *67*, 589 (1971).

[65] *V. I. Dianov-Klokov*, Opt. Spectrosc. (USSR) *16*, 409 (1964).

[66] *C. W. Cho, E. J. Allin*, and *H. L. Welsh*, Can. J. Phys. *41*, 1991 (1963).

[67] *J. Robin*, J. Rech. Centre Natl. Rech. Sci. Lab. Bellevue (Paris) *10*, 89 (1959).

[68] *R. P. Blickensderfer* and *G. Ewing*, J. Chem. Phys. *51*, 873 (1969).

[69] *E. A. Ogryzlo* and *B. C. Sanctuary*, J. Phys. Chem. *69*, 4422 (1965).

[70] *M. Tamres, W. K. Duerksen*, and *J. W. Goodenow*, J. Phys. Chem. *72*, 966 (1968); *A. Passchier* and *N. W. Gregory, ibid. 72*, 2697 (1968).

[71] *L. F. Kemper* and *G. W. Robinson*, J. Chem. Phys. *45*, 1694 (1966).

[72] *W. A. Guillory* and *C. E. Hunter*, J. Chem. Phys. *50*, 3516 (1969).

[73] *M. Van Thiel, E. D. Becker*, and *G. C. Pimentel*, J. Chem. Phys. *27*, 486 (1957).

[74] *T. Dyke, B. Howard*, and *W. Klemperer*, Paper R 4, 26th Symp. Mol. Struc. Spectrosc., Ohio State University 1971.

[75] *R. E. Leckenby* and *E. J. Robbins*, Nature *207*, 1253 (1965); Proc. Roy. Soc. (London) *291 A*, 389 (1966).

[76] *J. D. Lambert* in *D. R. Bates*: Atomic and Molecular Processes. Academic Press, New York 1962.

[77] *W. Henkes*, Z. Naturforsch. *16a*, 842 (1961); *17a*, 786 (1962); *J. Bauchert* and *O. F. Hagena, ibid. 20a*, 1135 (1965); *O. F. Hagena* and *W. Henkes, ibid. 20a*, 1344 (1965).

[78] *F. T. Greene* and *T. A. Milne*: Advances in Mass Spectrometry. The Institute of Petroleum, London 1965, Vol. 3, p. 841.

[79] *J. Cuthbert, E. R. Preece*, and *A. H. Turnbull*, Appl. Spectrosc. *19*, 18 (1965).

[80] *P. G. Bentley*, Nature *190*, 432 (1961); *R. E. Leckenby, E. J. Robbins*, and *P. A. Trevalion*, Proc. Roy. Soc. (London) *280 A*, 409 (1964).

[81] *T. A. Milne* and *F. T. Greene*, J. Chem. Phys. *47*, 4095 (1967).

Structure and Function of Chromosomal Nucleohistones

By Eberhard Zimmermann[*]

The progress made in molecular biology has provided definite evidence that DNA is the genetic material of all cellular organisms. It is mainly localized within the cell nuclei and, in association with histones and acidic proteins, forms the fundamental structure of the chromosomes. The DNA-protein complex, called nucleohistone or chromatin, represents the sum of all existing genes of one cell type and can be considered as a functional genetic unit. All genetic structures contain this fundamental element and only their steric arrangement or multiplicity determine the species-specific differences in chromosomal morphology. The preservation of the three-dimensional structure seems to be the function of histones which, in general, are associated with densely packed and metabolically inactive DNA sequences. The lysine-rich histone I probably has a specific regulatory function since it inhibits the transcription of certain genes. Acidic proteins are mainly to be found in stretched chromosomal structures of high metabolic activity which accentuate the correlation between structure and function of nucleohistones. Approximately 50% of the DNA of the nucleohistone complex is not masked by proteins though only a small percentage of the free nucleotide sequences can be transcribed by RNA polymerase. The "open" structure of nucleohistones finds a plausible explanation in the fact that amino acid sequence analysis of several histones revealed an asymmetric distribution of charged groups and that therefore only these protein fractions can interact with DNA. In *Crick*'s recently published model of the chromosomal organization the unique structure of histones is taken into account and it is assumed that the histone-rich heterochromatin contains multiple but untranscribable control elements. Functional genes are represented by a single stranded DNA duplex within the interbands which utilize a special protein to preserve this unique conformation.

1. Introduction

Nucleohistones (chromatins) are naturally occurring biological macromolecules consisting of DNA and proteins (Section 3). They exist in all cell types of the animal and plant world and represent the main element of the chromosomal structure. Chromosomes of eucaryotic cells with true nuclei are 200 to 500 Å in diameter and are totally dispersed during the interphase of the cell division cycle (mitosis) and therefore cannot be detected by optical methods. In the prophase internal structural changes take place, aggregations of the nucleohistone filaments occur and the dense chromosomal structure is formed. In the continuation of this process chromosomes move in the equatorial plane of the metaphasic cell and are then divided into two identical chromatids, which are connected to each other by the centromer. This linkage disappears during the anaphase and after attachment of the filament to the centromeric region of the chromatids the two sets of daughter chromosomes are distributed in two new cells. The subsequent gradual fusion of these chromosomes into compact nuclei is the most dramatic effect of the telophase and the daughter cells pass into the interphase condition (Fig. 1). The doubling of the chromosomes and consequently the synthesis of new DNA is accomplished in the middle of the interphase. Another correlated reaction is the formation of new histones associated with nuclear DNA in all animal and plant cells. (Only in the mature sperms of some fish species are histones replaced by protamines, a specific class of basic proteins containing as much as 60% arginine.)

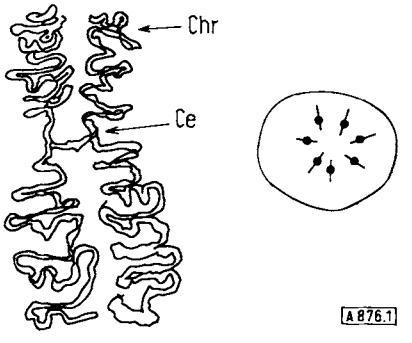


Fig. 1. Left: Metaphasic chromosome, consisting of two chromatids (Chr) held together by the centromer (Ce). Right: Arrangement of chromosomes in the equatorial plane of the metaphasic cell. Both diagrams highly schematized.

The detection of DNA in chromosomes was a result of *Feulgen*'s pioneering work in 1924; later estimations proved that a single nucleus may contain as much as 1.7×10^{-13} to 15.0×10^{-13} g DNA[1]. The most detailed information available about chromosomal structures originates from the study of giant chromosomes, which are especially well formed and easily detectable in the interphase nuclei of the salivary glands from Diptera larvae (flies and mosquitos). Their length is one hundred times that of normal chromosomes and they are 4 to 5×10^{-3} cm in diameter; con-

[*] Priv.-Doz. Dr. E. Zimmermann
Harvard University, Chemical Department
Cambridge, Massachusetts 02138 (USA)
Present address: Physiologisches Institut der Universität
Allgemeines Verfügungszentrum
44 Münster, Robert-Koch-Strasse 28 (Germany)

sequently, they contain essentially more DNA per cell nucleus than the corresponding diploid cell of mammalia.

The giant chromosomes, whose detailed structure is readily revealed by suitable staining, represent numerous genes with different biological functions, of which hundreds of identical copies can exist. Their transversal pattern of alternating bands of chromatic and achromatic material suggested the terms heterochromatin and euchromatin. Electron microscopic studies by *Ris* provided evidence that this pattern is mainly a result of different three-dimensional folding and packing of nucleohistone filaments. These staining patterns are so highly specific and colinear with phenotypic expressions that they are used by the cytologist as a basis for heriditary theories. Most of the heterochromatin regions do not appear to represent active genes and do not participate in the transference of genetic information. Their capability of reacting with specific stains is correlated with their high protein content[2, 3]. Localized structural modifications on giant chromosomes are characterized as "puffs" discernable as highly active metabolic regions associated with an enhanced RNA and protein synthesis (Fig. 2).

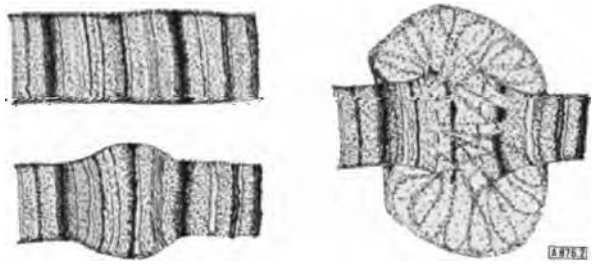


Fig. 2. Model of puff formation in giant chromosomes of the salivary glands of Diptera larvae.

2. Structure of Chromosomes

The fine filament structure of metaphasic chromosomes implies that nucleohistone elements of different diameter are contributing to their complex texture. Several theories were developed for a sophisticated explanation of the existence of different sized nucleohistone complexes. *Ris*[4] considers their characteristic appearance to result from the parallel aggregation of four DNA duplexes that are laden with histones and loosely twisted around one another. In accordance with the multistrand hypothesis, two nucleohistone filaments, each 40 Å in diameter, form the 100 Å subunit of the chromosomal structure. Two subunits randomly folded and packed represent one chromosome 200 to 500 Å in diameter. This concept found its strongest support in the highly specific arrangement of DNA in sperm nuclei. X-ray diffraction studies revealed a very compact alignment of parallel oriented nucleoprotamine subunits within the intact sperm head, forming a unique structure with a characteristic property in polarized light: it exhibits negative birefringence[5].

There is enough evidence to support the belief that same organization prevails in the case of giant chromosomes of Diptera larvae; about 1000 to 4000 single nucleohistone filaments with an average diameter of 200 to 400 Å, each of them representing one chromatid, are arranged in parallel. Stretched and densely folded regions alternate—whereby each nucleohistone molecule extends through the entire chromosome (Fig. 3). These subunits of the Diptera chromosomes are comparable with the fibrous nucleohistone structure of metaphasic eucariotic cells.

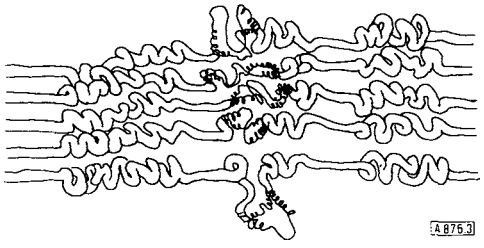


Fig. 3. Parallel arrangement of nucleohistone fibers with partial unwinding of the DNA double helix.

The single-strand hypothesis is based on the assumption that only one DNA molecule coated with basic and acidic proteins is randomly folded and packed to form the three-dimensional lattice of the 200 to 500 Å chromosomes. This theory has the appeal that it can most easily be brought into accord with *Watson* and *Crick*'s model[6] of semi-conservative replication of DNA[*]. During the mitotic cell division cycle each chain of the DNA duplex is transfered to one daughter cell and serves as template for the synthesis of a complementary chain.

On the basis of his investigations, *Taylor*[7] developed a quite different idea about the complexing of chromosomal elements: he suggested that transversally arranged short DNA helices are alternatively connected by proteinous linkers (Fig. 4). All attempts to isolate such structure-preserving proteins failed, as did also experiments designed to release the short DNA chains with proteolytic enzymes[8].

The behavior of the metaphasic chromosomes during cell division and the arrangement of nearly all chromosomes in the equatorial plane of the cell support the concept that

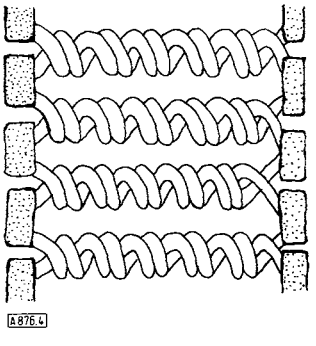


Fig. 4. *Taylor*'s model of the coupling of DNA helices by short proteinous linkers [7].

[*] In semi-conservative replication of DNA, both strands of the duplex are copied at the same time.

interchromosomal linkages do exist. In the case of some animal species all chromosomes are arranged in a circular pattern within the equatorial plane. It thus seems extremely likely that several chromosomes originate from one DNA helix and that the interchromosomal bridges represent only different and specific nucleotide sequences of the same DNA molecule[9].

The single-strand hypothesis is further confirmed by the more specialized structure of lampbrush chromosomes which exist in oocytes[*] of amphibians and other vertebrates. In this type of diploid cell the chromosomes are formed by two chromatids and develop a number of paired loops along the main axis of the DNA backbone. These loops proliferate from the two chromatids, exhibit very intensive RNA and protein synthesis, and seem to represent what we call a gene[10]. Taking into consideration the actual size of chromosomal loops *Gall* and *Callan*[11] elaborated their exciting hypothesis of "master" and "slave" genes. If we assume that these loops contain only one original gene and a number of more or less correct copies of the same nucleotide sequence, the discrepancy between the possible extension of one gene and the dimension of the existing loops is eliminated. Furthermore, the two authors believe that only the slave genes serve as a template for RNA synthesis.

The existence of one master gene coincides with the fundamental idea of classic genetics that one gene fulfills one biological function. According to *Beermann*'s concept of the "operative organization" of chromosomes the master gene serves as template for RNA polymerase transcription, while slave genes only bind and stabilize such RNA molecules[12].

The ingeniously predicted existence of reiterated sequences could be experimentally proved by *Spiegelman*'s hybridization technique, and such redundant genes were found in all higher developed organisms[13–17]. The copies of the original sequences are sometimes inaccurate, so that repeated genes exist which are incongruous with the master gene. It is still an open question whether these incompletely or incorrectly transcribed nucleotide sequences represent functional genes or are only parts of them with a specific regulatory activity.

3. Chemical Composition of Nucleohistones

Histones and a small percentage of acidic proteins can be extracted together from chromosomal nucleohistones by acidic solutions and precipitated in pure form with ethanol. The large scale extraction and fractionation procedure elaborated by *Johns*[18] is most commonly used for this purpose. However, it should be mentioned that heterogeneous histones prepared by this method contain a certain percentage of related material which increases the tendency for protein-protein interactions to take place in aqueous solutions. The application of more improved procedures made it possible to differentiate between several histone species and, furthermore, to classify them according to their characteristic amino acid content and their N-terminal residues (Table 1). Their elution sequence in column chromatographic fractionation was used for the enumeration of the histone fractions (I to IV); additional indices are used for the purpose of labeling their subfractions—*e.g.*, histone I is partially resolved into histone Ia and Ib, and histone II can be split into fractions IIa, IIb_1, and IIb_2[19].

Table 1. Amino acid composition of histone fractions in mol-%. F_1: very lysine rich; F_{2a}, F_{2b}: slightly lysine rich; F_3, F_4: arginine rich.

Aminoacid \ Fraction	F I	F IIa	F IIb	F III	F IV
Alanine	23.5	10.5	10.5	12.5	6.9
Arginine	2.5	11.5	7.5	13.0	13.7
Aspartic acid	2.8	6.0	5.5	5.0	4.9
Glutamic acid	6.0	8.5	9.0	11.0	5.9
Glycine	6.8	12.5	7.0	6.5	16.7
Histidine	0.5	2.0	2.5	2.1	2.0
Isoleucine	1.6	4.5	5.0	5.0	6.0
Leucine	4.4	10.5	6.0	8.5	7.0
Lysine	26.3	10.5	14.5	9.0	11.0
Methionine	—	—	0.7	0.7	2.0
Phenylalanine	0.8	1.6	2.0	2.5	2.0
Proline	7.9	3.0	4.5	4.5	0.9
Serine	6.2	3.1	9.0	7.0	2.0
Threonine	5.5	5.6	6.5	7.0	7.0
Tyrosine	0.5	3.0	3.1	2.0	3.9
Valine	5.0	7.0	6.8	6.0	8.8
	100.3	101.8	100.1	102.3	100.7
N-terminal residue	Acetyl	Acetyl	Proline or Alanine	Alanine	Acetyl

The lysine-rich histone I was carefully purified by *Peacocke*[20] and the molecular weight of this relatively monodisperse fraction was determined as 20000. Surprisingly, *Kinkade* and *Cole*[21] were able to resolve the same histone on Amberlite CG-50 columns into four subfractions and thus indicate the possible existence of modifications having slightly different amino acid compositions. Meanwhile, the arginine-rich histone IIb, containing acetylated alanine or proline as N-terminal groups, was fractionated by *Johns*[22] on carboxymethyl cellulose; three of the five subfractions thus obtained proved to have different amino acid compositions. Such observations justified the question whether these so-called subfractions were artificial complexes with impurities of obscure origin[23, 24]. It is notable in this context that *Stellwagen*[25] was able to demonstrate conclusively that even histones extracted from purified nuclei are contaminated by cytoplasmic proteins. More detailed information about this problem was provided by *Johns*[26], who investigated the binding conditions of cytoplasmic acidic proteins to the chromosomal nucleohistones.

In spite of all these difficulties *Bonner et al.*[27] were able to isolate histone IV in homogeneous form from calf thymus and from pea seeds and to analyze their amino acid sequences. In agreement with *Stellwagen*'s[28] and *Ogawa*'s results[29] they were able to establish that the lysine residues are accumulated in the N-terminal half of the molecule. On the other hand, acidic and aromatic amino acids, as well as the hydrophobic compounds, are clustered in the C-terminal half of the molecule[30] (Fig. 5). Surprisingly, both the histones investigated contain 102 amino acids with only two amino acid replacements; furthermore, certain

[*] Oocytes are cells which on undergoing meiosis form the ovum.

peptide sequences occur in which only one amino acid is replaced, thus implying that the histone IV gene may be formed from repeating sequences.

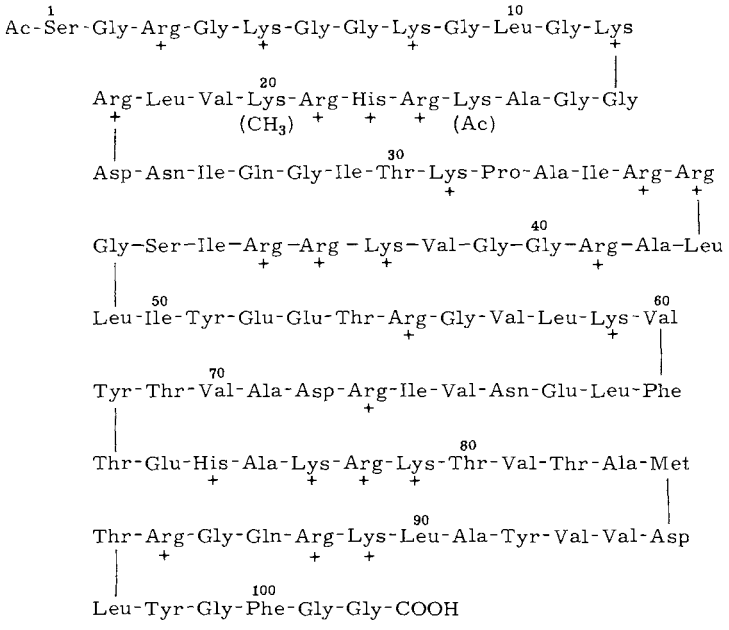


Fig. 5. Amino acid sequence of histone IV [23] (basic amino acid residues are marked).

The amino acid sequence analysis of histone IIb and a subfraction of F1 reveals a similar asymmetric distribution of amino acids within these histone molecules[31, 32]. The specific accumulation of positively charged groups on the ends of histone molecules opens up new aspects regarding the interaction between histones and DNA (Section 8).

Our fragmentary knowledge of the function of histones and their derivatives does not allow any conclusive statements to made regarding whether the steric conformation of these proteins contributes to their ability to associate with DNA[33]. All that we do know is that isolated lysine-rich histone I dissolved in ethylene chlorohydrin has a 46% helical conformation, whereas the fractions IIa and IIb have about 65 to 70%[34]. The values are drastically reduced

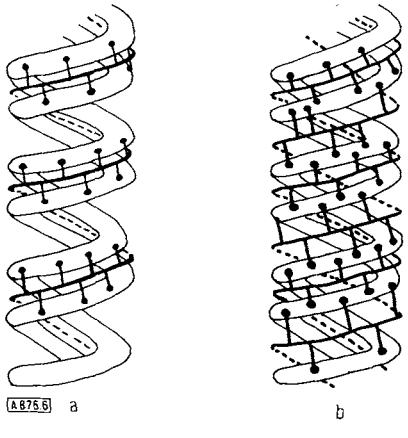


Fig. 6. a) Binding of protamine in the shallow groove of the DNA duplex. b) Binding of histones in the deep groove of the DNA duplex [37].

to about 20% in aqueous solutions but vary with the protein concentration and the age of the solution[35].

Zubay and *Doty*[36] conclude from their ORD measurements that half of the DNA bound histones exist in the α-helical configuration. This result gives strong support to *Wilkin*'s model of the tertiary structure of nucleohistones which is based on the assumption that only the α-helical conformation favors the binding of histones in the deeper groove of the DNA duplex (Fig. 6)[37]. A more questionable assumption that has been made regarding the DNA/histone interaction is that of a symmetric distribution of charged groups within the protein molecules. This requirement is not fulfilled in the case of histone IIb and IV; however, it seems likely that the DNA/protein interaction involves phosphorylating, acetylating, or methylating enzymatic mechanisms as essential metabolic procedures which differentiate both the structure and function of histones. Valuable information pertinent to this point has been provided by *Stocken*[38] who was able to prove that a significant correlation between the extent of phosphorylation and the biological activity of histone I really does exist. By contrast arginine-rich fractions IIb and III seem to be more susceptible to acetylating reactions[39, 40]. Since the biological activity of RNA and DNA synthesis reaches its maximum rate after one to two hours in the regenerating rat liver, it can be assumed that the rapid acetylation reaction is the first step in gene activation. Histone methylation occurs subsequently when DNA and histone synthesis have exceeded their highest values. Obviously such a reaction has nothing to do with regulatory processes, but it may be connected with the transport of newly synthesized histones from the cytoplasm to the cell nuclei.

4. Metabolism of Histones

Studies on the cellular mechanism of histone synthesis tend to confirm the conclusions reached above. *Robbins* and *Borun*[41], for example, proved experimentally that arginine-rich histone is synthesized in the cytoplasm in HeLa cells[*] and is subsequently transported to the cell nuclei. The synthesis of protamine in salmon testis also occurs outside the nuclei but within the cytoplasmic compartment[42]. Of particular interest in this connection is the investigation of a specific class of small polysomes which are detectable in the cytoplasm of histone synthesizing cells; they disappear shortly after cell division and thus emphasize their specific role in histone synthesis[43]. Furthermore, they contain a specific 7—9S RNA which is attached to the polysomes only during the time of histone synthesis and is therefore considered to represent the messenger RNA for histones IIa, IIb, and III.

A somewhat different result was reported by *Reid* and *Cole*[44] for isolated thymus nuclei which were found to be metabolically active and capable of synthesizing the arginine-rich histone III. *Birnstiel* and *Flamm* investigated the principal pathway of nuclear protein synthesis using

[*] HeLa cells are a strain of human cells originating from a carcinoma of the cervix and named after *Helen Lane* the patient from whom they were obtained.

pea seeds and cell cultures of tobacco leaves[45]. After pulse labeling and mechanical disruption of the cells the cellular particles were fractionated by centrifugation and their content of incorporated amino acids was determined. The nucleoli[*] of both cell types were found to have a significantly higher amino-acid incorporation rate, thus indicating that the histone synthesis is mainly located in these nuclear compartments. It was a crucial and decisive experiment to characterize some of the newly synthesized proteins as histones since it is a well known fact that the nucleoli are also responsible for the synthesis of ribosomal proteins.

The connection between nuclear and cytoplasmic histone synthesis becomes more understandable when one considers that the nuclear histone synthesis also involves a 9S RNA as messenger. The bulk of RNA isolated from cytoplasmic polysomes could be fractionated into three major species indicating their metabolic relation to the three main histone fractions described above[46]. Furthermore, there is sufficient evidence to prove that histone genes are reiterated and clustered within the chromosomes. This is an interesting but not surprising feature since we know that repeated nucleotide sequences can make up to 20 to 80% of the nuclear DNA of eucariocytes[47].

That a special mode and codon for chain initiation might exist is suggested by *Allfrey*'s finding that the initiation of histone IIa synthesis appears to involve *N*-acetyl-seryl-tRNA[48]. This possibility cannot be overlooked since the synthesis of ovalbumin[49] and of hemoglobin[50] is also initiated by acetylated seryl-tRNA. Our present knowledge is far too fragmentary to understand clearly the complicated functional correlation between DNA and histone synthesis. In general, however, it can be stated that the histone synthesis of dividing cells with chromosome replication coincides with the multiplication of DNA. In addition, the specific inhibition of the DNA synthesis supresses the synthesis of lysine-rich histones while the production of arginine-rich histones within the cytoplasmic compartment is unaffected[51].

5. Acidic Nuclear Proteins

The fundamental concept that acidic proteins may play a decisive role in the regulation of the biological activity of nucleohistones was originally put forth by *Stedman* and *Stedman*[52]. This idea has been frequently challenged during the past few years by the assumption that certain histones might play a more important role in regulation mechanisms. However, the high concentration of acidic proteins within the nuclei and their enormous metabolic activity compared to the nearly inert histones implies their possible involvement in gene regulation, but this cannot, as yet, be supported by conclusive experimental results. The isolation and quantitative determination of acid proteins is relatively difficult since they are partly dissolved during extraction of the histones. In addition, extraction of the acid proteins with dilute alkaline solutions according to the method of *Busch et al.*[53] has the disadvantage that part of these proteins are irreversibly denaturated. The deoxycholate procedure used by *Wang*[54], and later improved by *Bonner*[55], however, partially overcomes this difficulty and acidic proteins may even be fractionated on DEAE cellulose. Another equally promising method of isolation is the extraction of all proteins by sodium dodecyl sulfate or NaCl followed by fractionation on agarose columns, both operations being carried out in a single step[56, 57]. Unfortunately, a large percentage of the eluted material is still heterogeneous[58]. It has been argued that contamination with lipoproteins and phosphoproteins, concentrated within the nuclei[59, 60], may be the reason for this abnormal chromatographic behavior. An additional problem encountered in their fractionation and purification is the extreme tendency to interact with basic proteins. On consideration of the technical difficulties mentioned above in isolation and purification of acidic proteins it can be readily appreciated why insufficient experimental data are available for evaluation of the metabolic function and activity of these proteins.

Wang[61] has investigated the metabolic activity of some isolated nuclei in the cell-free system reported by *Allfrey*[62]. Purified nuclear fractions have been obtained that contain 40% to 50% protein together with about the same amount of DNA and 1 to 2% RNA; such nuclei may be considered as biologically functional elements[63]. *Wang*'s experiments indicate that especially the nuclear ribosomes and the "residual particles" (complexes between acidic proteins and RNA) have a significantly high metabolic activity.

Steele and *Busch*[64] have compared the metabolic activity of the nuclei of normal cells with that of Walker tumor cells. These authors used salt solutions of increasing concentration for the stepwise extraction of different histones from Walker tumor cells. The histone fractions isolated in this way from the nuclei of tumor cells take up a higher proportion of labeled amino acids than do the acidic proteins.

These studies would seem to confirm that acidic proteins fulfill a specific function in normal cells. More recent experimental results strongly support the assumption that acidic proteins may counteract the inhibition of RNA synthesis by histones and that they are likely to be involved in control mechanisms[65, 66]. The phosphorylation processes appear to control the interactions between acid proteins, DNA, and RNA polymerase. In addition, there exists a direct relation between enhanced RNA synthesis by hydrocortisone and estradiol and increased concentration of certain acidic proteins[67, 68].

6. Histone-Bound Nuclear RNA

Huang and *Bonner*[69] were the first to make the outstanding observation that a specific RNA/histone complex may exist within the chromatin. Quantitative nucleotide and phosphorus analyses led to the conclusion that this RNA has a molecular size of 40 nucleotides. The authors assume that this "c-RNA" is associated with as many as 15 to 20 histone molecules and may represent a nucleohistone sub-

[*] Nucleoli are spherical bodies associated with specific chromosomal segments, the nucleolus organizer, where the synthesis of ribosomal RNA takes place.

Table 2. Protein/DNA relation in nucleohistones from various tissues (after Ref. [108]).

Tissue	DNA	Histone	Other proteins	RNA
Rat liver	1.00	1.00	0.67	0.043
Rat ascites tumor	1.00	1.16	1.00	0.13
HeLa cells	1.00	1.02	0.71	0.09
Calf thymus	1.00	1.14	0.33	0.007
Sea urchin blastula	1.00	1.04	0.48	0.039
Pea embryonic axis	1.00	1.03	0.29	0.26

unit. Since 1 to 2 RNA molecules are related to one gene it seems likely that the c-RNA may participate in gene regulation (Table 2). Similar RNA-histone complexes could also be isolated from mammalian cells: rat liver cells[70], KB cells[71], Novikoff hepatoma cells[72], and calf thymus cells[73]. *Bonner*'s group succeeded somewhat later in isolating this RNA from rat ascites cells and embryonic chick tissue[74]. The true identity of a specific chromosomal RNA, distinguishable from cytoplasmic components by its high uracil content, is still a matter for discussion and becomes even more controversial since *Heyden* and *Zachau*[75] demonstrated that the existence of smaller RNA fragments is mainly caused by the nuclease degradation of pellicle-bound tRNA.

7. Dissociation and Reassociation of Nucleohistone

Numerous investigations have been carried out in an effort to gain a better understanding of the conformational changes of DNA under the influence of bound proteins and the mechanisms of complex formation in general. Evidently native nucleohistone presents such a complicated three-dimensional structure that simple recombination of its basic components rarely yields a reassociation product having comparatively similar biological activity: acidic proteins complex with histones; both of these proteins may interact with DNA as well as RNA; and, furthermore, sequence analog RNA may hybridize with DNA. The scope of complex formation is broad indeed. Step-by-step degradation of the chromosomal nucleohistone and monitoring the change in biological activity appears to be as equally promising a method as others for gaining an insight into the three-dimensional structure of genetic material.

In naturally occurring nucleohistones acidic and basic proteins are strongly but noncovalently bound to DNA. Although the positive charges of the basic amino acid residues are not uniformly distributed over the histone molecules, recent physicochemical experiments carried out by *Olins*[76] furnish evidence, in agreement with *Wilkin*'s model[33], that lysine-rich histones bind to the large groove along the DNA duplex and neutralize effectively the DNA phosphate groups. It is still an open question, however, whether attachment of basic proteins to DNA creates intermolecular crosslinking of parallel arranged DNA helices or contributes to formation of superhelices[77–79] (Fig. 7).

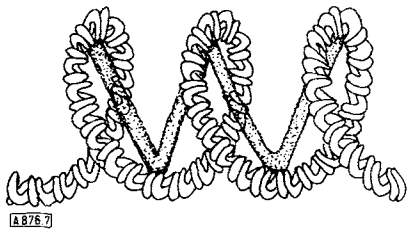


Fig. 7. Model of supercoiled DNA helices stabilized by protein linkers.

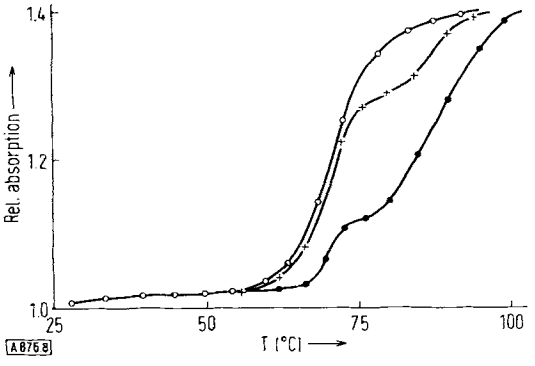


Fig. 8. Temperature dependent denaturation profiles for DNA (-○-○-), partially dehistonized nucleohistone (-+-+-), and intact nucleohistone (-●-●-).

Luzzati and *Nicolaieff*[80] elaborated the idea that the three-dimensional structure of nucleohistone is based on subunits formed by 4 DNA molecules complexed and surrounded with histones, whereas the nucleoprotamine structure tends more to a concentric arrangement of protamine molecules around a DNA backbone with water in the intermediate space. Reassociation experiments with nucleohistones show that the native conformation is restorable, even after almost complete dissociation in 3.5 M salt solution, by prolonged dialysis against water[81].

The outcome of this simple experiment implies that either the dissociation effect is totally reversible or cores of organizing structural elements are preserved under such experimental conditions.

Electron microscopic studies on preextracted nucleohistones show that the successive removal of histones at different ionic strengths leads to the formation of DNA loops which originate from structure-preserving cores of DNA and proteins[82,83]. It is possible that these morphological structures are identical with preexisting elements in the intact nuclei, as anticipated by *Bonner*, and are closely related to the DNA loops of lampbrush chromosomes[84]. Their degree of integration may explain the surprising observation that the dissociation of nucleohistones in high salt solutions is reversible. More detailed information about the histone-dependent conformational changes has been reported by *Allfrey* and *Mirsky*[85]. These authors showed that the removal of lysine-rich histone I causes a reversible formation of DNA loops while the subsequent extraction of arginine-rich fractions (III and IV) loosens irreversibly the entire chromosomal structure. The authors conclude that the two proteins fulfill different functions: arginine-rich histone forms intermolecular bridges between

different DNA molecules, whereas lysine-rich histone promotes condensation of chromatin.

The correlation between histone attachment and nucleohistone configuration has been intensively studied by *Murray*[86]. On decreasing the pH values of the solution the histones dissociate stepwise from the complex in a reversed manner, *i.e.* the lysine-rich fractions are the last to be released. The T_m-values for the temperature-dependent denaturation decrease as the amount of histone removed increases (Fig. 8). Since the histones, with an average molecular weight of 10000 to 50000, are much smaller than the native DNA, and the chromosomal nucleohistone contains approximately 50% to 60% protein, several histone molecules must be attached to one DNA duplex.

The distribution of the different histones along the main axis of the DNA may follow two extremly different patterns: either (i) histone molecules of one type are arranged consecutively or (ii) histone molecules of one type are never adjacent. The step-by-step extraction of histones should therefore result either in mixtures of free DNA and nucleohistone or in randomly deproteinized nucleohistone molecules. *Murray*'s results[86] demonstrate unequivocally that only DNA-protein complexes can be obtained which have T_m-values higher than protein-free DNA, and that their template activity for RNA polymerase is still significantly reduced.

In considering this evidence we have to assume that, in principle at least, histones are heterogeneously bound to DNA helices. This concept is supported by *Peacocke*'s studies on the influence of high salt concentrations on the conformation of nucleohistones[87]. The molecular weight decreases sharply to about 25% of the normal value of native material on increasing the salt concentration, while the radius of gyration of the DNA helix remains unchanged. Evidently the histones contribute far less to the conformation of the nucleohistone than assumed heretofore; consequently the stability of the three-dimensional structure, including superimposed foldings and twistings, is mainly dependent upon the existence of hydrogen bridges.

Nucleohistones dissolved in 4 M urea solutions show a distinct and reversible increase in viscosity[88]. Sedimentation experiments in the same solvent reveal that only 2% bound protein is dissociable and that the hyperchromatism of the temperature-dependent denaturation still amounts to 38%; this would suggest that the reversible conformation change may be caused by disruption of superhelical structures as was proposed by *Zubay* and *Doty*[32] on the basis of their hydrodynamic and light-scattering measurements. X-ray diffraction diagrams lead to the conclusion that the radius of gyration of such a superimposed helix could be in the range of 120 Å[89, 90].

8. Interactions between DNA and Histones

Our fragmentary knowledge about the tertiary structure and conformation of nucleohistones permits only a rough, overall assessment of the intricate binding conditions between the different components. An alternative way of elucidating the structural requirements for the formation of biologically active complexes is to examine reassociated DNA/polypeptide complexes. *Touvet* and *Champagne*[91] published some results of light-scattering and sedimentation studies on reassociated complexes and conclude that lysine-rich histone evidently reacts specifically but not covalently with definite binding sites of the DNA, whereby the helix becomes expanded longitudinally. The steric effect of bound arginine-rich histone is comparatively antagonistic and leads to contraction of the DNA duplex.

The preferential binding of histones or homogeneous polypeptides to definite nucleotide sequences was first investigated by *Chargaff*[92] and *Lucy*[93]. Further systematic studies on this very important phenomenon by *Felsenfeld et al.*[94] markedly clarified some important features of DNA-protein interactions; it was found that polylysine reacts cooperatively with adenine (A) and thymine (T) while polyarginine exhibits a certain preference for cytosine(C)- and guanine(G)-rich sequences of free DNA. *Felsenfeld* pointed out that these reactions are selective, reversible, cooperative, and stoichiometric; the end product of the complex-forming interaction consists of highly hydrated micelle-like particles of remarkably uniformity, with an average radius of 1700 Å[95]. Furthermore, the specificity of the polyarginine-DNA interaction is concentration-dependent and approaches optimal values of effectivity when the percentage of arginine is higher than 60%. There is only one protein known which fulfills this requirement and appears to be a natural binding partner of DNA: protamine. On the basis of results obtained from carefully conducted ORD studies it could be deduced that interactions between polylysine and DNA stabilize the DNA conformation, either by coil contraction or by superimposing a secondary helical structure[96, 97].

Unfortunately, all attempts to estimate the binding parameters and to reveal a sufficient degree of selectivity for the different reactants failed[98]. It should occasion no surprise therefore that pyrimidines do not exhibit any individual differences in their reactivity towards polypeptides, whereas a somewhat different situation is apparent in the case of purines. Polyarginine and polylysine show a slightly increased affinity for CG-rich polynucleotides[99]. This interaction can be inhibited quite strongly by sodium ions, which obviously compete with the ε-amino groups of the lysine residues for the binding sites of DNA[100]. Since sodium ions and bivalent metallic ions reveal a high affinity for AU- or AT-rich nucleotide sequences such competitive reactions could possibly limit specific translocation and thus interfere in gene regulatory mechanisms. On the other hand, aliphatic polyamines, like spermine or spermidine, are considerably more reactive than bivalent cations, though their specificity for AT-rich sequences is very much in doubt[101–104]. The temperature-dependent denaturation profiles are monophasic and thus indicate decisively that the interaction of these components with nucleotide sequences is non-cooperative; there is also evidence that a similar mode of interaction prevails in the case of short-chain polypeptides such as tetraarginine and tetralysine. Octalysine, however, preferentially reacts with certain nucleotide sequences. Interestingly, the DNA-protamine interaction, unlike the interaction of all other polypeptides so far discussed, is both a cooperative and an equilibrium

reaction. In accordance with a cooperative binding type, the denaturation profiles of nucleoprotamine are biphasic and the two T_m-values are correspondingly higher than in the case of free DNA. Related to this observation is the fact that the structure specificity as well as the affinity of protamine to DNA is illustrated by the first T_m-value of the complex being directly dependent on the amount of associated protein[105].

9. Biological Activity of the Chromosomal Nucleohistones

Further evidence suggesting a specific interaction between DNA and proteins in native as well as reassociated complexes derives from comparative studies of the template activity in RNA polymerase transcription. Native chromosomal nucleohistone generally contains RNA polymerase, DNA polymerase, and nucleoside-triphosphatase; the concentration and specific activity of these enzymes change with the development of the cells. Whereas it is not possible to decide whether RNA polymerase is specifically or unspecifically attached to this complex, sufficient experimental evidence is available to prove that DNA polymerase is bound to the complexed DNA duplex.

The susceptibility of nucleohistones for RNA polymerase transcription appeared to be one of the most appropriate methods for elucidating the efficacy of protein-DNA interactions in terms of gene regulation. RNA polymerase of *Escherichia coli* is commonly used in such experiments, the enzyme being incubated with increasing amounts of DNA or nucleohistone. Two important findings emerge from these studies:

i) The template activity of nucleohistones is significantly reduced in comparison to free DNA[106,107]. (A plausible explanation for this observation would be that the nucleotide sequences are partially masked by bound proteins.)

ii) RNA transcribed on nucleohistone templates hybridizes with DNA to a lesser extent than RNA synthesized on protein-free matrices[108].

These results lend support to the conclusion that restriction of RNA polymerase transcription must be due to the resultant steric alterations of the nucleohistone template by DNA-protein interactions. This effect can be specified by the fundamental observation that RNA chains synthesized on nucleohistone templates are 4 to 5 times shorter than in RNA synthesized on DNA templates[109,110].

Paul and *Gilmour*[111] were the first to recognize that some nucleotide sequences of chromatin are inaccessible for RNA polymerase transcription. Nucleohistones isolated from bone marrow cells and from calf thymus contain tissue-specific sequences which are transcribable by RNA polymerase but represent only 5 to 12% of the genetic information available in free DNA. In addition, these RNA do not contain any non-specific sequences, thus confirming the assumption that the chosen extraction procedure does not lead to conformational changes.

The hybridization capacity of RNA synthesized on nucleohistones partially deproteinized by 0.5 to 0.6 M salt solutions approaches values comparable with those observed for RNA synthesized with DNA templates[106]. Under these experimental conditions only histone I is selectively removed; this finding would appear to cast doubt on the validity of our working hypothesis that only the masking effect of bound histones suffices to explain this restricted

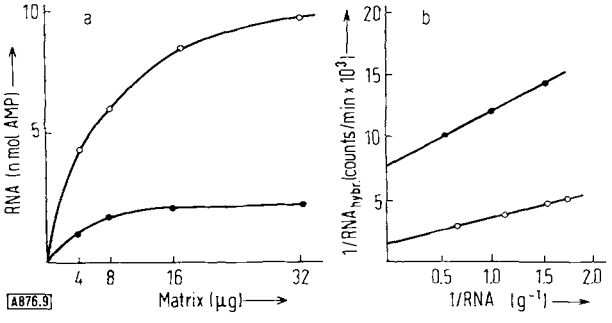


Fig. 9. a) RNA synthesis on DNA- (-○-○-) and nucleohistone matrices (-●-●-) with *E. coli* polymerase. b) Hybridization of *in vitro* synthesized RNA from DNA (-○-○-) and nucleohistone (-●-●-) matrices (after Ref. [130]).

template activity of nucleohistones. Recently, the view that extraction with 0.5 to 0.6 M salt solutions removes a repressor which directly influences either the steric conformation or the activity of the RNA polymerase has found more support. For example, it has been found that only 50% of the nucleotide sequences in nucleohistone are associated with proteins[112,113].

Spelsberg and *Hnilica*[114,115], however, have reported findings that are not in accord with this recent point of view: The selective extraction of histone I did not lead to an increase in the biological activity of the partially deproteinized nucleohistone. These authors are of the opinion that an activation of the RNA synthesis by the increased salt concentration is involved. Even after all the histones and part of the acidic proteins were removed, the biological activity of the extracted nucleohistone was still essentially restricted.

Insofar as experimental evaluation is concerned it should be noted that the available standard methods of transcription and hybridization are applicable only to those multiple genes which are repeatedly transcribed. However, the acceptance of technical limitations does not reduce the fundamental importance of these methods since repeated sequences represent highly specified operational genes with different activities corresponding to the stage of development of the cell. One example will suffice to illustrate this fact: RNA synthesis is detectable in the four-cell stage of sea urchin development whilst only those cistrons required for the synthesis of ribosomal RNA and tRNA are specifically activated during gastrulation[116].

The relative paucity of differences in the histone molecules of one cell, and the conservation of their amino acid sequences during phylogenesis, points to their being responsible for the general regulatory function in gene repression. As to whether arginine-rich histones take precedence over lysine-rich histones, or *vice versa*, for this function cannot

as yet be determined experimentally—available experimental evidence does not show any significant differences between the repressive action of arginine-rich and lysine-rich histones[117,118].

Johns and *Hoare* describe[119] an alternative solution to this problem. Investigations have shown that precipitating artificial DNA/histone complexes partly regain their solubility as well as template activity on reacting with an excess of histone. On the basis of this evidence it seems justified to assume that the repressive function of histones is more or less unspecific and related to the actual ratio of the reactants involved.

Acidic proteins probably play the most important role in gene regulation, since the concentration of these proteins is significantly increased in metabolically active regions of chromosomes while the histone concentration remains unaltered[120,122]. In this connection *Paul* and *Gilmour* have shown that the reassociation of nucleohistones with comparable biological activity depends on the actual concentration of acidic proteins involved[123]. The tissue-specific restrictions of nucleohistones as templates for RNA synthesis are due to the binding of acidic proteins[124]. The interactions between DNA and these proteins appear to be exceptionally complicated, since the addition of acid proteins leads, as *Wang* has reported[125], to enhanced RNA transcription on nucleohistone matrices. Somewhat contradictive to this observation, however, are the experimental results obtained by *Bonner*'s group[126], who support the view that the exceptionally crucial function of chromosomal RNA is to preserve and maintain the three-dimensional structure of nucleohistones as well as to regulate their biological activity. According to these authors it appears legitimate to equate the function of an operational factor with the existence of a specific RNA-histone complex.

This challenging conclusion does not seem too far fetched if we take into account the long known fact that the template activity of DNA for DNA polymerase is independent of the amount of associated histone[127] and that neither the amino acid composition nor amino acid sequence—and therefore charge distribution—of the histones seem to be related in any way to the activity of the RNA polymerase.

A very recent theory developed by *Crick*[128] partly circumvents these difficulties but retains the essential feature of protein-controlled genetic activity; it is based on the so-called "unpairing postulate".

Before considering the regulatory function of chromosomal proteins attention is again directed to the structure of nucleohistone. The alternating transversal bands of heterochromatin and euchromatin represent a densely packed and stretched tertiary structure, such as can be detected in the giant chromosomes of Diptera larvae. *Crick* bases his theory on these facts and assumes that the interbands or euchromatic regions contain single strand stretches of the DNA duplex. Only these nucleotide sequences represent recognition sites for RNA polymerase transcription and are large enough to code proteins having an average molecular weight of 30000 to 40000. The unwound conformation of DNA is due the action of chromosomal proteins, probably histones, which also preserve this unique structure. The much larger heterochromatin bands, on the other hand, are biologically inactive and are considered to contain multiple control elements which are essential for a graded and regulated biological activity of the euchromatin.

Further experimental information is now required in order to confirm this theory and to improve our understanding of chromosomal structures. It is obviously impossible to draw a correct and sophisticated picture of the correlation between structure and biological activity of chromosomal nucleohistones on the basis of our present fragmentary knowledge of DNA/protein interactions. *Mirsky*'s recent statement[129] sums up the situation by expressing that probably all the DNA in chromatin is linked to proteins and only the actual binding forces decide the accessibility of certain genes.

Received: March 15, 1971 [A 876 IE]
German version: Angew. Chem. *84*, 451 (1972)

[1] *R. Sager* and *F. J. Ryan*: Cell Heredity. Wiley, London 1961.

[2] *H. Ris* in *D. McElroy* and *B. Glas*: Chemical Basis of Heredity. Johns Hopkins Press, Baltimore 1957.

[3] *H. L. K. Whitehouse*: Mechanism of Heredity. St. Martins Press, New York 1969.

[4] *H. Ris*, Colloq. Ges. Physiol. Chemie, Mosbach/Baden, 1958/1959.

[5] *M. H. F. Wilkins*, Cold Spring Harbor Symp. Quant. Biol. *11*, 75 (1956).

[6] *J. D. Watson* and *F. D. Crick*, Nature *171*, 964 (1953).

[7] *J. H. Taylor*, Proc. 10th Intern. Congr. Genet. Montreal *1*, 63 (1958).

[8] *J. A. Huberman* and *A. D. Riggs*, Proc. Nat. Acad. Sci. U. S. *55*, 599 (1966).

[9] *G. C. Hoskins*, Nature *217*, 748 (1968).

[10] *H. G. Callan*, J. Cell. Sci. *2*, 1 (1967).

[11] *J. G. Gall* and *H. G. Callan*, Proc. Nat. Acad. Sci. U. S. *48*, 562 (1962).

[12] *W. Beermann*, Naturwissenschaften *52*, 365 (1967).

[13] *D. D. Brown* and *C. S. Weber*, J. Mol. Biol. *34*, 661 (1968).

[14] *S. A. Yankovsky* and *S. Spiegelman*, Proc. Nat. Acad. Sci. U. S. *48*, 1466 (1962).

[15] *F. M. Ritossa, K. C. Atwood*, and *S. Spiegelman*, Genetics *54*, 663 (1966).

[16] *R. A. Gilmour, J. W. Steward*, and *F. Sherman*, Biochim. Biophys. Acta *161*, 270 (1968).

[17] *H. M. Goodman, J. Bilson, A. Landy, S. Brenner*, and *J. D. Smith*, Nature *217*, 1019 (1968).

[18] *E. W. Johns*, Biochem. J. *92*, 55 (1964).

[19] *K. Murray* in *J. Bonner* and *P. Ts'o*: The Nucleohistones. Holden Day, San Francisco 1964.

[20] *A. J. Hayden* and *A. R. Peacocke*, Biochem. J. *110*, 243 (1968).

[21] *J. M. Kinkade* and *R. Cole*, J. Biol. Chem. *241*, 5798 (1966).

[22] *E. W. Johns*, European J. Biochem. *4*, 437 (1968).

[23] *J. Leclerc, A. Martinage, M. Dautrevaux*, and *G. Biserte*, Biochim. Biophys. Acta *194*, 342 (1969).

[24] *J. Magliozzi, D. Puro, C. Lin, R. Ortmann*, and *A. L. Dounce*, Exp. Cell Res. *67*, 11 (1971).

[25] *R. H. Stellwagen* and *R. D. Cole*, J. Biol. Chem. *234*, 4452 (1968).

[26] *E. W. Johns* and *S. Forrester*, European J. Biochem. *8*, 547 (1969).

[27] *R. J. DeLang, M. Fambrough, E. L. Smith*, and *J. Bonner*, J. Biol. Chem. *243*, 5906 (1968); *244*, 319 (1969).

[28] *M. Bustin, S. Rall, R. H. Stellwagen*, and *R. D. Cole*, Science *163*, 391 (1969).

[29] *Y. Ogawa, G. Quagliarotti, J. Jordan, C. W. Taylor, W. C. Starbuck*, and *H. Busch*, J. Biol. Chem. *244*, 4387 (1969).

[30] *P. Santiere, W. C. Starbuck, C. Roth*, and *H. Busch*, J. Biol. Chem. *243*, 5899 (1968).

[31] *K. Iwai, K. Ishikawa*, and *H. Hayashi*, Nature *226*, 1056 (1970).

[32] *M. Bustin, S. C. Rall, R. H. Stellwagen*, and *R. D. Cole*, Science *163*, 391 (1969).

[33] *A. M. Tamburro, A. Scatturin*, and *G. Vidali*, Int. J. Protein Res. *2*, 127 (1970).

[34] *E. M. Bradbury, C. Crane-Robinson, D. M. P. Phillips, E. W. Johns,* and *K. Murray*, Nature *205*, 1315 (1965).

[35] *P. J. Urnes* and *P. Doty*, Advan. Protein Chem. *16*, p. 401 (1961).

[36] *G. Zubay* and *P. Doty*, J. Mol. Biol. *1*, 1 (1959).

[37] *M. H. F. Wilkins, G. Zubay,* and *H. R. Wilson*, Trans. Faraday Soc. *55*, 497 (1959).

[38] *W. S. Stevely* and *L. A. Stocken*, Biochem. J. *110*, 187 (1968).

[39] *E. L. Gershey, G. Vidali,* and *V. G. Allfrey*, J. Biol. Chem. *243*, 5018 (1968).

[40] *B. G. T. Pogo, A. O. Pogo, V. G. Allfrey,* and *A. Mirsky*, Proc. Nat. Acad. Sci. U. S. *59*, 1337 (1968).

[41] *E. Robbins* and *T. W. Borun*, Proc. Nat. Acad. Sci. U. S. *57*, 409 (1967).

[42] *J. R. Tevitnick, C. J. Ingles,* and *G. H. Dixon*, Fed. Proc. *26*, 603 (1967).

[43] *T. W. Borun, M. D. Scharff,* and *E. Robbins*, Proc. Nat. Acad. Sci. U. S. *58*, 1977 (1967).

[44] *B. R. Reid* and *R. D. Cole*, Proc. Nat. Acad. Sci. U. S. *51*, 1044 (1964).

[45] *M. L. Birnstiel* and *W. G. Flamm*, Science *145*, 1434 (1964).

[46] *L. H. Kedes* and *M. L. Birnstiel*, Nature New Biology *230*, 165 (1971).

[47] *L. H. Kedes* and *P. R. Gross*, Nature *223*, 1335 (1969).

[48] *C. C. Liew, G. W. Haslett,* and *V. G. Allfrey*, Nature *226*, 414 (1970).

[49] *K. Marita, I. Tsuchida, S. Tsunazawa,* and *K. Ogata*, Biochem. Biophys. Res. Commun. *37*, 327 (1969).

[50] *D. G. Laycock* and *J. A. Hunt*, Nature *221*, 1118 (1969).

[51] *G. Chalkley* and *H. Maurer*, Proc. Nat. Acad. Sci. U. S. *54*, 498 (1965).

[52] *E. Stedman* and *E. Stedman*, Nature *153*, 500 (1944).

[53] *H. Busch*: Histones and Other Nuclear Proteins. Academic Press, New York 1965.

[54] *T. Y. Wang*, J. Biol. Chem. *241*, 2913 (1966).

[55] *K. Marushige, D. Brutlag,* and *J. Bonner*, Biochemistry *7*, 3149 (1968).

[56] *T. Shirey* and *R. C. Huang*, Biochemistry *8*, 4138 (1969).

[57] *J. E. Loeb*, Biochim. Biophys. Acta *157*, 424 (1968).

[58] *G. Patel, V. Patel, T. Y. Wang,* and *C. R. Zobel*, Arch. Biochem. Biophys. *128*, 654 (1968).

[59] *L. J. Kleinsmith, V. G. Allfrey,* and *A. E. Mirsky*, Proc. Nat. Acad. Sci. U. S. *55*, 1128 (1966).

[60] *H. G. Rose* and *J. H. Frenster*, Biochim. Biophys. Acta *106*, 577 (1965).

[61] *T. Y. Wang*, Biochim. Biophys. Acta *68*, 52 (1963).

[62] *V. G. Allfrey, R. Meudt, J. W. Hopkins,* and *A. E. Mirsky*, Proc. Nat. Acad. Sci. U. S. *47*, 907 (1961).

[63] *G. Patel* and *T. Y. Wang*, Biochim. Biophys. Acta *95*, 314 (1965).

[64] *W. J. Steele* and *H. Busch*, Cancer Res. *23*, 1153 (1963).

[65] *L. J. Kleinsmith, J. Heidema,* and *A. Carroll*, Nature *226*, 1025 (1970).

[66] *C. S. Teng, C. T. Teng,* and *V. G. Allfrey*, J. Biol. Chem. *246*, 3597 (1971).

[67] *J. A. Smith* and *R. J. King*, Brit. J. Cancer *24*, 861 (1970).

[68] *K. R. Shelton* and *V. G. Allfrey*, Nature *228*, 132 (1970).

[69] *R. C. Huang* and *J. Bonner*, Proc. Nat. Acad. Sci. U. S. *54*, 960 (1965).

[70] *A. C. Peacocke* and *C. W. Dingmann*, Biochemistry *6*, 1818 (1967).

[71] *C. J. Larsen, F. Galibert, J. C. Lelong,* and *M. Boiron*, C. R. Acad. Sci. Paris *264*, 1523 (1967).

[72] *T. Nakamura, A. W. Prestayko,* and *H. Busch*, J. Biol. Chem. *243*, 1368 (1968).

[73] *A. W. Prestayko* and *H. Busch*, Biochim. Biophys. Acta *169*, 327 (1968).

[74] *M. Dahmus*, Dissertation, California Inst. Technol. 1968.

[75] *H. W. von Heyden* and *H. G. Zachau*, Biochim. Biophys. Acta *232*, 651 (1970).

[76] *D. E. Olins*, J. Mol. Biol. *43*, 439 (1969).

[77] *G. Zubay*: The Nucleohistones. Holden-Day, San Francisco 1964.

[78] *E. W. Johns*, Homeostatic Regul. Ciba Found. Symp. 1969.

[79] *P. Henson* and *I. O. Walker*, Eur. J. Biochem. *14*, 345 (1970).

[80] *V. Luzzati* and *A. Nicolaieff*, J. Mol. Biol. *7*, 142 (1963).

[81] *J. Paulau, J. F. Pardon,* and *B. M. Richards*, Biochim. Biophys. Acta *138*, 633 (1967).

[82] *J. Sonnenbichler*, Nature *223*, 205 (1969).

[83] *J. Sonnenbichler* and *P. Nobis*, Hoppe-Seylers Z. Physiol. Chem. *349*, 1556 (1968).

[84] *E. Fredericq* and *C. Houssier*, European J. Biochem. *1*, 51 (1967).

[85] *V. C. Littau, C. J. Burdick, V. G. Allfrey,* and *A. E. Mirsky*, Proc. Nat. Acad. Sci. U. S. *54*, 1204 (1965).

[86] *K. Murray*, J. Mol. Biol. *15*, 409 (1966); *39*, 125 (1969).

[87] *P. M. Bayley, B. N. Preston,* and *A. Peacocke*, Biochim. Biophys. Acta *66*, 943 (1968).

[88] *J. A. Bartley* and *R. Chakley*, Biochim. Biophys. Acta *160*, 224 (1968).

[89] *J. F. Pardon, M. H. F. Wilkins,* and *B. M. Richards*, Nature *215*, 508 (1967).

[90] *Y. Ohba*, Biochim. Biophys. Acta *123*, 76 (1966).

[91] *M.-C. Touvet* and *M. Champagne*, J. Chem. Phys. *63*, 696 (1966).

[92] *P. Spitnik, R. Lipshitz,* and *E. Chargaff*, J. Biol. Chem. *215*, 7651 (1955).

[93] *J. A. Lucy* and *J. A. V. Butler*, Biochim. Biophys. Acta *16*, 431 (1955).

[94] *M. Leng* and *G. Felsenfeld*, Proc. Nat. Acad. Sci. U. S. *56*, 1325 (1966).

[95] *J. T. Shapiro, M. Leng,* and *G. Felsenfeld*, Biochemistry *8*, 3219 (1969).

[96] *M. Tsuboi* and *K. Matsuo*, J. Mol. Biol. *15*, 256 (1966).

[97] *D. E. Olins, A. L. Olins,* and *P. H. von Hippel*, J. Mol. Biol. *33*, 265 (1968).

[98] *K. G. Wagner* and *R. Arav*, Biochemistry *7*, 1771 (1968).

[99] *S. A. Latt* and *H. A. Sober*, Biochemistry *6*, 3293 (1967).

[100] *S. A. Latt* and *H. A. Sober*, Biochemistry *6*, 3307 (1967).

[101] *H. R. Mahler* and *B. D. Mehrotra*, Biochim. Biophys. Acta *68*, 211 (1963).

[102] *S. Z. Hirschmann, M. Leng,* and *G. Felsenfeld*, Biopolymers *5*, 227 (1967).

[103] *O. Heby* and *I. Agrell*, Hoppe-Seylers Z. Physiol. Chem. *352*, 29 (1971).

[104] *I. Agrell* and *O. Heby*, Hoppe-Seylers Z. Physiol. Chem. *352*, 39 (1971).

[105] *E. O. Akiurimisi, J. Bonner,* and *P. O. P. Tso*, J. Mol. Biol. *11*, 1281 (1965).

[106] *Y. V. Koslov* and *G. P. Georgiev*, Nature *228*, 245 (1970).

[107] *T. C. Spelsberg, L. S. Hnilica,* and *A. T. Ansevin*, Biochim. Biophys. Acta *228*, 550 (1971).

[108] *J. Bonner, M. E. Dahmus, D. Fambrough, R. C. Huang, K. Marushige,* and *D. Y. H. Tuan*, Science *159*, 147 (1968).

[109] *T. Hoare* and *E. W. Johns*, Biochem. J. *119*, 931 (1970).

[110] *C. H. Tan* and *M. Miyagi*, J. Mol. Biol. *50*, 641 (1970).

[111] *J. Paul* and *R. S. Gilmour*, J. Mol. Biol. *16*, 242 (1966).

[112] *R. F. Itzhaki*, Biochem. Biophys. Res. Commun. *41*, 25 (1970).

[113] *R. J. Clark* and *G. Felsenfeld*, Nature New Biology *229*, 101 (1971).

[114] *T. C. Spelsberg* and *L. S. Hnilica*, Biochim. Biophys. Acta *228*, 202 (1971).

[115] *T. C. Spelsberg* and *L. S. Hnilica*, Biochim. Biophys. Acta *228*, 212 (1971).

[116] *P. R. Gross, K. Kraemer,* and *L. I. Malkin*, Biochem. Biophys. Res. Commun. *18*, 569 (1965).

[117] *J. Hindley*, Biochem. Biophys. Res. Commun. *12*, 175 (1963).

[118] *G. C. Barr* and *J. A. V. Butler*, Nature *199*, 1170 (1963).

[119] *E. Johns* and *T. A. Hoare*, Nature *226*, 650 (1970).

[120] *H. J. Frenster*, Nature *206*, 680 (1965).

[121] *Y. Kurashina* and *Y. Oba*, Protein (Tokyo) *15*, 2 (1970).

[122] *G. Rovera* and *R. Barega*, J. Cell. Physiol. *77*, 201 (1971).

[123] *J. Paul* and *R. S. Gilmour*, J. Mol. Biol. *34*, 305 (1968).

[124] *T. C. Spelsberg, L. S. Hnilica,* and *T. Ansevin*, Biochim. Biophys. Acta *228*, 550 (1971).

[125] *M. Kamiyama* and *T. Y. Wang*, Biochim. Biophys. Acta *228*, 563 (1971).

[126] *I. Bekhor, G. Kung,* and *J. Bonner*, J. Mol. Biol. *39*, 351 (1969).

[127] *S. Schwimmer* and *J. Bonner*, Biochim. Biophys. Acta *108*, 67 (1965).

[128] *F. Crick*, Nature *234*, 25 (1971).

[129] *A. E. Mirsky*, Proc. Nat. Acad. Sci. U. S. *68*, 2945 (1971).

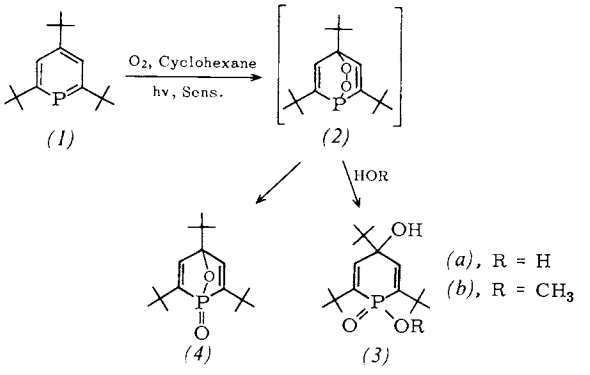
[130] *K. Marushige* and *J. Bonner*, J. Mol. Biol. *15*, 160 (1966).

Photochemical Oxygenation of 2,4,6-Tri-*tert*-butyl-λ^3-phosphorin and 2,4,6-Tri-*tert*-butyl-1,1-dimethoxy-λ^5-phosphorin

By *Karl Dimroth*, *Anastasios Chatzidakis*, and *Ortwin Schaffer*[*]

Dedicated to Professor G. Wittig in grateful appreciation on his 75th birthday

Oxygenation of heterocycles by singlet oxygen produced by photosensitization[1] has recently excited great interest[2].



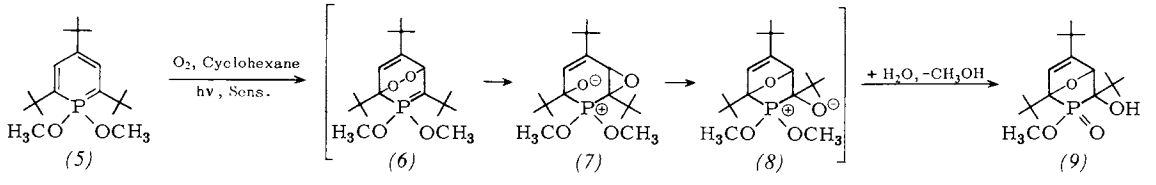
(1) (2) (4) (3)

Sensitized photooxygenation of 2,4,6-tri-*tert*-butyl-1,1-dimethoxy-λ^5-phosphorin *(5)* takes a different course. In this case the oxygen is added normally in the primary step at 1,4-positions, namely to *carbon atoms* 2 and 5. Again the primary product *(6)* could not be isolated. It probably rearranges with cleavage of the O—O bond, yielding the methyl 2-hydroxy phosphinate *(9)* by way of *(7)* and *(8)*. Its constitution follows from elemental analysis and spectroscopic data.

Experimental

Compound *(1)* (528 mg, 2 mmol) and eosin (15 mg) in anhydrous cyclohexane (60 ml) are irradiated for 45 min with a high-pressure mercury lamp (Hanau NK 6/20; emission maximum 366 nm) while anhydrous oxygen is passed into the solution. After removal of 2/3 of the solvent by distillation, addition of a little methanol precipitates the phosphinic acid *(3a)*, which melts at 167 °C when recrystallized from ethanol/water. With diazomethane it forms the *cis-trans*-isomeric methyl esters *(3b)*, m. p. 274 and 280 °C (dec.)[4] that are separable by thin-layer chromatography.

Preparative layer chromatography on silica gel with benzene/methanol as mobile phase affords *(4)* which after recrystallization from ligroin melts at 152 °C.



(5) (6) (7) (8) (9)

We have observed a new type of reaction in which in the primary step the oxygen is added at the 1,4-positions *with involvement of the heteroatom*: If 2,4,6-tri-*tert*-butylphosphor(III)-in *(1)*[3] in anhydrous cyclohexane containing eosin as sensitizer is irradiated by a high-pressure mercury lamp while oxygen is passed through the solution, then two crystalline compounds, m. p. 167 and 152 °C, can be isolated in 15% yield each. The higher-melting material is identical with the known 4-hydroxy phosphinic acid *(3a)* previously obtained by oxidation with HNO_3/H_2SO_4[4]. On the basis of elemental analysis and UV, NMR, and mass spectra, the compound of m. p. 152 °C has structure *(4)*. We assume the reaction course shown in formulas *(1)* to *(4)*. The primary product *(2)* was not isolated, as is generally also the case in other oxygenations[5].

On photooxygenation 2,4,6-triphenyl-λ^3-phosphorin[**] affords a larger number of products that are difficult to separate[6].

Irradiation and working up of *(5)* (yield 20%) are carried out analogously. The methyl hydroxy phosphinate *(9)* of m. p. 180 °C could not be separated into two diastereoisomers.

Received: February 4, 1972 [Z 596 IE]
German version: Angew. Chem. *84*, 526 (1972)
Publication delayed at the authors' request

[*] Prof. Dr. K. Dimroth, Dr. A. Chatzidakis, and Dipl.-Chem. O. Schaffer
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

[**] According to a suggestion by the IUPAC Commission on the Nomenclature of Organic Chemistry the valence of hetero atoms in heterocyclic systems is denoted by the number λ^n of bonds radiating from the atom in question (connecting number).

[1] Nachr. Chem. Techn. *19*, 446 (1971); *W. Adam* and *Ju-Chao Liu*, Chem. Commun. *1972*, 73.

[2] *G. N. Skold* and *R. H. Schlessinger*, Tetrahedron Lett. *1970*, 791; *Zen-ichi Yoshida*, *T. Sugimoto*, and *S. Yonada*, *ibid. 1971*, 4259; *T. S. Reid*, Advan. Heterocycl. Chem. *11*, 1 (1970); *K. Gollnick* and *G. O. Schenck* in *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1969.

[3] *K. Dimroth* and *W. Mach*, Angew. Chem. *80*, 489 (1968); Angew. Chem. internat. Edit. *7*, 460 (1968).

[4] *W. Mach*, Dissertation, Universität Marburg 1968; see also, Oxidation in Moist Benzene, *K. Dimroth*, *K. Vogel*, *W. Mach*, and *U. Schoeler*, Angew. Chem. *80*, 359 (1968); Angew. Chem. internat. Edit. *7*, 371 (1968).

[5] See, *e. g.*, *K. H. Schulte-Elte*, *B. Wilhalm*, and *G. Ohloff*, Angew. Chem. *81*, 1045 (1969); Angew. Chem. internat. Edit. *8*, 985 (1969); *W. Skorianetz*, *K. H. Schulte-Elte*, and *G. Ohloff*, Helv. Chim. Acta *54*, 1913 (1971).

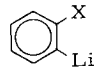
[6] *A. Chatzidakis* and *K. Dimroth*, unpublished work.

DTA Studies on Formation of Dehydrobenzene and Dichlorocarbene from Haloorganolithium Compounds

By *Oleg M. Nefedov* and *Andrej I. Dyachenko*[*]

Dedicated to Professor Georg Wittig on the occasion of his 75th birthday

In the present communication we report differential thermal analysis (DTA)[1] studies on the decomposition of *o*-halophenyllithiums, *o*-XC_6H_4Li *(1)*[1-3], and trichloromethyllithium *(2)*[3-5] in the present of ethers and amines. Compounds *(1)* and *(2)* were obtained by the addition of 1.0—10 ml of a 1.0 N solution of *o*-XC_6H_4Br



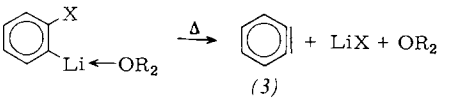
(1), X = F, Cl, Br

Cl_3CLi

(2)

(X = F, Cl, Br) or Cl_3CX' (X' = H, Br) in isopentane or *n*-pentane to an equal volume of 1.0 N *n*-C_4H_9Li in the same solvent at −150 °C. The mixture was then allowed to warm to room temperature (≈1 h) in a DTA instrument. The results are shown in Table 1. Independent experiments have shown that the observed exothermic effects are due to the decomposition of *(1)* or *(2)*[6].

Decomposition of the complex is evidently initiated by thermal dissociation of the Li←O coordinative bond. A free coordinative site becomes available at the lithium,



(3)

thus resulting in immediate elimination of lithium halide owing to intramolecular coordination X→Li. If this concept is correct complexes of *(1)* with cyclic ethers and other ligands of high basicity (*e.g.* dimethoxyethane or tetramethylethylenediamine) should be more stable that those with dialkyl ethers owing to a stronger Li←O bond.

Since the stability of complexes of *(1)* with cyclic ethers, dimethoxyethane, and tetramethylethylenediamine was indeed found to be independent of polarity, it seems reasonable to conclude that the Li←O bond strength is mainly determined by the steric requirements of the solvent in connection with its ability to undergo inversion.

As is also evident from the data in Table 1, the stability of complexes *(1)* increases in the sequence X = Br < Cl < F. This corresponds to the donor strengths of the halogens[7,8].

An analogous, albeit less pronounced, stabilization was also found for *(2)* in polar solvents (Table 1). This doubtless means that dichlorocarbene formation does not proceed

Table 1. Thermal stability of haloorganolithium compounds in polar solvents.

Solvent	Dipole moment (D)	Decomposition temperature (°C) [a] *o*-XC_6H_4Li *(1)* from *o*-XC_6H_4Br X = F	X = Cl	X = Br	Cl_3CLi *(2)* from Cl_3CX' X' = H	X' = Br
Diethyl ether	1.15	−48	−73	−85	−88	−89
Di-*n*-propyl ether	1.18	−50	−73	−83	−84	—
Di-*n*-butyl ether	1.22	—	−70	—	−87	−85
Triethylamine	0.82	—	—	—	−87	−85
Tetrahydropyran	1.55	−21	−50	−75	−65	−67
Tetrahydrofuran	1.75	−20	−51	−75	−66	−66
Oxetane	1.92	−19	−50	−76	−65	−65
Methyloxirane	1.95	−20	−52	−73	—	—
1,2-Dimethoxyethane	1.72	−19	−50	−80	−75	−75
Tetramethylethylenediamine	—	−16	−48	—	−76	—

[a] Average of 3—4 experiments.

As is seen from Table 1 the thermal stability of *(1)* increases substantially only on going from acyclic to cyclic ethers. Within the two series of ethers the stability remains practically unchanged in spite of the varying polarity.



(3)



(4)

These results are not in accord with formation of dehydrobenzene *(3)* *via* an *o*-halophenyl anion intermediate *(4)*[7], since such a mechanism would require a decrease in stability of *(1)* with increasing solvent polarity. Hence, we assume that *(3)* is formed by a concerted β-elimination of LiX from a complex of *(1)* with ether (or trialkylamine)[2,3].

[*] Prof. Dr. O. M. Nefedov and A. I. Dyachenko
N. D. Zelinsky Institute of Organic Chemistry
Academy of Science of the USSR
Moscow B-334, Leninsky prospect 47 (UdSSR)

[1] *O. M. Nefedov* and *A. I. Dyachenko*, Doklady Akad. Nauk SSSR *198*, 593 (1971).

[2] *O. M. Nefedov*, *A. I. Dyachenko*, and *A. Ya. Shteinshneider*, Izv. Akad. Nauk SSSR, Ser. Khim. *1971*, 1845.

[3] *O. M. Nefedov*, *A. I. Dyachenko*, and *A. Ya. Shteinshneider*: V. International Conference on Organometallic Chemistry, Abstracts. Moscow 1971, Vol. 1, p. 598.

[4] *G. Köbrich*, Angew. Chem. *79*, 15 (1967); Angew. Chem. internat. Edit. *6*, 41 (1967).

[5] *G. Köbrich*, *H. Büttner*, and *E. Wagner*, Angew. Chem. *82*, 177 (1970); Angew. Chem. internat. Edit. *9*, 169 (1970).

[6] Reaction mixtures of *(1)* or *(2)*, preheated to temperatures 10 to 20 °C below the decomposition temperature, gave *o*-XC_6H_4COOH or Cl_3CCOOH (80—100% yields) with CO_2 (after acidification), and XC_6H_5 or Cl_3CH (85—100% yields) with alcohols.

[7] *R. W. Hoffmann*: Dehydrobenzene and Cycloalkynes. Academic Press, New York 1967, pp. 9 ff, 43 ff.

[8] *H. Gilman* and *R. D. Gorsich*, J. Amer. Chem. Soc. *78*, 2217 (1956).

[9] EHT calculations on the Cl_3CLi molecule have shown that an electron transfer from Cl to Li corresponds to the transition from the ground state of the molecule to the first excited state.

[10] *H. L. Lewis* and *T. L. Brown*, J. Amer. Chem. Soc. *92*, 4664 (1970).

via the intermediate anion (Cl_3C^-) but occurs as a concerted α-elimination of LiCl from the complex of *(2)* with ether or amine[9].

It is noteworthy that the temperatures of decomposition of *(2)* in triethylamine and acyclic ethers are the same. This fact may serve as further evidence for the above mechanism, because, according to *Lewis* and *Brown*[10], complexes of alkyllithium compounds with dialkyl ethers and corresponding trialkylamines are equally stable.

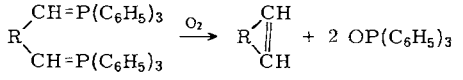
Received: February 28, 1972 [Z 610 IE]
German version: Angew. Chem. *84*, 527 (1972)

Formation of Macrocyclic Polyolefins on Autoxidation of Bifunctional Alkylenephosphoranes

By *Hans Jürgen Bestmann* and *Hans Pfüller*[*]

Dedicated to Professor Georg Wittig on his 75th birthday

Autoxidation of alkylenephosphoranes (ylides) of structure $R—CH=P(C_6H_5)_3$ affords olefins $R—CH=CH—R$[1] and triphenylphosphane oxide. If bifunctional alkylenephosphoranes (bisylides) *(1)* are used, cycloolefins *(2)*[2,3] are obtained. *(1)*, R = $—(CH_2)_2—$, reacts with cyclizing



(1) *(2)*

dimerization to yield 1,5-cyclooctadiene[2]. Our further investigations have given the following results:

If the structure of the starting bisylide of type *(1)* permits intramolecular ring closure on autoxidation, yielding a five-, six- or seven-membered ring, such a ring is formed either mainly or exclusively. A compound such as *(3)*, however, does not yield any medium-size ring compounds, *e.g. (4)*, but macrocyclic polyolefins such as *(5)—(9)* are obtained by dimerization, trimerization *etc.* Further examples are collected in Table 1.

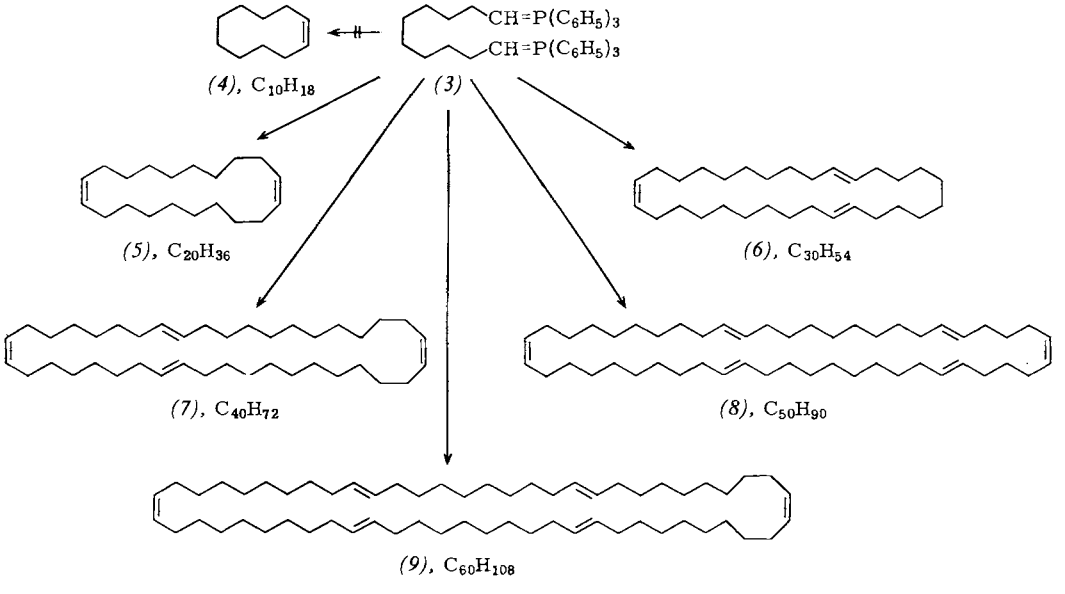
Correct analytical data and NMR and mass spectra are available for all the pure mono-, di-, and tri-mers listed in the Table. Formation of further cyclooligomers, of which in some cases only the trimer could be isolated, can be recognized by C, H analyses, NMR spectra, and clearly from the field ions in the mass spectrum; here the molecular ions gave the strongest mass lines, *e.g. (6)* $M^+ = 414$, *(7)* $M^+ = 552$, *(8)* $M^+ = 690$, *(9)* $M^+ = 828$. After hydrogenation, correspondingly heavier molecular ions appear.

For examples 4, 6 and 7, the proportion of *cis,cis*-isomer in the dimer was determined (silver nitrate complex). It was then shown that this isomer was formed preferentially: *cis,cis*-1,9-cyclohexadecadiene·$2AgNO_3$, m.p. 142 to 143 °C, 78%; *cis,cis*-1,10-dioxa-5,14-cyclooctadecadiene·$2AgNO_3$, m.p. 153 °C, 62%; *cis,cis*-1,11-cycloeicosadiene·$2AgNO_3$, m.p. 135—136 °C (m.p. 136—137 °C[6]) 78%.

All the bifunctional alkylenephosphoranes, except that used for No. 5 of the Table (poor yield), are sparingly soluble in dimethyl sulfoxide. We therefore assume that formation of macrocyclic rings on autoxidation of the bisylides in an intermolecular Wittig reaction (according to Ref. [1]) begins with formation of a *cis*-double bond. Subsequently, either an intramolecular reaction may occur or the chain may grow by further intermolecular C=C junctions before ring closure to the cyclooligomer follows.

1,11-Cycloeicosadiene (5) and oligomers (6)—(9)

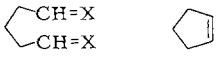
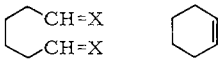
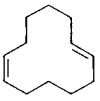
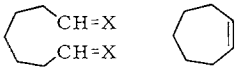
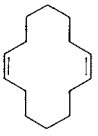
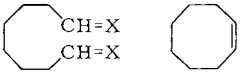
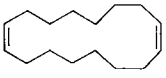
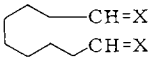
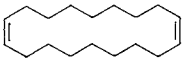
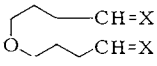
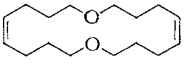
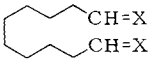
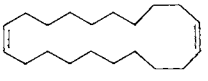
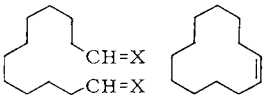
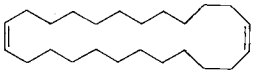
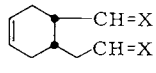
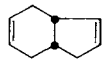
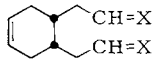
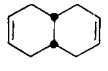
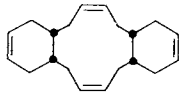
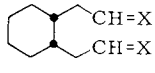
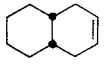
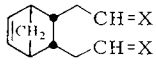
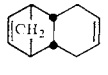
1,10-Decamethylenebis(triphenylphosphonium bromide) (49.5 g, 0.06 mol) is converted by the dimethyl sulfinate method[4] into a suspension of the corresponding bisylide in dimethyl sulfoxide, through which, in the apparatus



described previously[1], oxygen is passed with ice-cooling and magnetic stirring until the ylide precipitate has dissolved and a brown solution results (oxidation time 3 h;

[*] Prof. Dr. H. J. Bestmann and Dr. H. Pfüller
Institut für Organische Chemie der Universität Erlangen-Nürnberg
8520 Erlangen, Henkestrasse 42 (Germany)

Table 1. Autoxidation of bisylides. The bisylides were prepared from the phosphonium bromides in dimethyl sulfoxide with the dimethylsulfinate ion [4] as base [5].

No.	Ylide $X=P(C_6H_5)_3$	Monomer	Yield [%] B. p. [°C/torr]	Dimer	Yield [%] B. p. [°C/torr]	Cyclooligomers Yield [%] B. p. [°C/torr]	Total yield [%]
1			62 [a]	—	—	—	—
2			22 [a]		2.7 (51/0.4)	$C_{18}H_{30}$ (4.1; 112/0.4); $C_{24}H_{40}$; $C_{30}H_{50}$; $C_{36}H_{60}$	6
3			22 [a]		1.5 48/0.001	$C_{21}H_{36}$ (2.7; 116/0.001) $C_{28}H_{48}$	2.7
4			2.3 [b]		12 (89/0.05)	$C_{24}H_{42}$ (5.5; 130/0.05) $C_{32}H_{56}$; $C_{40}H_{70}$ $C_{48}H_{84}$	11
5		—	—		5.0 (122/0.3)	$C_{27}H_{48}$	1.5
6		—	—		11 (102/0.1)	$C_{24}H_{42}O_3$; $C_{32}H_{56}O_4$	12
7	 *(3)*	—	—	 *(5)*	14 m. p. = 30–31 °C	$C_{30}H_{54}$ *(6)*; $C_{40}H_{72}$ *(7)*; $C_{50}H_{90}$ *(8)*; $C_{60}H_{108}$ *(9)*	17
8			1.2 [b]		8.0 m. p. = 54–55 °C	$C_{36}H_{66}$; $C_{48}H_{88}$	3
9			53 54/14	—	—	—	—
10		 [c]	30 68/14		3.2 143/0.02	$C_{30}H_{42}$; $C_{40}H_{56}$	1.6
11			26 68/14	?	—	—	—
12			32 77/14	—	—	—	—

[a] Yields were determined by means of the dibromides.
[b] Identified by gas chromatography.
[c] NMR, 20 °C: $\tau = 8$ ppm (non-olefinic protons); −75 to −100 °C: Splitting to a multiplet because of slower conformational change.

oxygen uptake 1140 ml, 85%). The solution is then left overnight, after which it is extracted with light petroleum. The extracts are united, washed twice with water, dried over sodium sulfate, filtered and freed from solvent. The residue is boiled for a short time under reflux with methyl iodide (3—4 ml), then treated with light petroleum (200 ml), which precipitates the triphenylphosphane from the extract as methyltriphenylphosphonium iodide. The filtrate therefrom is concentrated and poured on an aluminum oxide column (length 20 cm, diameter 1.5 cm, neutral Al_2O_3 Woelm, activity II) for removal of triphenylphosphane oxide. Elution is with cyclohexane. On evaporation of the cyclohexane the hydrocarbon mixture separates as a mass of colorless crystals. *(5)* distils at 123—124 °C/0.15 torr (yield 1.1 g, 13.7%). The residue is distilled in a rotating tube at 180—240 °C/0.001 torr, affording 1.4 g (17%) of *(6)*, *(7)*, *(8)*, and *(9)*.

Received: March 16, 1972 [Z 620 IE]
German version: Angew. Chem. *84*, 528 (1972)

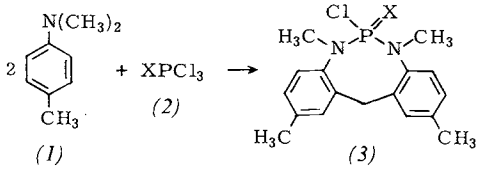
[1] *H. J. Bestmann* and *O. Kratzer*, Chem. Ber. *96*, 1899 (1963).
[2] *H. J. Bestmann*, *H. Häberlein*, and *O. Kratzer*, Angew. Chem. *76*, 226 (1964); Angew. Chem. internat. Edit. *3*, 226 (1964).
[3] *H. J. Bestmann*, *H. Häberlein*, *H. Wagner*, and *O. Kratzer*, Chem. Ber. *99*, 2849 (1966).
[4] *E. J. Corey* and *M. Chaykovsky*, J. Amer. Chem. Soc. *84*, 866 (1962).
[5] For the examples described in [2] the bisylides were prepared by either the sodium amide or the organolithium method; *H. J. Bestmann*, Angew. Chem. *77*, 609 (1965); Angew. Chem. internat. Edit. *4*, 583 (1967).
[6] *J. Dale*, *A. J. Hubert*, and *G. S. D. King*, J. Chem. Soc. *1963*, 73, 13.

Structure and Mechanisms of Formation of a Novel Phosphorus-containing Heterocycle; P—Cl Bond Length and ^{35}Cl-NQR Frequency[**]

By *T. S. Cameron, C. Y. Cheng, T. Demir, K. D. Howlett, R. Keat, A. L. Porte, C. K. Prout*, and *R. A. Shaw*[*]

Dedicated to Professor G. Wittig on the occasion of his 75th birthday

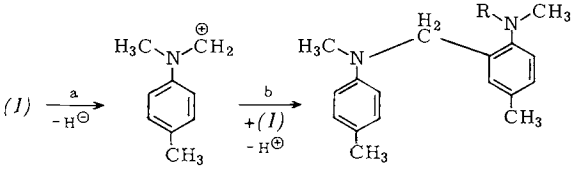
We recently reported an unusual reaction between *N,N*-dimethyl-*p*-toluidine *(1)* and phosphorus oxide trichloride *(2a)* leading to a novel heterocycle *(3a)* m. p. 172 °C, yield 6%[1]. The X-ray structure analysis[1] has in the meantime been refined[2].

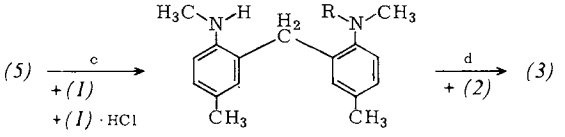


a, X = O
b, X = S

We have now found that a similar reaction occurs with phosphorus sulfide trichloride *(2b)* to give the sulfur analog of *(3a)*, 6-chloro-2,5,7,10-tetramethyl-6-thioxo-6,7-dihydro-5*H*,12*H*-dibenzo[*d*,*g*]-[1,3,2λ^5]diazaphosphocine *(3b)* (m. p. 209—210 °C, yield 6%).

We suggest a four-step mechanism for the formation of *(3)*. We have not yet established how Step a occurs, but the postulated electrophile *(4)* is well documented in the system *N*-methyl-*p*-toluidine/formaldehyde/H$^+$. It is probable that compounds *(3)* are formed *via* the intermediates *(5)* and *(6)* with R = CH_3. To date, we have shown that Steps c and d occur under the above reaction conditions for compounds *(5)* and *(6)*, when R = H. Indeed Step d





occurs under milder conditions (25—80 °C) with *(6)*, R = H, and gives better yields of *(3a)* and *(3b)* (*ca.* 70%).

(3b) crystallizes from CCl_4 in the monoclinic space group $P2_1/n$, with $a = 11.19 \pm 0.01$, $b = 10.95 \pm 0.01$, $c = 15.43 \pm 0.01$ Å, $\gamma = 109.5 \pm 0.1°$; $V = 1783$ Å^3, $d_{calc} = 1.30$ g/cm^3 for $Z = 4$, $d_{exp} = 1.29$, MW = 350; 1471 independent reflections using $Mo_{K\alpha}$ radiation; R = 0.10 (refinement continuing). Although the molecules *(3a)* and *(3b)* are isostructural, the crystals are not isomorphous.

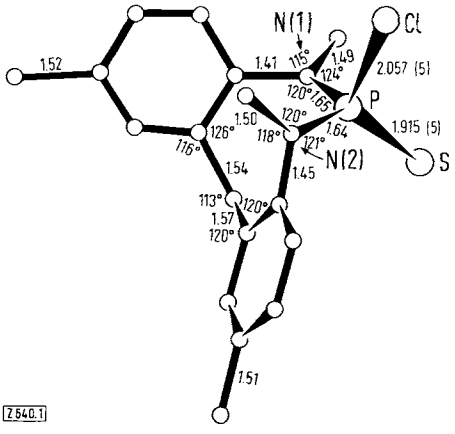
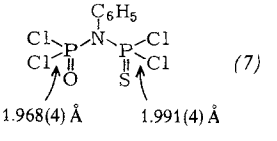


Fig. 1.

All bond lengths and angles are as expected (see Fig. 1). The two *N*-methyl groups can be seen to be non-equivalent (as suggested by NMR) owing to differences in the local environment of the ring. The length of the P—Cl bond in compound *(3b)* is 2.057(5) Å and that of the same bond in *(3a)* 2.069(3) Å (refined value)[2]. Different P—Cl bond lengths were also observed in the case of the acyclic-derivative *(7)*[3]. In comparison, the P—Cl bond length in gaseous $PSCl_3$ *(2b)* is longer than that in gaseous $POCl_3$ *(2a)*[4]. No other P—Cl bond lengths are available for strictly comparable *pairs* of compounds containing P(O)Cl and P(S)Cl.



(7)

Since we have recently demonstrated[5] an approximately linear relationship between P—Cl bond-length and ^{35}Cl nuclear quadrupole resonance (NQR) frequency in some chlorocyclophosphazenes containing the $\equiv PCl_2$ or $\equiv P(Cl)N(CH_3)_2$ structural units, it was of interest to extend this study to compounds *(3a)*, *(3b)*, and *(7)*. As has been reported, the ^{35}Cl-NQR frequencies of thiophosphoryl-derivatives always exceed those of analogous phosphoryl-derivatives (usually by about 0.5—2 MHz)[6, 7]. If the lowest frequencies are associated with the longest P—Cl bonds—as is the case in the chlorocyclophosphazenes—then longer P—Cl bonds would be expected for the phosphoryl-derivatives relative to the analogous thiophosphoryl-derivatives by consideration of the ^{35}Cl-NQR frequencies (see Table 1).

In the case of the cyclic compounds *(3a)* and *(3b)* the former appears to have the longer P—Cl bond length. Unfortunately, no reproducible ^{35}Cl-NQR signal was obtain-

[*] Dr. T. S. Cameron, K. D. Howlett, and Dr. C. K. Prout
Chemical Crystallography Laboratory
South Parks Road, Oxford (England)
Dr. C. Y. Cheng, T. Demir, and Prof. R. A. Shaw
Department of Chemistry, Birkbeck College
Malet Street, London WC1E 7HX (England)
Dr. R. Keat and Dr. A. L. Porte
Department of Chemistry
The University, Glasgow W.2 (Scotland)

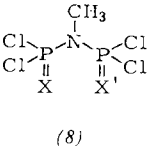
[**] We are indebted to the following: T. S. C. (to the S. R. C. for a Fellowship), C. Y. C. (to the Henry Lester Trust for a grant), T. D. (Turkish Research Council for a grant), K. D. H. (to the S. R. C. for a Studentship).

Table 1. Relation between the length of P—Cl bond and ^{35}Cl-NQR frequency of a few compounds containing the XPCl grouping.

Cpd.	X	Bond Length (Å)	^{35}Cl-NQR frequency (MHz)	T (°K)
(3a)	O	2.069(3)	23.97_7	293 [e]
(3b)	S	2.057(5)	[a]	293, 77
(7)	O	1.968(4)	27.81_3 [b]	77
	S	1.991(4)	29.08_4 [c]	77
(8a)	O		27.93_8 [d]	77
(8b)	S		28.91_3 [d]	77
(8c)	O		27.57_1	77
	S		29.31_0	77

[a] No reproducible signal obtained.
[b] Mean value from 27.61_7 and 28.00_9.
[c] Mean value from 28.79_3 and 29.37_5.
[d] Mean of four values.
[e] To date, no signals have been obtained at 77°K; in general, a frequency increase of 0.5—0.8 MHz is obtained on decreasing the temperature from *ca.* 290 to 77°K.

ed from compound *(3b)*. The reverse relationship (as compared with the chlorocyclophosphazenes) is observed for compound *(7)*. The assignment of the frequencies was supported by comparison with the structurally related acyclic compounds *(8)*[8,9]. It is noteworthy that the difference in signals in the mixed compound *(8c)* is greater (*ca.* 1.7 MHz) than the difference (*ca.* 1 MHz) between the symmetric compounds *(8a)* and *(8b)*. This may be a reflection of the better π-acceptor properties of the phosphoryl compared to the thiophosphoryl group.



(8)

(8a), X = X' = O
(8b), X = X' = S
(8c), X = O, X' = S

In *(7)* both sets of P—Cl bonds are considerably shorter than in the cyclic compounds *(3a)* and *(3b)*, and this is reflected in their ^{35}Cl NQR frequencies; those of *(7)* are higher than the frequencies of *(3a)*.

Experimental:

24 ml (22.5 g, 0.166 mol) of *(1)* was placed in a 250 ml, two-necked flask, to which was attached a condenser and a dropping funnel containing 8.6 ml (14 g, 0.082 mol) of thiophosphoryl chloride. This was added dropwise to the tertiary amine while the flask was heated to 130°C in an oil-bath, and the mixture was maintained at this temperature for 9—36 hours. The mixture was then cooled, treated with sodium ethoxide (*ca.* 0.166 mol) in absolute ethanol, and the resulting suspension boiled on a water-bath for three hours, diluted with distilled water to 400 ml, extracted with ether, dried over Na_2SO_4, concentrated and eluted through a column packed with alumina, using a solvent mixture of toluene-ethyl acetate (9:1). *(3b)* was first eluted. It was recrystallized from ethyl acetate, m.p. 209—210°C (yield 0.9 g, 6%).

Received: April 4, 1972 [Z 640 IE]
German version: Angew. Chem. *84*, 530 (1972)

[1] *C. Y. Cheng, R. A. Shaw, T. S. Cameron,* and *C. K. Prout*, Chem. Commun. *1968*, 616.
[2] *T. S. Cameron*, J. Chem. Soc. (Perkin II) *1972*, 591.
[3] *T. S. Cameron, K. M. Ghouse, K. D. Howlett, R. Keat, H. H. Mills, C. K. Prout,* and *J. M. Robertson*, Phosphorus, in the press.
[4] *T. Moritani, K. Kuchitsu,* and *Y. Morino*, Inorg. Chem. *10*, 344 (1971).
[5] *R. Keat, A. L. Porte, R. A. Shaw,* and *D. A. Tong*, J. Chem. Soc. (Dalton), in the press.
[6] *R. M. Hart* and *M. A. Whitehead*, J. Chem. Soc. *A 1971*, 1738.
[7] *D. J. Osokin, I. A. Safin,* and *I. A. Nuretdinov*, Dokl. Akad. Nauk SSSR *201*, 393 (1971).
[8] *R. Keat*, J. Chem. Soc. *A 1970*, 2732.
[9] *R. Keat*, J. Chem. Soc. (Dalton), in the press.

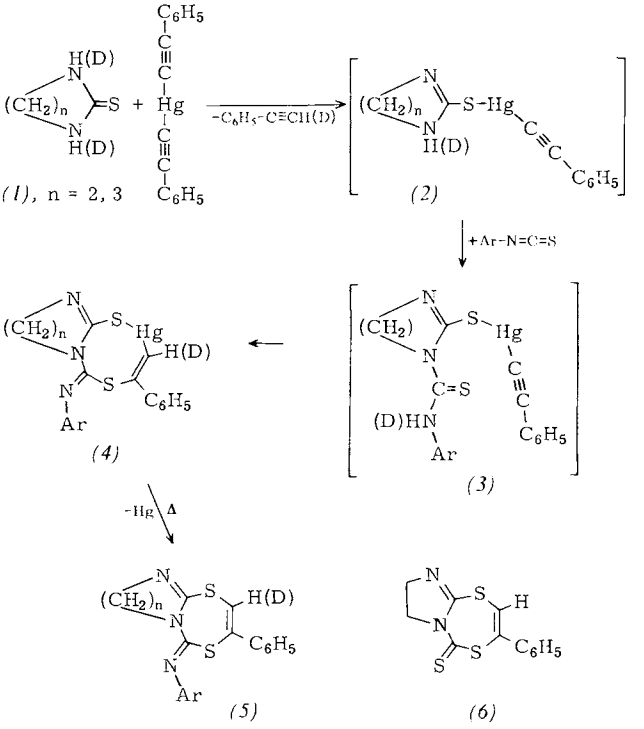
A New Principle for Preparation of Bicyclic Dithiazepine Systems

By *Walter Ried, Rüdiger Oxenius,* and *Wulf Merkel*[*]

Dedicated to Professor H. J. Bielig on his 60th birthday

Mercury bis(phenylacetylide)[2] can be used as a mild desulfurizing agent for preparation of carbodiimides or cyanamides from thioureas. Reaction of trisubstituted thioureas with mercury bis(phenylacetylide), however, gives the corresponding mercury dithiolates[3].

Cyclic *N,N'*-disubstituted thioureas such as *(1)*, which, because of their angular structure, cannot be converted into carbodiimides, yield thermally unstable mercury dithiolates still having two relatively basic NH groups available which it appeared possible to treat with reactive isothiocyanates.



(1), n = 2, 3 *(2)* *(3)* *(4)* *(5)* *(6)*

We therefore carried out a single-batch reaction with, as reactants, 1 molar proportion each of *(1)*, mercury bis(phenylacetylide) and isothiocyanate in pyridine.

[*] Prof. Dr. W. Ried, Dipl.-Chem. R. Oxenius [1] and Dipl.-Chem. W. Merkel
Institut für Organische Chemie der Universität
6 Frankfurt, Robert-Mayer-Strasse 7—9 (Germany)

The monothiolate first formed was converted by the trapping isothiocyanate into the intermediate *(3)* which cyclized immediately by attack of the nucleophilic sulfur on the triple bond[4], yielding *(4)* and thus preventing removal of the second phenylacetylene group. By careful working, the bicyclic thiolate *(4)* containing the eight-membered ring could be isolated. When even gently warmed it loses elemental mercury and passes by ring contraction into the dithiazepine *(5)*. The thiourea component may be *(1)* with a five- or a six-membered ring; the seven-membered ring analog, however, apparently yields the carbodiimide with loss of HgS. Only reactive isothiocyanates such as phenyl or *o*-tolyl isothiocyanate can be used as isothiocyanate component.

Satisfactory elemental analyses and IR, NMR, and mass spectra prove the assigned structures (see Table 1). The molecular ion does not appear in the mass spectra since it at once splits off the isothiocyanate which forms the reference mass line. By using deuterated thioureas *(1)* it can be shown that the original N—H proton appears in the product *(5)* as the olefinic C—H proton.

The phenylimino group in compound *(5a)* can be split off by several hours' heating with sulfur in carbon disulfide, being replaced by a thiooxo group *(6)*.

To the best of our knowledge the bicyclic dithiazepines prepared by this single-batch process belong to a new heterocyclic system, whose parent compound is unknown. This synthesis would not be possible without collaboration of the mercury atom as bonding agent.

7,8-Dihydro-3-phenyl-5-(phenylimino)-5H-imidazo-[2,1-b]-[1,5,3]dithiazepine (5a)

Equimolar amounts of 2-imidazolidinethione *(1)*, $n=2$, mercury bis(phenylacetylide) and phenyl isothiocyanate were heated in pyridine for about 30 min under reflux. Mercury separates. After the filtrate has been concentrated, the yellow-white *(5a)* crystallizes either directly or on addition of ether. *(5b)* and *(5c)* are prepared analogously.

7,8-Dihydro-3-phenyl-5-thio-5H-imidazo[2,1-b]-[1,5,3]-dithiazepine (6)

(5a) (1.7 g, 0.005 mol) is heated with sulfur (1 g) in CS_2 (100 ml) for some hours under reflux. After a short time the yellow compound *(6)* separates and can be recrystallized from pyridine [m.p. 168—171 °C (dec., loss of CS_2); yield 1.3 g, 93%].

Received: February 17, 1972 [Z 613 IE]
German version: Angew. Chem. *84*, 535 (1972)

Table 1. Properties and spectroscopic data for the dithiazepines *(5)*.

Cpd.	*n*	Ar	M.p. (uncorr.) Recryst. from	Yield (%)	IR (cm^{-1})	NMR (δ, ppm) [a]	Conditions
(5a)	2	Phenyl	192 *n*-Butanol	75	3115 (=CH)	4.65 (4H/s) 6.8–7.7 (11H/m)	60 MHz $[D_6]$-DMSO
(5b)	2	*o*-Tolyl	150 *n*-Butanol	70	3100 (=CH)	2.06 (3H/s) 4.63 (4H/s) 6.7–7.7 (10H/m)	60 MHz $[D_6]$-DMSO
(5c)	3	Phenyl	147 $HCCl_3$/ether	70	3090 (=CH) 2310 (=CD)	1.72 (2H/m) 3.42 (4H/m) 5.52 (1H/s) 7.0–7.5 (10H/m)	100 MHz $CDCl_3$

[a] Internal standard: hexamethyldisiloxane (HMDSO).

[1] Part of the Dissertation of *R. Oxenius*, Universität Frankfurt 1972. We thank the Hermann-Schlosser-Stiftung for a stipendium.

[2] *J. R. Johnson* and *W. L. McEwen*, J. Amer. Chem. Soc. *48*, 474 (1926).

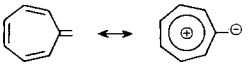
[3] *W. Ried, W. Merkel*, and *R. Oxenius*, Chem. Ber. *103*, 32 (1970).

[4] *N. R. Easton* and *D. R. Cassady*, J. Org. Chem. *29*, 1851 (1964).

Methylenenorbornadiene, a Bicycloheptafulvene[1][**]

By *Reinhard W. Hoffmann, Reinhard Schüttler, Werner Schäfer*, and *Armin Schweig*[*]

The reactivity of heptafulvene is to be ascribed to strong polarization with formation of an aromatic system[2].



This phenomenon is not restricted to classical aromatic compounds but can be demonstrated also for bicycloaromatic systems, as we wish to illustrate for methylenenorbornadiene *(1)*[3].

Crossed longicyclic interaction[4] of the exocyclic double bond of *(1)* with the norbornadiene π-system should destabilize the norbornadiene system[4]. This interaction can be demonstrated by photoelectron spectroscopy[5,6] in a comparison with norbornadiene *(2)*[6] and 7-methylenenorbornane *(3)*. It can be seen in Figures 1 and 2 that the HOMO (highest occupied MO) of *(1)* is raised by 0.2 eV relative to that of *(2)*. A direct consequence of this interaction is the tendency to formation of the bicycloaromatic state *(4)*, which causes polarization of the exocyclic double bond of *(1)*.

[*] Prof. Dr. R. W. Hoffmann and Dipl.-Chem. R. Schüttler
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)
Dipl.-Chem. W. Schäfer and Prof. Dr. A. Schweig
Physikalisch-Chemisches Institut der Universität
355 Marburg, Biegenstrasse 12 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The calculations were carried out by the Deutsches Rechenzentrum at Darmstadt.

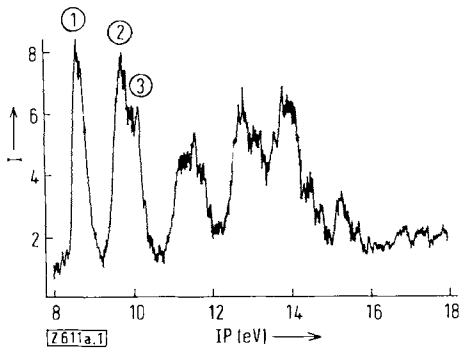


Fig. 1. Photoelectron spectrum of methylenenorbornadiene *(1)* [12].

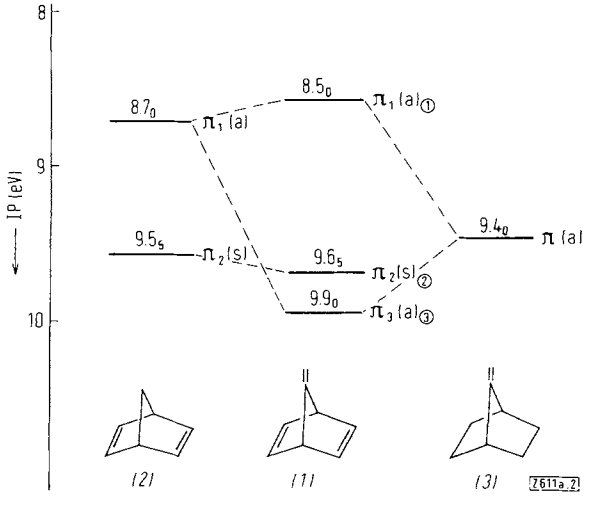
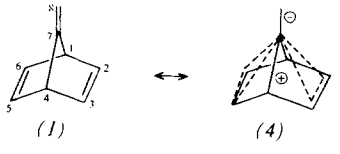
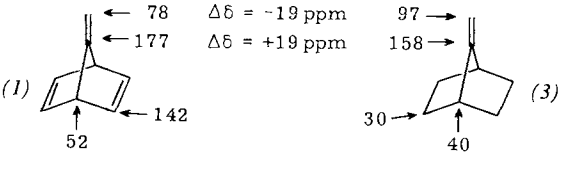


Fig. 2. Vertical ionization potentials of the relevant π-bands of norbornadiene *(2)* [6], 7-methylenenorbornane *(3)*, and methylenenorbornadiene *(1)*. The π-MO's are classified relative to the C^1—C^7—C^4 plane (s symmetrical, a antisymmetrical).—The assignments made for *(1)* are supported by the orbital sequence obtained by the MINDO/2 method [13].

This polarization[7] is evident even in the ^{1}H-NMR spectrum: Thus the signal of the methylene protons of *(1)* at $\tau = 6.48$ appears at unusually high field, about 0.9 ppm higher than in the comparison system *(3)*[8] ($\tau = 5.55$).



While this difference may or may not be solely the consequence of a charge effect, more sensitive and more certain information about the charge distribution may be obtained from ^{13}C-NMR spectra[9]. Thus comparison of the ^{13}C-NMR spectra of *(1)* and *(3)* (chemical shifts in ppm to lower field from TMS) shows clearly the strong polarization of the exocyclic double bond of *(1)*.



The chemical shift and thus the charge density at C-8 of *(1)* are comparable with those at the β-C atom of enol ethers ($\delta = 89$–83 ppm[9]), whilst the chemical shift for C-7 lies in the region typical of carbonyl-C atoms. The other ^{13}C-NMR signals of *(1)* and *(3)* are at positions similar to those of comparable parent compounds (±3 ppm)[10].

A dipole moment of 0.76 D for *(1)* can be estimated from the change in the chemical shift by 19 ppm. A CNDO/2 calculation[11] gave the same value; the experimental value was 0.71 D. Thus *(1)* is more than merely formally a bicycloheptafulvene.

Received: February 8, 1972 [Z 611a IE]
German version: Angew. Chem. *84*, 533 (1972)

[1] Theory and Application of Photoelectron Spectroscopy, Part 6.—Part 5: [14].

[2] *D. Lloyd:* Carbocyclic Non-Benzenoid Aromatic Compounds. Elsevier, Amsterdam 1966, p. 153.

[3] Prepared from quadricyclanone by a Wittig reaction in THF, giving 3-methylenetetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane (50%) [b.p. 143°C; NMR (CCl_4): $\tau = 4.95$ (s), 8.17 (d), 8.52 ppm (t) as 2:4:2; IR: 3075, 1680, 1232, 748 cm^{-1}], and rearrangement thereof to *(1)* by catalysis with norbornadiene-palladium chloride. After gas-chromatographic separation, yield 40% [b.p. 119°C; NMR (CCl_4): $\tau = 3.28$ (t), 6.26 (p), 6.48 (s) as 4:2:2; UV (CH_3OH): shoulder at 235 nm ($\varepsilon = 60$); IR: 3070, 2995, 1685, 1665, 850, 730, 720, 623 cm^{-1}; $m/e = 104$, 103, 78].

[4] *M. J. Goldstein* and *R. Hoffmann*, J. Amer. Chem. Soc. *93*, 6193 (1971).

[5] *E. Heilbronner* and *H. D. Martin*, Helv. Chim. Acta, in press, discuss extensively this type of interaction for a derivative of *(1)*, cf. *H. D. Martin* and *B. Forster*, Angew. Chem. *84*, 65 (1972); Angew. Chem. internat. Edit. *11*, 54 (1972).

[6] *P. Bischof, J. A. Hashmall, E. Heilbronner*, and *V. Hornung*, Helv. Chim. Acta *52*, 1745 (1969).

[7] 9-Methylenebicyclo[4.2.1]nona-2,4,7-triene should have the opposite polarization; this is under investigation.

[8] Prepared from 7-norbornanone by a Wittig reaction in THF [b.p. 118.5°C; NMR (CCl_4): $\tau = 5.55$ (s), 7.75 (p), 8.55 ppm (m) as 2:2:8; IR: 1675, 885, 685 cm^{-1}].

[9] *K. Hatada, K. Nagata*, and *H. Yuki*, Bull. Chem. Soc. Japan *43*, 3195, 3267 (1970); cf. *R. C. Haddon, V. R. Haddon*, and *L. M. Jackman*, Fortschr. Chem. Forsch. *16*, 103 (1971).

[10] *J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith*, and *J. D. Roberts*, J. Amer. Chem. Soc. *92*, 7107 (1970).

[11] *J. A. Pople* and *D. L. Beveridge:* Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970.

[12] The HeI (584 Å) photoelectron spectra were determined with a PS 16 spectrometer from Perkin-Elmer Ltd., Beaconsfield (England).

[13] *M. J. S. Dewar:* The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.

[14] *U. Weidner* and *A. Schweig*, J. Organometal. Chem., in press.

Sigmatropic [1,5]-Ester Migrations[**]

By *Peter Schmidt, Reinhard W. Hoffmann*, and *Jutta Backes*[*]

Dedicated to Professor B. Helferich on his 85th birthday

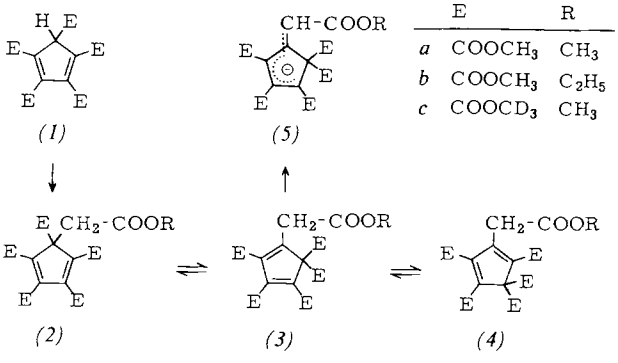
There has recently been increasing interest in migration of ester groups[1]: Thus, sigmatropic [1,5]-ester migrations on the 1,3-cyclohexadiene skeleton have been reported to

[*] Dr. P. Schmidt, Prof. Dr. R. W. Hoffmann, and Dipl.-Chem. J. Backes
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

[**] This work was supported by the Verband der Chemischen Industrie and the Max-Buchner-Forschungsstiftung.

occur [2], but only above 300 °C. We have now found an ester migration that proceeds even at 100 °C.

Pentamethyl 1,3-cyclopentadiene-1,2,3,4,5-pentacarboxylate *(1)* [3], on alkylation with silver oxide and methyl or ethyl iodoacetate in boiling benzene, gave 71% of *(2a)* [m.p. 87—88 °C; NMR ($CDCl_3$): singlets at $\tau = 6.15$, 6.20, 6.28, 6.38, and 6.64 ppm as 6:6:3:3:2; M^+ at $m/e = 428$, $M^+ - OCH_3$ at m/e 397] and 90% of *(2b)* [4] (m.p. 83 °C).



(1) *(5)* *(2)* *(3)* *(4)*

Heating in an inert solvent such as toluene at 100—130 °C sets up an equilibrium between *(2)* and *(3)* from which the vinylogous malonic ester *(3)* can be trapped in the form of the anion *(5)* by addition of sodium hydride. The esters *(3a)* [20%; m.p. 99—100 °C; NMR ($CDCl_3$): singlets at $\tau = 6.05$, 6.07, 6.17, 6.24, 6.27 ppm as 3:2:6:6:3] and *(3b)* (m.p. 103 °C) thus obtained show in their mass spectra the ($M^+ - CH_3OH$) signal characteristic of this type of structure.

Equilibration of *(2)* and *(3)* is more than 99% intramolecular; when a 0.23 M solution of *(2a)* and *(2c)* is heated for three half-lives of the rearrangement, no notable amount of cross-product could be detected by mass spectrometry. Thus the observed rearrangement probably involves a sigmatropic [1,5]-ester migration [5]. It was established by means of NMR spectroscopy that the reactions cleanly followed first order kinetics for more than three half-lives, setting up a 1:1 equilibrium between *(2)* and *(3)* in all cases (Table 1).

Table 1. The reaction *(2)* ⇌ *(3)*.

Reaction	Temp. (°C)	Solvent	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (cal mol deg^{-1})
(2a) → *(3a)*	113–150	Chlorobenzene	25.3 ± 2.5	− 9.7 ± 4.4
(2b) → *(3b)*	97–120	Toluene	25.3 ± 2.3	− 10.9 ± 3.5
(3a) → *(2a)*	113–134	Chlorobenzene	25.1 ± 3.7	− 10.4 ± 4.2
(3b) → *(2b)*	97–120	Toluene	26.9 ± 2.5	− 6.6 ± 3.5

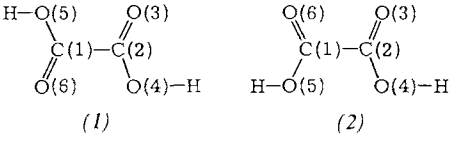
A further ester migration, giving *(4)*, occurred above 150 °C; this process could be followed only in the case of *(2c)*, it having the simpler NMR spectrum, where rearrangement to *(4c)* in *o*-dichlorobenzene resulted in two further signals $\tau = 6.03$ and 6.45 ppm as 2:3. The position of the equilibria between the isomers *(2c)*:*(3c)*:*(4c)* in *o*-dichlorobenzene at 160 °C was estimated as 1:1:1.5. That the second ester migration *(3)* → *(4)* is slower than the first migration *(2)* → *(3)* corresponds to analogous hydrogen migrations [6] on the cyclopentadiene skeleton.

Received: February 8, 1972 [Z 611 b IE]
German version: Angew. Chem. *84*, 534 (1972)

syn-Planar Conformation of Oxalic Acid: Crystal Structure of the Oxalic Acid-Acetamide Complex

By *Leslie Leiserowitz* and *Franz Nader* [*]

We have studied, *inter alia*, the 1:1 complex of acetamide with oxalic acid as part of our X-ray investigation of molecular packing and its dependence on functional groups. Although the molecular dimensions of the components in carboxylic acid—amide complexes [1, 2] compare well with those of the individual species, as far as the latter are known, we find striking deviations in this case. Here, oxalic acid does not exist, as is usually found, in the *anti*-planar conformation *(1)*, but rather in the energetically unfavorable *syn*-planar arrangement *(2)*.



(1) *(2)*

Colorless crystals of the (hygroscopic) complex [3] are obtained by slowly cooling a solution of equimolar parts of acetamide and anhydrous oxalic acid in ethyl acetate or nitromethane.

Crystallographic data: monoclinic, $a = 20.542$, $b = 9.709$, $c = 13.931$ Å; $\beta = 112° 5'$; space group A2/a; $Z = 8$ (the unit cell contains two molecules each of oxalic acid and acetamide); $d_{calc} = 1.537$ g/cm^3.

The structure was solved by the direct method [4]. Refinement with 2813 independent reflections gave an *R* factor of 7.6%. The positions of all the hydrogen atoms could be determined from the difference map (after anisotropic refinement of the heavy atoms). This is shown in Fig. 1 for the plane of one of the two independent oxalic acid molecules. Together with the experimental C—O bond lengths this proves the *syn*-planar conformation of the oxalic acid.

Table 1 permits a comparison of the geometrical parameters of *(2)* with those of the numerous published structural studies of *(1)* in the solid [1, 5] and gaseous [6] state. No significant difference in the bond lengths between the two conformers can be found, but there are such differences

[*] Dr. L. Leiserowitz and Dr. F. Nader [**]
Department of Chemistry
Weizmann Institute of Science
Rehovot (Israel)

[**] Stipendiary of the Stiftung Volkswagenwerk.

[1] *R. M. Acheson*, Accounts Chem. Res. *4*, 177 (1971).

[2] *J. A. Berson* and *R. G. Salomon*, J. Amer. Chem. Soc. *93*, 4620 (1971); *R. A. Baylouny*, *ibid.* *93*, 4621 (1971).

[3] *E. LeGoff* and *R. B. LaCount*, J. Org. Chem. *29*, 423 (1964); *R. C. Cookson*, *J. B. Henstock*, *J. Hudec*, and *B. R. D. Whitear*, J. Chem. Soc. *C 1967*, 1986.

[4] *(2b)* is accessible also from *(1)* and ethyl diazoacetate, albeit in poorer yield.

[5] A conceivable migration of the acetate side chain is degenerate in this system and is thus not directly recognizable.

[6] *W. R. Roth*, Chimia *20*, 229 (1966).

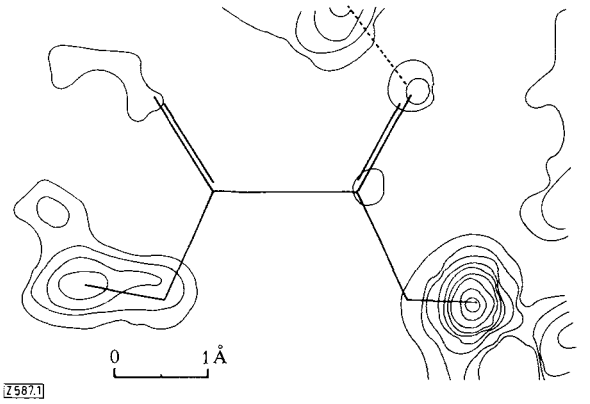


Fig. 1. Difference map for one of the two independent oxalic acid molecules in the 1:1 complex with acetamide; contour intervals 0.1/Å^3.

in bond angles. In *(2)* the angle C(1)—C(2)—O(4) is widened by about 2° in comparison with *(1)*, and the angle C(1)—C(2)=O(3) is decreased by a corresponding amount. In addition, *(2)* departs minimally from coplanarity, the torsion angle between the two COOH fragments being 2.1°.

Table 1. Structural parameters of oxalic acid *(1)* and *(2)*.

Bond lengths [Å]	in the complex [a] *(2)*	Ref. [b] [1, 5, 6] *(1)*
C(1)–C(2)	1.529 ± 0.007	1.536 ± 0.003
C(2)=O(3)	1.212 ± 0.006	1.202 ± 0.006
C(2)–O(4)	1.298 ± 0.006	1.291 ± 0.010
O(4)···O(5)	2.590	
O(3)···O(6)	2.728	
Bond angles [°]		
C(1)–C(2)=O(3)	119.6 ± 0.5	121.7 ± 0.4
C(1)–C(2)–O(4)	114.1 ± 0.4	112.0 ± 0.3
O(3)=C(2)–O(4)	126.2 ± 0.5	126.3 ± 0.4
O(3)=C(2)–C(1)=O(6)	2.1	180

[a] Mean values from two independent oxalic acid molecules.
[b] Mean values from six structure analyses.

Intramolecular interactions are clearly the cause of these deviations. If the intramolecular O···O distances are calculated for the *syn*-planar conformation *(2)* on the basis of the geometrical parameters of the *anti*-planar conformation *(1)*, the separation of the two carbonyl-oxygen atoms [O(3)···O(6)] comes out at 2.80 Å but that for the two hydroxyl-oxygen atoms [O(4)···O(5)] at 2.48 Å [compare the O···O separations of 2.70—2.74 Å in *(1)*]. At least partial balance can be achieved by altering the bond angles, so that a separation of 2.59 Å is found for O(4)···O(5). The deviation from coplanarity (2.1°) and its influence on the O···O separation in question are so small that *(2)* can well be designated as the *syn*-planar conformation.

[1] *Chi-Min Huang, L. Leiserowitz*, and *G. M. J. Schmidt*, to be published; *L. Leiserowitz, F. Nader*, and *G. M. J. Schmidt*, to be published.

[2] *I. Nahringbauer* and *G. Larsson*, Arkiv Kemi *30*, 91 (1968).

[3] *MacKenzie Rawles*, Ind. Engl. Chem. Anal. *12*, 737 (1940).

[4] *J. Karle* and *I. L. Karle*, Acta Crystallogr. *21*, 849 (1966).

[5] *R. G. Delaplane* and *J. A. Ibers*, Acta Crystallogr. *B 25*, 2432 (1969); *F. F. Iwasaki, H. Iwasaki*, and *Y. Saito, ibid. 23*, 64, 56 (1967); *F. R. Ahmed* and *D. W. J. Cruickshank, ibid. 6*, 385 (1953).

[6] *Z. Nahlovska, B. Nahlovsky*, and *T. G. Strand*, Acta Chem. Scand. *24*, 2617 (1970).

[7] *E. G. Cox, H. W. Dougill*, and *G. A. Jeffrey*, J. Chem. Soc. *1952*, 4855.

This finding throws some doubt on the validity of the arguments used to explain the planarity of *(1)*. On the basis of the C—C bond length of 1.54 Å, which corresponds to a normal sp^3-sp^3 single bond, conjugation between the two carbonyl groups was ruled out[6, 7]. The coplanarity was therefore explained as due to attractive forces between the various hybridized O atoms[7]. This situation does not exist in *(2)*; but nevertheless here too a strong tendency to coplanarity is evident.

Received: November 19, 1971 [Z 587 IE]
German version: Angew. Chem. *84*, 536 (1972)

Preparation of Non-noble Metals (Li, Ca, Sr, Ba, Am, Cf) by Reduction of Their Oxides and Fluorides with Hydrogen[**]

By *Uwe Berndt, Bernhard Erdmann*, and *Cornelius Keller*[*]

It is known (*e.g.* see Ref. [1]) that intermetallic compounds are formed on reduction of mixtures of metal oxides and noble metals with extremely pure hydrogen ($p_{O_2} \leq 10^{-26}$, $p_{H_2O} \leq 10^{-7}$ torr), the process being termed "coupled reduction". With oxides of actinoids, lanthanoids, and other non-noble elements (*e.g.* Zr, Hf, Nb, Ta) on the one hand and Pt, Pd, Rh, or Ir on the other in the starting materials at the requisite reaction temperatures (1100—1550°C), the same ratio of metal to noble metal is found in the product as in the starting mixture, but with Am/Pt, particularly at higher temperatures, the product is poorer in Am[1a, 2-4].

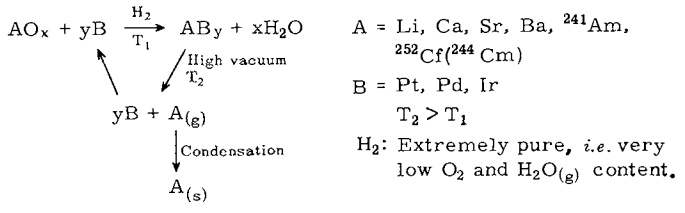
A more detailed study of this and analogous systems has led to surprising results: On preparation of intermetallic phases of the elements Li, Ca, Sr, Ba, Am, and Cf (=A) from their oxides and/or fluorides with powdered noble metals (=B) in flowing hydrogen at the lowest possible temperature, the desired phase of composition AB_2, AB_3, AB_5, and/or AB_7 was obtained in high purity without change in the introduced proportions. At higher temperatures, however, part of the more volatile component A evaporated from these phases, so that a different A:B ratio was produced.

These observations make it possible to propose a method, simple in principle, for preparing non-noble metals from their oxides, fluorides, or other suitable compounds by reduction with hydrogen: If a very finely powdered mixture of metal oxide (Li_2O, CaO, SrO, BaO, $AmO_{1.5}$, or $CfO_{1.5}$) and noble metal is heated above 1100°C in a stream of pure H_2, one obtains the corresponding intermetallic phase in very pure form (typical analytical values: O_2 300—500 ppm, $N_2 < 100$ ppm, $H_2 < 100$ torr—on cooling under He). If these phases are further heated in a high vacuum (10^{-5} to 10^{-6} torr), the readily volatile components (Li, Ca, Sr, Ba, Am, Cf) evaporate and can be isolated by condensation. Because of its appreciably lower vapor pressure, the noble metal—so far Pt, Pd, and Ir have been investigated—remains as solid phase and is available for a further reaction, *i.e.* the noble metal functions wholly as catalyst for the reduction of the metal oxide to metal by hydrogen (direct reduction of the oxides in question is impossible because of their low partial pressure of oxygen or their high bond

[*] Prof. Dr. C. Keller, U. Berndt, and Dr. B. Erdmann
Institut für Radiochemie, Kernforschungszentrum
75 Karsruhe, Postfach 3640 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

enthalpy). Thus is obtained the following cyclic process for the catalyst in the preparation of the non-noble metal $A_{(s)}$:



Using the ^{241}Am/Pt and ^{244}Cm/Pt alloy phases prepared by us, *Spirlet* and *Müller*[5, 6] obtained ^{241}Am and ^{244}Cm metal in high yield and purity on a gram or milligram scale. In that work this volatilization process proved superior to all the methods described previously for preparation of americium.

Actinoids have very different vapor pressures, owing to the differing "valences" of the element in the metallic state[7], and this can be utilized for a relatively very simple separation of transplutonium elements: If an alloy mixed phase Pt_5(Am,Cm,Cf) produced by coupled reduction is heated in a high vacuum, californium evaporates out of it first at low temperatures ($\leq$1200 °C), followed by americium above 1300 °C, whilst curium, the least volatile actinoid component, remains behind or, in accordance with *Müller*'s results[6], can be evaporated above 1500 °C. These experiments have so far been carried out only with submicro quantities of ^{252}Cf (determination by neutron counting[8]), but on the basis of the results the process can doubtless be applied to larger amounts of material.

Also of interest was the finding that, *e.g.*, metallic Ca can be prepared from CaF_2 (mineral fluorite) by indirect reduction with hydrogen in almost a single step with "platinum as catalyst".

The metals isolated by evaporation were identified by X-ray diffraction and by chemical analysis. No attention has yet been paid to their quantitative recovery.

A detailed study of such reactions and of possible methods of separation (determination of enthalpies of formation and vapor pressures of the intermetallic phases) and the introduction of other metals (*e.g.* Eu, Es) is in progress. We wish to find in particular whether this process can be carried out with the "cheaper" elements of the eighth sub-group of the Periodic System—we are thinking of Co and Ni—and what special demands must be set on the hydrogen used for reduction in individual cases.

Received: November 19, 1971 [Z 588 IE]
German version: Angew. Chem. *84*, 537 (1972)

[1] a) *B. Erdmann* and *C. Keller*, Inorg. Nucl. Chem. Lett. *7*, 675 (1971); b) *H. Schulz, K. Ritapal, W. Banger*, and *W. Klemm*, Z. Anorg. Allg. Chem. *357*, 299 (1968); *W. Banger* and *W. Klemm*, *ibid. 319*, 58 (1962).

[2] *C. Keller* and *B. Erdmann*, Lecture, Transplutonium Element Symp., 3rd, Argonne/Ill., October 22, 1971.

[3] *B. Erdmann*, Thesis, Universität Karlsruhe 1971; see Ber. Kernforschungszentrum Karlsruhe KFK-1444 (1971).

[4] *B. Erdmann* and *C. Keller*, J. Solid State Chem., in press (1972).

[5] *J. C. Spirlet* and *W. Müller*, Angew. Chem. *83*, 932 (1971); Angew. Chem. internat. Edit. *10*, 857 (1971).

[6] W. Müller, Lecture, Int. Transplutonium Element Symp., 3rd, Argonne/Ill., October 22, 1971.

[7] *C. Keller*: The Chemistry of the Transuranium Elements. Verlag Chemie, Weinheim 1971.

[8] We thank Dr. *Gantner* for the neutron measurements.

Coordination Compounds with Silicon-Molybdenum and Silicon-Tungsten Bonds

By *Wolfgang Malisch, Hubert Schmidbaur*, and *Max Kuhn*[*]

For some time much interest has been attached to transition metal-silicon compounds[1]. Although this type of complex has been relatively well studied for metals of Group VII (Mn[2]) and VIII (Fe[3], Co[4]), there is little information about the formation or reactivity of analogous species with metals of Group VI[5–7], mainly owing to lack of good methods for their preparation.

The "alkali salt method", usually the simplest way of forming IVb-element-metal bonds[8, 9], has, with one exception[7], so far failed to yield the expected products[9–11] for various reasons.

We have found, however, that this process can be used in modified form, namely by taking into account the thermal instability of the compounds produced and their pronounced tendency to decompose in *polar* solvents. Satisfactory yields (40—90%) can thus be achieved if a halosilane and an alkali-metal metalate are brought into reaction in cyclohexane or methylcyclohexane, *e.g.*:

$$[\pi\text{-}C_5H_5(CO)_3M]\,Na + HSiCl_3 \xrightarrow[15\ h]{C_6H_{12}/25\,^{\circ}C} \pi\text{-}C_5H_5(CO)_3M\text{-}SiHC + NaCl$$

M = Mo, W

The composition and structure of the compounds listed in Table 1 were proved by elemental analysis and NMR and IR spectroscopy (three strong carbonyl stretching vibrations). The molecular ion appeared in the mass spectrum (70 eV) in all cases[12].

Table 1. Properties of the complex compounds *(1)*—*(11)* of type π-$C_5H_5(CO)_3M$—R.

Reactant	Product M	Product R	No.	M. p. (°C)	Subl. (°C) [b]
$(CH_3)_3SiBr$	Mo	$Si(CH_3)_3$	*(1)*	80 [a]	[c]
	W	$Si(CH_3)_3$	*(2)*	90–92 [a]	[c]
$H(CH_3)SiCl_2$	Mo	$SiH(CH_3)Cl$	*(3)*	26–27	[c]
	W	$SiH(CH_3)Cl$	*(4)*	31–32	85–87
CH_3SiCl_3	W	$SiCH_3Cl_2$	*(5)*	86–87	65
$HSiCl_3$	Mo	$SiHCl_2$	*(6)*	80–81 [a]	65–67 [c]
	W	$SiHCl_2$	*(7)*	87–88	83–85
$SiCl_4$	Mo	$SiCl_3$	*(8)*	102–104 [a]	78–80 [c]
	W	$SiCl_3$	*(9)*	142–143	100–103
$SiBr_4$	Mo	$SiBr_3$	*(10)*	107–110	[c]
	W	$SiBr_3$	*(11)*	140 (dec.)	133–135

[a] Melting point difficultly reproducible because partial decomposition of the complex occurs on heating.
[b] Sublimation at 10^{-2} torr.
[c] Precipitated from pentane at −78 °C.

The complexes *(1)*—*(11)* are colorless to pale yellow crystals at room temperature but very sensitive to light. They have a strong tendency to decompose in solution,

[*] Dr. W. Malisch [**], Prof. Dr. H. Schmidbaur, and M. Kuhn
Institut für Anorganische Chemie der Universität
87 Würzburg, Landwehr (Germany)
[**] Author to whom correspondence should be addressed.

except in cyclohexane, methylcyclohexane, or pentane; this property depends strongly on the nature of the metal atom M (Mo > W) and the substituents on the silicon:

$$(CH_3)_3Si > CH_3SiHCl \approx CH_3SiCl_2 > HSiCl_2 \approx SiBr_3 > SiCl_3$$

The fact that compounds of type $(\pi\text{-}C_5H_5)(CO)_3M—M(CO)_3(\pi\text{-}C_5H_5)$ are found after decomposition indicates that the metal-silicon bond is more labile in these cases than in the Co, Fe, and Mn analogs.

This is also shown in the smooth replacement of the trimethylsilyl group in reactions with heterosiloxanes[13]:

$$\pi\text{-}C_5H_5(CO)_3M\text{-}Si(CH_3)_3 + (CH_3)_3XOSi(CH_3)_3 \longrightarrow$$

$$\pi\text{-}C_5H_5(CO)_3M\text{-}X(CH_3)_3 + (CH_3)_3SiOSi(CH_3)_3$$

M = Mo, W

X = Ge[14], Sn[15]

The strong tendency to form the siloxane group provides additional driving force in this reaction[16].

General procedure:

A 3—5-fold excess of the halosilane (12—20 mmol) is added to a suspension of $Na[Mo(CO)_3(\pi\text{-}C_5H_5)]$ (1.1 g, 4.1 mmol). After 15—45 hours' stirring in a closed vessel at 25 °C the insoluble material is removed from the reaction mixture, and the filtrate is evaporated to dryness in an oil-pump vacuum. The crude product is extracted with pentane; from this solution the silyl complex can be obtained pure on cooling (−78 °C).

Received: December 28, 1971 [Z 590 IE]
German version: Angew. Chem. *84*, 538 (1972)

[1] *L. H. Sommer*, Pure Appl. Chem. *19*, 525 (1969).

[2] *A. D. Berry* and *A. G. MacDiarmid*, Inorg. Nucl. Chem. Lett. *5*, 601 (1969).

[3] *Y. L. Baay* and *A. G. MacDiarmid*, Inorg. Chem. *8*, 987 (1969).

[4] *M. A. Nasta* and *A. G. MacDiarmid*, J. Organometal. Chem. *18*, P 11 (1969).

[5] *W. Jetz* and *W. A. G. Graham*, J. Amer. Chem. Soc. *89*, 2773 (1967).

[6] *D. J. Cardin, S. A. Keppie, B. M. Kingston*, and *M. F. Lappert*, Chem. Commun. *1967*, 1035; *D. J. Cardin, S. A. Keppie*, and *M. F. Lappert*, J. Chem. Soc. *A 1970*, 2594.

[7] *A. P. Hagen, C. R. Higgins*, and *P. J. Russo*, Inorg. Chem. *10*, 1657 (1971).

[8] *H. R. H. Patil* and *W. A. G. Graham*, Inorg. Chem. *5*, 1401 (1966).

[9] *D. J. Cardin, S. A. Keppie*, and *M. F. Lappert*, Inorg. Nucl. Chem. Lett. *4*, 365 (1968).

[10] *R. B. King, K. H. Pannel, C. R. Bennett*, and *M. Ishaq*, J. Organometal. Chem. *19*, 327 (1969).

[11] *R. B. King*, Accounts Chem. Res. *3*, 424 (1970).

[12] We thank *N. Pelz* for determining the mass spectra.

[13] A part of the substance is decomposed during the ligand exchange reaction.

[14] *H. Schmidbaur*, Angew. Chem. *77*, 206 (1965); Angew. Chem. internat. Edit. *4*, 201 (1965).

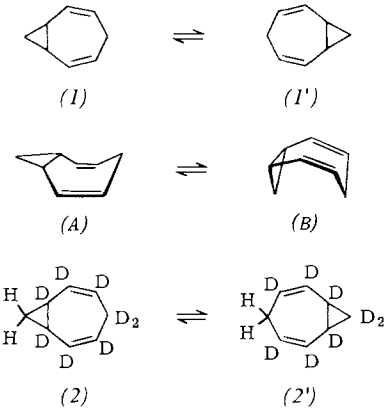
[15] *H. Schmidbaur* and *H. Hussek*, J. Organometal. Chem. *1*, 244 (1964).

[16] *H. Schmidbaur* and *W. Tronich*, Chem. Ber. *101*, 3545 (1968).

Kinetics of the Homotropilidene Valence Tautomerism[**]

By *Harald Günther, Josef Bernd Pawliczek, Joachim Ulmen*, and *Wolfram Grimme*[*]

The ability to detect fluxional systems by NMR spectroscopy was impressively demonstrated for the first time in the case of bicyclo[5.1.0]octa-2,5-diene (3,4-homotropilidene) *(1)*[1]. There has as yet, however, been no study of the kinetics of this rearrangement, which is preceded by a conformational equilibrium $[(A) \rightleftharpoons (B)]$[1,2], because the spin system of *(1)* (10 H) is too complicated for exact NMR line shape analysis.



We have therefore synthesized the mixture of octadeuteriobicyclo[5.1.0]octa-2,5-dienes *(2)*⇌*(2')*, each component having one dihydro-methylene group[3], and have, for the

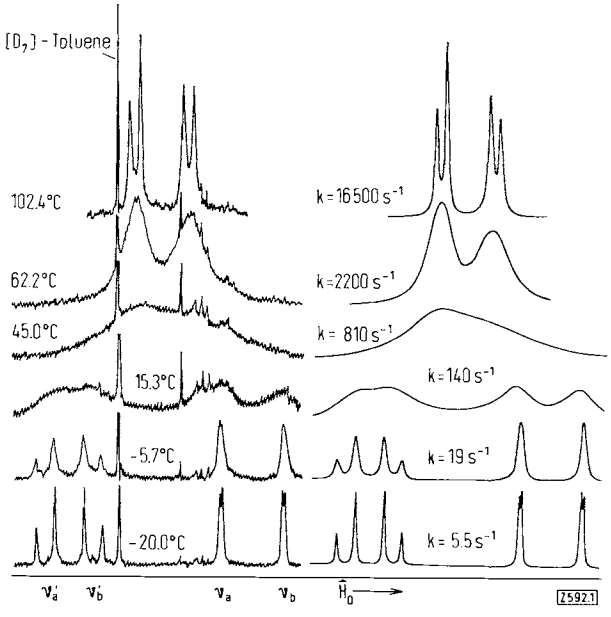


Fig. 1. Temperature-dependent experimental (left) and theoretical (right) ^{1}H-NMR spectra of the methylene protons of *(2)*⇌*(2')* on H{D}-decoupling; signals of incompletely deuteriated material appear below ν_A.

[*] Prof. Dr. H. Günther, Dr. J. B. Pawliczek, Dipl.-Chem. J. Ulmen, and Prof. Dr. W. Grimme
Institut für Organische Chemie der Universität
5 Köln, Zülpicher Str. 47 (Germany)

[**] Support of this work by the Landesamt für Forschung of Nordrhein-Westfalen and the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

first time, derived data for the rearrangement *(2)*⇌*(2')* between −65 and 102 °C from the temperature-dependent line shape of the ^{1}H-NMR spectrum (solvent [D_8]toluene, frequency 100 MHz, internal reference benzene).

With H{D}-decoupling, two AB systems ($\nu_a = 620.6_4$, $\nu_b = 685.4_8$, and $J = 2.6_7$ Hz, and $\nu'_a = 424.0_5$, $\nu'_b = 474.9_6$, and $J = 20.6_5$ Hz) are observed for *(2)*⇌*(2')* in the slow exchange region (−65 °C) which must be assigned to the CH_2 groups in structure *(2)* and *(2')*, respectively (Fig. 1).

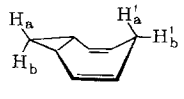
Temperature increase leads to line broadening, coalescence (*ca.* 35 °C) and finally in the region of fast exchange (40 °C) to an averaged spectrum: $\tilde{\nu} = 523.0_4$, $\tilde{\nu}_b = 582.2_2$, and $\tilde{J} = 11.4_9$ Hz. Integration of the low-temperature spectrum gave different concentrations for *(2)* and *(2')*: $K(-35\,°C) \approx 0.9$. A similar isotope effect, namely that hydrogen in competition with deuterium prefers the cyclopropyl to the allyl position, was recently observed for barbaralone[4] and for octadeuteriobicyclo[5.1.0]octa-2,4-diene[3].

To determine the rate constants k, the temperature-dependent line shape of the spectrum was calculated quantum-mechanically[5] for the exchange process $AB \rightleftarrows A'B'$ (Fig. 1), taking into account changes in the spectral parameters[6] and the mole fractions. With 20 experimental points the best Arrhenius equation for the reaction *(2')*→*(2)* was:

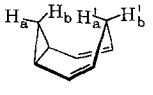
$$k = 10^{11.5 \pm 0.1} \exp\left[-(12450 \pm 220)/RT\right] s^{-1}$$

and from a log $(k/T)/(1/T)$ diagram the activation parameters $\Delta H^{+} = 11.8 \pm 0.2$ kcal/mol and $\Delta S^{+} = -8.0 \pm 0.3$ clausius were obtained. For 1,3,4,6-tetramethyl-3,4-homotropilidene ΔG^{+} (0 °C) was previously[2] estimated as 13.6 kcal/mol. From the temperature-dependence of the K values a ΔH^0 of 240±25 cal/mol in favor of *(2)* was calculated by van't Hoff's equation.

Our results also make it possible to decide whether the rearrangement *(1)*⇌*(1')* proceeds through a transoid or a cisoid transition state[1]. From the $^3J_{H,D}$ values found the proton assignments *(3A)* or *(4B)* can be made according to whether the ground state of *(1)* has the conformation *(A)* or *(B)*:

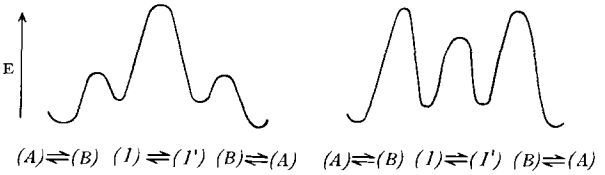


(3A)
⇅
(3B)



(4B)
⇅
(4A)

On the other hand, double resonance experiments[7] yielded the exchange schemes $H_a \rightleftarrows H'_a$ and $H_b \rightleftarrows H'_b$, *i. e.* $AB \rightleftarrows A'B'$. These agree with the assignments only if the valence tautomerism is preceded and followed by a conformational change into the respective alternative conformations [*(3A)*→*(3B)* or *(4B)*→*(4A)*], because the transition state for the rearrangement *(1)*⇌*(1')* has either C_{2h} or C_{2v}



(A)⇌*(B)* *(1)*⇌*(1')* *(B)*⇌*(A)*
(C)

(A)⇌*(B)* *(1)*⇌*(1')* *(B)*⇌*(A)*
(D)

symmetry according to whether it is derived from *(A)* (transoid) or *(B)* (cisoid), and the proton exchange must follow this symmetry. Since the results of photoelectron spectroscopy indicate conformation *(A)* for the ground state of *(1)*[8], the rearrangement must occur through the cisoid transition state[1,9].

The energy profile *(C)* or *(D)* may be discussed for the reaction *(1)*⇌*(1')* that is accompanied by the conformational equilibrium *(A)*⇌*(B)*. If the energy barriers for the valence tautomerism in dihydrobullvalene *(5)* (12.6 kcal/mol)[10] and barbaralane *(6)* (8.6 kcal/mol)[11] and for the



(5)



(6)

ring inversion of 1,3,5-cycloheptatriene (6 kcal/mol)[12] are considered, preference must be given to *(C)*. The energy difference between conformations *(A)* and *(B)* thus amounts to 3 kcal/mol at most.

Received: January 10, 1972 [Z 592IE]
German version: Angew. Chem. *84*, 539 (1972)

[1] *W. v. Doering* and *W. R. Roth*, Tetrahedron *19*, 715 (1963); Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 115 (1963).

[2] *L. Birladeanu, D. L. Harris*, and *S. Winstein*, J. Amer. Chem. Soc. *92*, 6387 (1970).

[3] *W. Grimme* and *W. von E. Doering*, to be published.

[4] *J. C. Barborak, S. Chari*, and *P. von R. Schleyer*, J. Amer. Chem. Soc. *93*, 5275 (1971).

[5] *C. J. Cresswell* and *R. K. Harris*, J. Magn. Res. *4*, 99 (1971). We thank Drs. *R. K. Harris* and *M. Kinns* for supplying a listing of their program.

[6] The temperature-dependence of the resonance frequencies was determined below the coalescence point.

[7] *S. Forsén* and *R. A. Hoffmann*, J. Chem. Phys. *39*, 2892 (1963).

[8] *P. Bischof, R. Gleiter, E. Heilbronner, V. Hornung*, and *G. Schröder*, Helv. Chim. Acta *53*, 1645 (1970).

[9] Ref. [2] contains similar interpretations, but closer examination shows that the experimental evidence given there is not sufficient to answer the question about the conformation of the transition state for the valence tautomerism *(1)*⇌*(1')* satisfactorily.

[10] *G. Schröder, J. F. M. Oth*, and *R. Merenyi*, Angew. Chem. *77*, 774 (1965); Angew. Chem. internat. Edit. *4*, 752 (1965).

[11] *W. v. E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin*, and *M. Saunders*, Tetrahedron *23*, 3943 (1967).

[12] a) *F. A. L. Anet*, J. Amer. Chem. Soc. *86*, 458 (1964); b) *F. R. Jensen* and *L. A. Smith, ibid. 86*, 956 (1964).

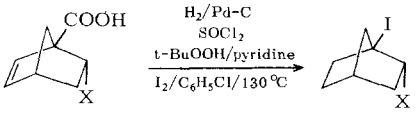
Does 1-Norbornene Exist?

By *Reinhart Keese* and *Ernst-Peter Krebs*[*]

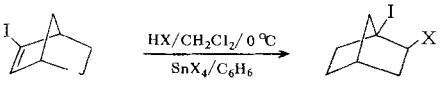
We have reported that 1,2-*exo*-dihalonorbornanes are bis-dehalogenated by butyllithium and that in the presence of furan the two diastereoisomers *(6)* and *(7)* result. The constant product ratio led us to assume that 1-norbornene was formed as an intermediate[1]. We now have strong evidence for the assumption that 1-norbornene is actually

[*] Dr. R. Keese and E.-P. Krebs, Dipl.-Natw. ETH
Organisch-chemisches Laboratorium der
Eidg. Techn. Hochschule
CH-8006 Zürich, Universitätsstrasse 6 (Switzerland)

formed in the bisdehalogenation of 1,2-dihalonorbornanes. The required diastereoisomeric dihalides *(2a)/(3a)* and *(2b)/(3b)* were prepared as shown in Scheme 1[2] or as described previously[1].



(1a), (1b) *(2a), (2b)*

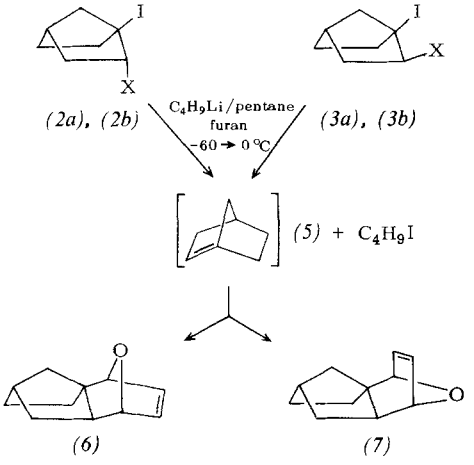


(4) *(3a), (3b)*

Scheme 1. *a*, X = Br; *b*, X = Cl.

Methyl cyclopentadienecarboxylate reacts with vinyl bromide or vinyl chloride in an autoclave at 170 °C to give a mixture of cycloaddition products, from which pure 6-*endo*-bromo- or 6-*endo*-chloro-bicyclo[2.2.1]hept-2-ene-1-carboxylate *(1a)* or *(1b)*, respectively[3a, b], can be isolated. (The *endo*-configuration follows from the NMR spectrum.) 2-*endo*-Bromo-1-iodonorbornane *(2a)* and 2-*endo*-chloro-1-iodonorbornane *(2b)*[3b] are obtained from *(1a)* and *(1b)* resp. according to Scheme 1. 2-*exo*-Bromo-1-iodonorbornane[1] *(3a)* and 2-*exo*-chloro-1-iodonorbornane *(3b)* were obtained from 2-iodo-2-norbornene *(4)*[4] as shown in Scheme 1.

Bisdehalogenation of the diastereoisomeric pairs *(2a)/(3a)* and *(2b)/(3b)* induced by butyllithium in the presence of furan gave the trapping products *(6)* and *(7)* in a constant ratio. We found the same product ratio from the reaction of *(2a)* and *(3b)* with sodium amalgam in a mixture of furan and tetrahydrofuran (cf. Scheme 2 and Table 1).



Scheme 2. *a*, X = Br; *b*, X = Cl.

In general, proof of a metastable intermediate resting on a trapping reaction is valid only under the following conditions: First, the structural element of the metastable intermediate must be unambiguously detectable in the trapping products; secondly, the trapping reactions must give a constant product ratio under competitive conditions, and this ratio must also be independent of the nature of the starting materials[5].

A trapping reaction can also be considered competitive if the trapping reagent gives two *diastereoisomeric* products. In this case, however, a constant product ratio leads to valid conclusions only if the starting materials differ at least in their configurations.

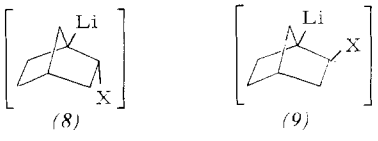
As shown in the Table, this condition is fulfilled: the ratio of the diastereoisomeric furan adducts *(6)* and *(7)* is independent of the configuration of the 1,2-dihalonorbornanes *(2a)/(3a)* and *(2b)/(3b)*.

Table 1. Results of trapping reactions according to Scheme 2.

Cpd.	R in RLi	Furan adducts Reaction [%]	Yield *(6)+(7)* [%]	*(6)*:*(7)* [a]
(2a)	*n*-Butyl	91	60	23:77
	tert-Butyl	66	33	24:76
(3a)	*tert*-Butyl	100	47	21:79
(2b)	*n*-Butyl	56	9	20:80
	tert-Butyl	87	9	21:79
	sec-Butyl	83	9	25:75
(3b)	*n*-Butyl	78	43	23:77
	tert-Butyl	100	30	22:78
	sec-Butyl	100	17	20:80
(3b)	Na/Hg	75	16 [b]	20:80
		60	3.5 [c]	25:75
(2a)	Na/Hg	100	5 [b]	25:75

[a] Ratio of peak areas in the gas-liquid chromatogram.
[b] At −65 °C.
[c] At +25 °C.

In the bisdehalogenation of *(2a)*, *(2b)* and *(3a)*, *(3b)* respectively it must be confirmed that lithium-halogen exchange yields only intermediates of type *(8)* and *(9)* because the consequent elimination of lithium halide is then dependent on the *exo*- and *endo*-configuration, thus reinforcing the evidence for the common intermediate.



(8) *(9)*

The following experimental facts prove an exclusive lithium-iodine exchange:

1. Both 2-*exo*- and 2-*endo*-bromonorbornane were stable to *tert*-butyllithium in furan under the conditions of the bisdehalogenation.

2. 2-*exo*- and 2-*endo*-Chloronorbornane can be recovered unchanged after treatment with *sec*-butyllithium under analogous conditions.

3. On dehalogenation of *(2a)* with *tert*-butyllithium, 2-*endo*-bromonorbornane was isolated when the reaction was quenched after a short time by addition of methanol.

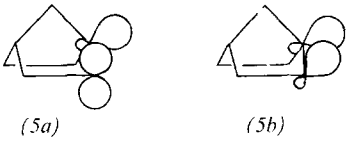
4. Butyl iodide was detected mass-spectrometrically in all the elimination reactions described. Further, in most cases,

n-, *sec*-, or *tert*-butyl iodide, corresponding to the isomeric butyllithium used, was isolated by gas chromatography and identified by its NMR or IR spectrum.

5. Under the conditions of the bisdehalogenation *tert*-butyl bromide reacts only to a limited extent with dehydrated lithium iodide in furan; *sec*-butyl bromide is inert to lithium iodide in furan even at room temperature.

The total experimental findings form the basis of our view that 1-norbornene occurs as a discrete intermediate in these reactions.

Our information regarding the nature of this double bond is still slight. We assume that the double bond can be described as a combination of a sp^x hybrid orbital ($x \approx 3$) on the bridgehead with a neighboring p- or sp^x-hybrid orbital—*(5a)* or *(5b)* (cf. Scheme 3).



(5a) *(5b)*



(10a) *(10b)*

Scheme 3.

Orienting extended Hückel calculations for ethylene which is taken to be sp^3-hybridized on one *(10a)* or both *(10b)* carbon centers show the following for a twisted structure with reasonable torsion angles[6]:

If one starts from a singlet ground state, *(10a)* with inclusion of all the σ-bonds is more stable than *(10b)*; the bond order decreases to half that of an unstrained double bond. Independently of the torsion angle, an excess of charge develops on the sp^3-hybridized carbon atom in the π-system of *(10a)*. If the energy difference between the highest occupied and lowest unoccupied molecular orbital in *(10a)* is compared with that for untwisted, planar ethylene, the electron excitation energy in *(10a)* is found to be only half that in ethylene; an absorption maximum above 300 nm would therefore be expected for *(10a)*. This energy difference is, however, of an order of magnitude that is assumed in the extended Hückel method to be an indication of a triplet ground state[7, 8]. We are presently investigating these questions.

Received: February 11, 1972 [Z 612 IE]
German version: Angew. Chem. *84*, 540 (1972)

[1] *R. Keese* and *E.-P. Krebs*, Angew. Chem. *83*, 254 (1971); Angew. Chem. internat. Edit. *10*, 262 (1971).

[2] All the new compounds gave correct analytical values.

[3] In collaboration with a) *F. Marti*, Diplomarbeit ETH 1970, and b) *H. Hauser*, Diplomarbeit ETH 1970/1971.

[4] Compound *(4)* is formed as by-product in the preparation of 2,2-diiodonorbornane from norcamphor hydrazone [1].

[5] In this connexion see *R. Huisgen*, Angew. Chem. *82*, 783 (1970); Angew. Chem. internat. Edit. *9*, 751 (1970).

[6] *R. Keese* and *E.-P. Krebs*, unpublished results.

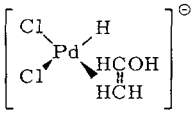
[7] *R. Gleiter* and *R. Hoffmann*, J. Amer. Chem. Soc. *90*, 5457 (1968).

[8] We are grateful to Prof. *R. Hoffmann* for his informative discussions.

Tetracarbonyl(π-vinyl alcohol)iron[1]

By *Helmut Thyret*[*]

The existence of vinyl alcohol has not been demonstrated previously, a fact that is rationalized by theoretical calculations according to which acetaldehyde is more stable than vinyl alcohol by 12.9 or 14.6 kcal/mole respectively[2]. The existence of a π-bonded vinyl alcohol is, however, more probable; for instance, *(1)* has been postulated as an intermediate[4] in the palladium-catalyzed oxidation of ethylene to acetaldehyde[3]. However, no experimental proof has yet become available.



(1)

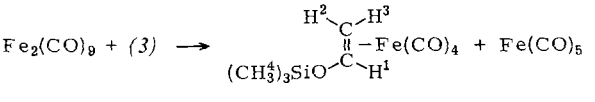
We have been unable to confirm the existence of a stable vinyl alcohol complex *(2)*[5] that is reported to be formed by a ligand exchange reaction of the ethylene complex with trimethylsilyl vinyl ether *(3)* and subsequent hydrolysis. Even at −10 °C the NMR spectrum indicates the immediate

$[(CH_2=CHOH)PtCl_2]_2$ *(2)* $CH_2=CHOSi(CH_3)_3$ *(3)*

formation of a mixture of products as results from the acid-catalyzed condensation of acetaldehyde—besides hexamethyldisiloxane; acetaldehyde and paraldehyde could be identified therein[6]. Furthermore, *(2)* could not be trapped by methyl isocyanate (see below). The formation of the vinyl alcohol complex *(2)* in this way can therefore be ruled out.

We report below the first π-complex of vinyl alcohol. In principle the route involving hydrolysis of a π-complex of *(3)* appeared promising. However, for this purpose it is clearly necessary to increase the energy of the d-orbitals of the metal atom in order to reduce the positive charge caused by the strong dative bonding—and the increased reactivity—at the oxygen atom; also, the metal atom should be coordinately saturated so that catalytic rearrangements cannot occur. From these points of view the tetracarbonyliron group seemed to be a suitable system for π-bonding to *(3)*.

Tetracarbonyl(π-trimethylsilyl vinyl ether)iron *(4)* was synthesized by analogy to a known procedure[7, 8]. By

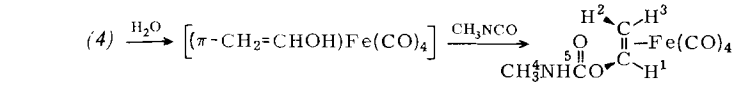


(4)

crystallization at −80 °C *(4)* can be isolated in pure form. It decomposes at as low a temperature as 0 °C. Its structure was proved by the NMR spectrum[9] [*(4)*: $\delta = 6.5$ (H^1), 2.75 (H^2), 2.35 (H^3), 0.12 ppm (H^4); $J_{12} = 9.7$, $J_{13} = 4.6$, $J_{23} = 3.0$ Hz. *(3)*: $\delta = 6.4$ (H^1), 4.3 (H^2), 4.0 (H^3), 0.1 ppm (H^4); $J_{12} = 14.0$, $J_{13} = 6.0$, $J_{23} \approx 0$ Hz].

[*] Dr. H. Thyret
Consortium für elektrochemische Industrie
8 München 25, Zielstattstrasse 20 (Germany)

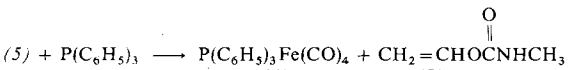
We first attempted an indirect proof of the formation of tetracarbonyl(π-vinyl alcohol)iron by a trapping reaction with methyl isocyanate. For this purpose *(4)* was hydrolyzed in acetone at −25 °C for several days in the presence of three equivalents of methyl isocyanate; the yellow crystals that precipitated in almost quantitative yield were identified as tetracarbonyl(π-*O*-vinyl *N*-methylcarbamate)-iron *(5)*, a compound that, like *(4)*, decomposes already



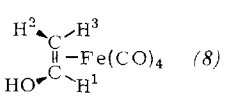
(5)

at about 0 °C. The NMR parameters of *(5)* are: $\delta = 6.6$ (H^1), 2.75 (H^2), 2.4 (H^3), 2.70 (H^4), 3.7 ppm (H^5); $J_{12} = 9.8$, $J_{13} = 5.2$, $J_{23} = 4.0$, $J_{45} = 5.0$ Hz.

An additional proof of the structure was provided by the reaction with triphenylphosphane:



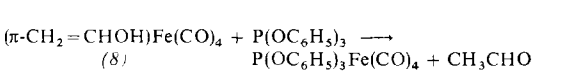
(6) was identified by its m. p. (190 °C; lit.[10]: 199—200 °C) and IR spectrum ($\nu_{C=O} = 2051$ (A_1), 1978 (A_1), and 1945 cm^{-1} (E)[10]), and *(7)* was characterized by its NMR spectrum [$\delta = 7.15$ (H^1), 4.55 (H^2), 4.3 (H^3), 2.7 (H^4), 3.0 ppm (H^5); $J_{12} = 14.0$, $J_{13} = 6.5$, $J_{23} = 1.0$, $J_{45} = 5.0$ Hz]. After having proved indirectly for the first time the existence of a π-vinyl alcohol complex[11], tetracarbonyl(π-vinyl alcohol)iron itself could be isolated by hydrolysis of *(4)* for several days with small amounts of 5% aqueous trifluoroacetic acid in acetone at −90 °C. The NMR spectrum[13] of tetracarbonyl(π-vinyl alcohol)iron *(8)* was obtained at −75 °C. The complex decomposes above −70 °C.



(8)

The NMR parameters are very similar to those of the other complexes: $\delta = 6.9$ (H^1), 2.8 (H^2), 2.35 ppm (H^3), $J_{12} = 10.0$, $J_{13} = 4.9$, $J_{23} = 3.0$ Hz.

The reaction with triphenyl phosphite in which acetaldehyde is formed quantitatively, constitutes an additional proof of structure *(8)*:



Received: March 10, 1972 [Z 614 IE]
German version: Angew. Chem. *84*, 581 (1972)

[1] Read at Vth Internat. Conf. Organomet. Chem., Moscow, 1971.

[2] *L. Radom, W. J. Hehre*, and *J. A. Pople*, J. Amer. Chem. Soc. *93*, 289 (1971).

[3] *J. Smidt, W. Hafner, R. Jira, J. Sedlmeier*, and *A. Sabel*, Angew. Chem. *74*, 93 (1962); Angew. Chem. internat. Edit. *1*, 80 (1962).

[4] *R. Jira, J. Sedlmeier*, and *J. Smidt*, Liebigs Ann. Chem. *693*, 99 (1966).

[5] *Y. Wakatsuki, S. Nozakura*, and *S. Murahashi*, Bull. Chem. Soc. Jap. *42*, 273 (1969).

[6] If ethyl vinyl ether is used in place of *(3)*, a completely analogous reaction occurs except that then acetaldehyde diethyl acetal is formed instead of hexamethyldisiloxane.

[7] *H. D. Murdoch* and *E. Weiss*, Helv. Chim. Acta *46*, 1588 (1963).

[8] *E. Körner von Gustorf, M. C. Henry*, and *C. DiPietro*, Z. Naturforsch. *21b*, 42 (1966).

[9] All spectra in [D_6]-acetone with hexamethyldisiloxane ($\delta = 0$) as internal standard.

[10] *A. Reckziegel* and *M. Birgogne*, J. Organometal. Chem. *3*, 41 (1965).

[11] A complex $[(\pi\text{-}C_5H_5)Fe(CO)_2CH_2CHOH]^+$, for which the structure of a π-vinyl alcohol complex was proposed [12], must be assigned the alternative structure $(\pi\text{-}C_5H_5)Fe(CO)_2CH_2CH{=}\overset{+}{O}H$ [12] according to its reported NMR spectrum.

[12] *J. K. P. Ariyaratne* and *M. L. H. Green*, J. Chem. Soc. *1964*, 1.

[13] The low-temperature NMR spectrum was recorded at the Anorganisch-chemisches Laboratorium of the Technische Universität München. We thank Dr. *C. G. Kreiter* for this.

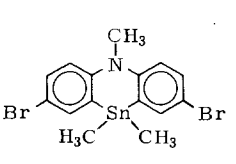
Electron-Impact Induced Rearrangements in Dibenzoazastannines

By *István Lengyel* and *Michael J. Aaronson*[*]

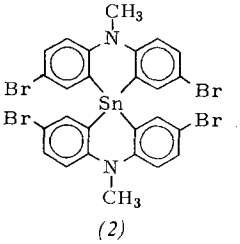
Many of the principal unimolecular ion-decompositions in the mass spectrometer have close thermal, photolytic, or chemical parallels. Indeed, information from mass spectra can occasionally[1] be used to predict the results of reactions initiated by other means in solution or in the gas phase.

On the other hand, some electron-impact induced transformations are typical high-energy reactions, difficult to reproduce in solution. The present communication deals with some unique, *a priori* not predictable, mass spectral fragmentation reactions involving complex molecular reorganizations and migrations in heterocyclic organotin compounds.

The 70-eV mass spectra[2] of 2,8-dibromo-5,10,10-trimethyl-5,10-dihydrodibenzoazastannine *(1)*[3] and 2,2',8,8'-tetrabromo-5,5'-dimethyl-10,10'-spirobi[5,10-dihydrodibenzoazastannine] *(2)* both exhibit an abundant metal-free odd-electron ion at *m/e* 179 (76 and 53% relative inten-



(1)
(1a), N-CD_3



(2)

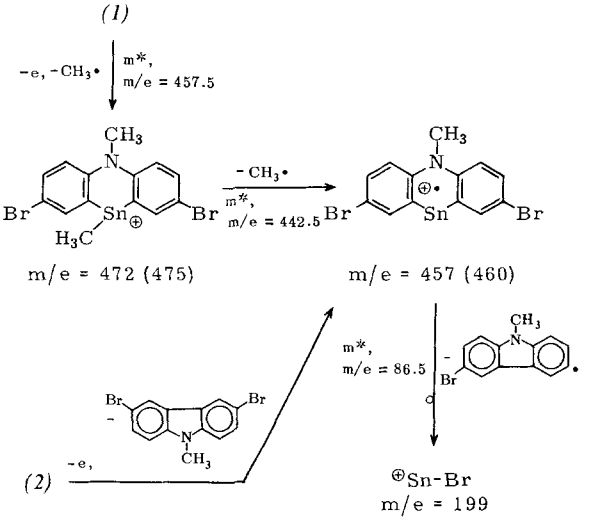
sity) and a tin-containing even-electron ion at *m/e* 199 (95 and 100% relative intensity). To learn more about the nature and genesis of these ions, a combination of specific isotope labeling, computer-coupled high resolution mass measurement[4], and metastable ion correlations[5] was employed.

High resolution elemental composition determination revealed both ions to consist of a single component,

[*] Prof. Dr. I. Lengyel and M. J. Aaronson, M. S.
Department of Chemistry, St. John's University
Jamaica, New York 11432 (USA)

$C_{13}H_9N$ and SnBr, respectively. Ion *m/e* 179 shifts to *m/e* 182 in the spectrum of the trideuterated compound *(1a)*, while no shift is observed for *m/e* 199. Both ions are absent in low energy (12 eV) scans.

Ion *m/e* 199 is formed from the molecular ion by ejection of the metal-ligands followed by expulsion of a resonance-stabilized radical (cf. Scheme 1), as supported by the appropriate metastable peaks. The last step of this sequence requires migration of a bromine atom from the aromatic ring to the electron-deficient tin.

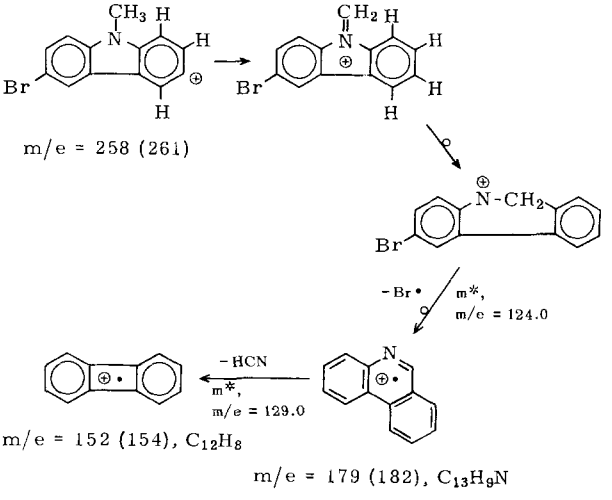


Scheme 1. The mass numbers in parentheses refer to degradation of *(1a)*.

Study of the metastable ions also reveals that ion *m/e* 179 is formed by elimination of the second bromine atom from even-electron ion *m/e* 258, which in turn is generated by the sequence:

$$M^{+\bullet} \xrightarrow{-(CH_3)_2Sn} m/e\ 339 \xrightarrow{-Br\bullet} m/e\ 258$$

Generally, even- to odd-electron transitions such as *m/e* 258 → *m/e* 179 are not energetically favorable[6]. A prominent path of subsequent decomposition of *m/e* 179 is *via* loss of HCN [DCN in *(1a)*] to give biphenylene, *m/e* 152.



Scheme 2. The mass numbers in parentheses refer to degradation of *(1a)*.

The latter ion shifts by *two masses* to *m/e* 154 in the spectrum of *(1a)*, indicating that two of the three deuterium atoms migrate from the N—CD_3 group to the aromatic rings (Scheme 2).

These pieces of evidence, combined, suggest that the driving force for the unexpected 258 → 179 transition is the rearomatization of the product ion which is formulated as phenanthridine. It is suggested that skeletal rearrangement occurs already in ion *m/e* 258 (before further fragmentation) involving both enlargement of the center heterocyclic ring and hydrogen migration.

Received: January 11, 1972 [Z 621 IE]
German version: Angew. Chem. *84*, 542 (1972)

[1] *E. K. Fields* and *S. Meyerson*, Accounts of Chem. Res. *2*, 273 (1969).

[2] The low resolution mass spectra were recorded on a Hitachi RMU-6D instrument at 50 μA, with direct sample introduction *via* the solid probe.

[3] *E. J. Kupchik* and *V. A. Perciaccante*, J. Organometal. Chem. *10*, 181 (1967). We thank Prof. *Kupchik* for kindly providing the samples used in this investigation.

[4] A complete high resolution mass spectrum for compound *(1)* was recorded on a CEC 21-110 B doubly focusing mass spectrometer coupled with an IBM 1800 computer at the Massachusetts Institute of Technology. We thank Prof. *Klaus Biemann* for the high resolution data.

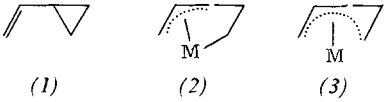
[5] Metastable ion correlations ($m^* = m_2^2/m_1$) were calculated by computer, using a program similar to the one written by *R. E. Rhodes, M. Barber*, and *R. L. Anderson*, Anal. Chem. *38*, 48 (1966). Final assignments were made manually, utilizing intensity data for m_1 and m_2.

[6] *F. W. McLafferty*: Interpretation of Mass Spectra. W. A. Benjamin, New York 1966, Chapter 8.

Reactions of Strained C—C Single Bonds with Transition Metals — Influence of Geometrical Factors on the Reactivity of Complex-bound Vinylcyclopropane Systems[1]

By *Rudolf Aumann*[*]

Vinylcyclopropane *(1)* can be converted into "homobutadiene"-transition metal complexes *(2)* or *(3)* in which four carbon atoms are bound to the metal M by π-allyl and σ-components[2–4, 13].

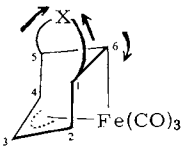


(1) *(2)* *(3)*

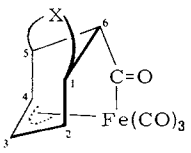
Competitive reactions of vinylcyclopropane systems of various conformations fixed in a polycyclic hydrocarbon showed that bonding in a complex occurs particularly rapidly if the four carbon atoms concerned therein are arranged optimally for a multicenter interaction with the metal[13].

The reactivity of *complex-bound* vinylcyclopropane systems is also strongly influenced by geometrical factors. For instance, distinctly different reactivities attach to the vinylcyclopropane complexes *(4a)*[5]—*(4d)* which are closely related structurally and in which there are only small differences in the C^6—Fe distance due to torsional forces [see arrows in *(4)*] from the bridges X.

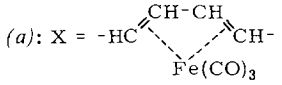
[*] Priv.-Doz. Dr. R. Aumann
Organisch-Chemisches Institut der Universität
44 Münster, Orléansring 23 (Germany)



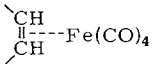
(4)



(5)

(a): X = 

(b): X = $-CH_2-CH=CH-$

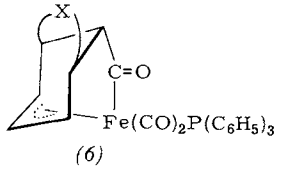
(c): X = 

(d): X = $-CH=CH-$

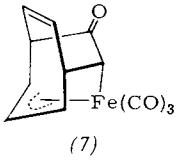
When carbon monoxide is led into a solution of *(4a)* or *(4b)* in hexane at 25 °C, yellow crystals of the adduct *(5a)* (m.p. 134—136 °C, from ether) or *(5b)* (m.p. 68—70 °C, from hexane), respectively, separate after a few minutes. However, *(4c)* takes up carbon monoxide only slowly at 25 °C and at *ca.* 100 atm, yielding *(4d)*. The adducts *(5c)* and *(5d)* are not formed.

Similar differences appear on treatment with triphenylphosphane. At 25 °C *(4a)* and *(4b)* give the thermally very stable adducts *(6)* within a few seconds. However, *(4c)* reacts with an excess of triphenylphosphane when warmed in benzene, yielding $P(C_6H_5)_3Fe(CO)_4$ and *(4d)*; at 70 °C more than 95% of compound *(4c)* is converted within two hours into *(4d)*, which is stable under these conditions for a further two hours.

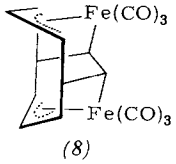
Like *(4d)*, the structurally related complexes *(7)* and *(8)*[4] do not react with carbon monoxide or triphenylphosphane at 25 °C.



(6)



(7)



(8)

The IR spectra of *(5a)* and *(5b)* show intense absorption bands at 1662 and 1670 cm^{-1}, respectively, which are indicative of bridging carbonyl groups[12]. In addition, insertion of carbon monoxide into the C^6—Fe σ bond of *(4)* shifts the proton resonance signal of H^6 in the ^{1}H-NMR spectrum downfield by *ca.* 1 ppm and reduces the proton coupling constants $J_{1,6}$ ($J_{5,6}$) and $J_{1,2}$ ($J_{4,5}$) by about 1—2 Hz. The latter observation points to an increase in the dihedral angles $\chi_{1,6}$ ($\chi_{5,6}$) and $\chi_{1,2}$ ($\chi_{4,5}$) on converting *(4)* into *(5)*. The insertion of carbon monoxide into the C^6—Fe σ bond is reversible; in boiling hexane, *(5a)* and *(5b)* are reconverted into the complexes *(4a)* and *(4b)* respectively[6].

Consideration of models leads one to expect smaller C^6—Fe separations in *(4c)*, *(4d)*, *(7)*, and *(8)* than in *(4a)* and *(4b)* but it is not yet possible to decide whether the differing reactivities of these two sets of compounds is due mainly to stabilization of the ground state by homoconjugation in the vinylcyclopropane system [see *(3)*] or to increase in the energy of the transition state for the carbon monoxide addition reaction caused by, *e.g.* greater rigidity of the carbon skeletons.

The complexes *(4c)*, *(5b)* and *(7)* (m.p. 135—136 °C, from ether), here described for the first time, can be obtained in good yields by treatment of, respectively, tricyclo[3.3.0.$0^{2,8}$]octa-3,6-diene ("semibullvalene") *(9)*[10], tricyclo[4.3.0.$0^{2,9}$]nona-3,7-diene ("homosemibullvalene") *(10)*[11], and tricyclo[3.3.1.$0^{2,8}$]nona-3,6-dien-9-one ("barbaralone") *(11)*[9] with $Fe_2(CO)_9$ in *n*-hexane at 55 °C[13].



(9)



(10)



(11)

The compounds were separated by column chromatography on silica gel with *n*-hexane or ether and were identified by means of their IR and mass spectra and elemental analyses[14]. *(4a)* is formed on thermolysis[3] of *(8)*[4], *(5a)* by the action of carbon monoxide on *(4a)*, and *(4b)* by warming *(5b)* in boiling hexane.

Received: November 16, 1971 [Z 622 IE]
Publication delayed at author's request
German version: Angew. Chem. *84*, 583 (1972)

---

[1] This work was supported by the Deutsche Forschungsgemeinschaft and constitutes Part I of the series, "Reactions of Strained C—C Single Bonds with Transition Metals". I thank Dr. *Askani*, Karlsruhe, for directions for synthesis of semibullvalene, and BASF, Ludwigshafen, for supplies of materials.

[2] *R. Aumann*, Angew. Chem. *83*, 175 (1971); Angew. Chem. internat. Edit. *10*, 189 (1971).

[3] *R. Aumann*, Angew. Chem. *83*, 177 (1971); Angew. Chem. internat. Edit. *10*, 190 (1971).

[4] *R. Aumann*, Angew. Chem. *83*, 176 (1971); Angew. Chem. internat. Edit. *10*, 188 (1971).

[5] The compound melts at 133—135 °C; m.p. 123 °C was recorded in [3] in error.

[6] We interpret the observation that vinylcyclopropane systems afford cyclohexanone derivatives on irradiation with UV light in the presence of iron carbonyl [7] as due to primary formation of a vinylcyclopropane complex analogous to *(5)*, which under UV irradiation decomposes to a six-membered ring ketone with loss of the metal [8].

[7] *R. Victor, R. Ben-Shoshan*, and *S. Sarel*, Tetrahedron Lett. *49*, 4253 (1970).

[8] *E. Koerner von Gustorf* and *F. W. Grevels*, Fortschr. Chem. Forschung *13*, 366 (1969).

[9] *W. von E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin*, and *M. Saunders*, Tetrahedron *23*, 3943 (1967).

[10] *H. E. Zimmerman* and *G. L. Grunewald*, J. Amer. Chem. Soc. *88*, 183 (1966); *J. Meinwald* and *D. Schmidt, ibid. 91*, 5877 (1969); *H. E. Zimmerman, J. D. Robbins*, and *J. Schantl, ibid. 91*, 5878 (1969); *R. Askani*, Tetrahedron Lett. *1970*, 3349; *L. A. Paquette*, J. Amer. Chem. Soc. *92*, 5765 (1970).

[11] *W. Grimme*, personal communication; *G. E. Petrowski*, Dissertation, University of California, Los Angeles 1969; *M. Sakai* and *S. Winstein*, personal communication.

[12] Cf., *e.g. R. B. King*, J. Amer. Chem. Soc. *85*, 1918 (1963).

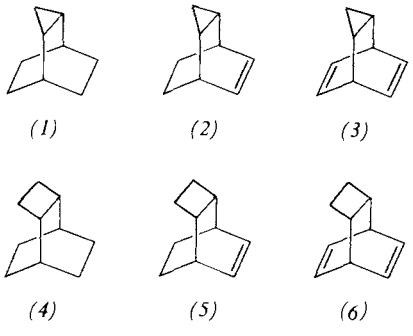
[13] *R. Aumann*, unpublished results.

[14] Note added in proof: In the meanwhile the structures of the complexes *(5a)* and *(7)* have been confirmed by Prof. *I. C. Paul*, Urbana, Ill. (USA) by X-ray crystallographic measurements.

Photoelectron Spectra of Unsaturated Systems Containing Cyclopropane and Cyclobutane Rings[1]

By *Peter Bruckmann* and *Martin Klessinger*[*]

Interaction of double bonds with the Walsh orbitals of cyclopropane depends mainly on the conformation. Thus *Heilbronner et al.*[2] showed from photoelectron spectra (PES) that the value $\beta_{\mu\nu}=\langle 2p_\mu|\mathfrak{H}|2p_\nu\rangle$ characteristic of this interaction is almost zero for *endo*-cyclopropanonorbornene, whereas for the *exo*-isomer with $\beta_{\mu\nu}=-0.3$ eV it has almost the same value as for interaction between non-conjugated double bonds of similar steric arrangement. In the present work we compare the PE spectra of *(1)*, *(2)*, and *(3)* with those of *(4)*, *(5)*, and *(6)*[3] in which the cyclopropane ring is replaced by a cyclobutane ring.



According to *Walsh*[5], the highest occupied degenerate orbital of cyclopropane (e' in D_{3h}) is built from pure p-orbitals; for cyclobutane, however, construction of symmetry orbitals according to D_{4h} leads, in addition to the occupied a_{1g} and b_{1u} orbitals, to a degenerate e_u orbital from pure p-AO's and a further e_u pair from sp^2 hybrid AO's[6], which to a first approximation are non-bonding and thus mix with one another. According to the coordinate system chosen, form (a) or (b) shown in Fig. 1 is obtained for the occupied e_u orbital.

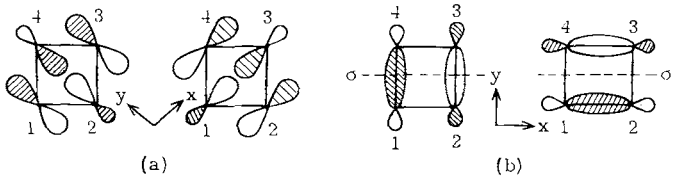


Fig. 1. The highest occupied orbitals of cyclobutane (e_u).

For symmetry reasons we use the orbitals (b), first given by *Salem*[7], which according to an INDO calculation[8] are given by the following linear combination of 2p- and 2s-AO's of the C-atoms μ and of 1s AO's h_μ and h'_μ of the H-atoms bonded to C_μ:

$$\phi(e_u)_S = 0.44\,(p_{y1}-p_{y2}+p_{y3}-p_{y4}) + 0.08\,(s_1-s_2-s_3+s_4) + 0.11\,(h_1+h'_1-h_2-h'_2-h_3-h'_3+h_4+h'_4)$$

(I)

$$\phi(e_u)_A = 0.44\,(p_{x1}-p_{x2}+p_{x3}-p_{x4}) + 0.08\,(s_1+s_2-s_3-s_4) + 0.11\,(h_1+h'_1+h_2+h'_2-h_3-h'_3-h_4-h'_4)$$

Experimental values and interpretation of the PE spectra[9] are listed in Table 1 and in Figs. 2 and 3. As in *exo*-cyclopropanonorbornene, so in *(2)* the π-MO (a') and the a' Walsh orbital repel each other mutually, whilst the a'' Walsh orbital has the same energy as in *(1)*. In *(3)* the a' Walsh orbital can interact only with that a' combination of the π-MO's, which corresponds to the b_1-π-MO in *(8)*, since in the other combination the interaction terms with the two double bonds have opposite signs and cancel each other. The second π-MO is thus hardly shifted relative to the a_1-π-MO in *(8)*. Quantitatively the behavior of *(2)* and *(3)* can be reproduced by a simple HMO calculation of the interaction, which affords the values given in parentheses in the Table. Here it is assumed that the cyclopropane orbitals are stabilized by 0.15 eV per double bond relative to *(1)*, and that $\beta_{\mu\nu}=-0.3$ eV for interaction between the a' Walsh orbital and the π-bond in *(2)* or the correspond-

Table 1. Vertical ionization potentials (in eV) of compounds *(1)*—*(6)* (calculated values in parentheses).

Orbital	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*
$\pi_1(a')$	—	8.8 (8.88)	8.6_5 (8.7)	—	9.0 (8.99)	8.8 (8.75)
$\pi_2(a')$	—	—	9.5 (9.4)	—	—	9.4_5 (9.50)
$e_S(a')$	9.3	9.5 (9.61)	9.8 (9.8)	9.4_5	9.5_5 (9.65)	9.8 (9.82)
$e_A(a'')$	10.0	10.0 (10.15)	10.1_5 (10.3)	9.9	9.9_5 (10.05)	10.3 (10.3)
$a_1(a')$	—	—	—	10.2	10.3	10.7
σ	10.4_5	10.5	11.3	10.8	11.3	11.5

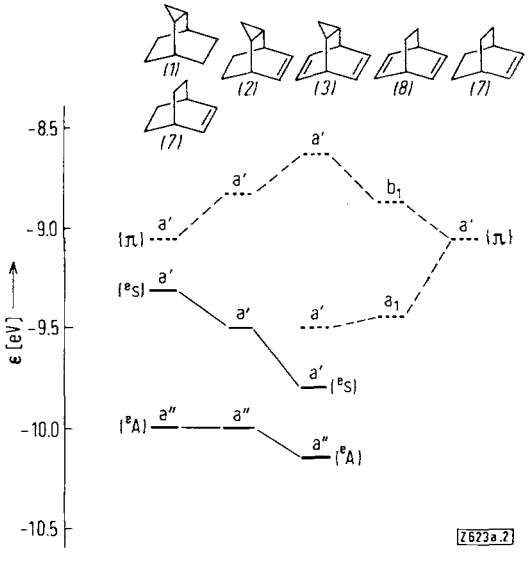


Fig. 2. Correlation diagram of compounds *(1)*—*(3)*.

[*] Dipl.-Chem. P. Bruckmann and Prof. Dr. M. Klessinger
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

ing π-bond in *(3)*, as for *exo*-cyclopropanonorbornene, whereas for interaction with the other π-bond in *(3)* $\beta_{\mu\nu}=0$, as for *endo*-cyclopropanonorbornene[10].

Assignment of the spectra of *(4)*, *(5)*, and *(6)* is simplified by a characteristic set of bands that corresponds to the two e_u orbitals and the a_1 orbital of cyclobutane[11]. As a result of substitution by two sp^3-centers, the center of the e_u orbitals is shifted by 1.7 eV from 11.35 in cyclobutane[11] to 9.65 eV in *(4)*. For the cyclopropane ring of *(1)* this effect is distinctly smaller, being 1.25 eV[2]. The correlation diagram for *(4)*, *(5)*, and *(6)* in Fig. 3 is very similar

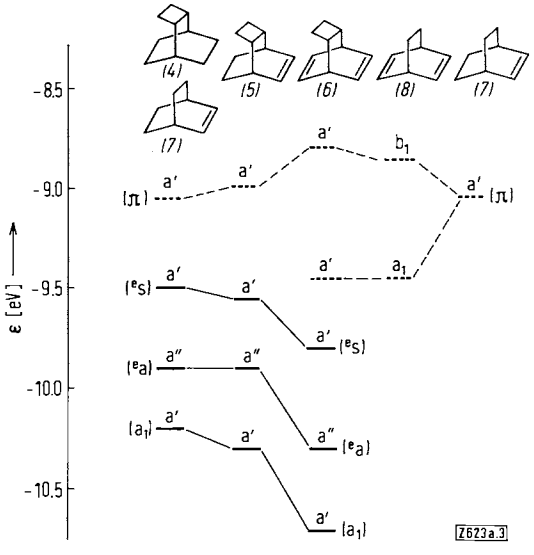


Fig. 3. Correlation diagram of compounds *(4)*—*(6)*.

to that in Fig. 2, but the interactions are smaller because of the reduced p-character of the cyclobutane orbitals; accordingly only the p-contribution of the cyclobutane orbitals given by eqn. (I) was considered in the HMO calculation of the interaction. Also, as for *(2)* and *(3)* it was taken that $\beta_{\mu\nu}=-0.3$ eV or $\beta_{\mu\nu}=0$ and it was assumed that the cyclobutane orbitals are stabilized by 0.15 eV per double bond with respect to *(4)*[10], which leads to good agreement with the experimental values.

The marked decrease in energy of the $a''(e_A)$ and the $a'(a_1)$ orbitals of the cyclobutane part on going from *(5)* to *(6)* is surprising. This may be due to the fact that the σ-contribution is greater than for cyclopropane, thus shifting these orbitals to lower energies on introduction of double bonds, similarly as for ordinary σ-orbitals.

Received: February 2, 1972 [Z 623a IE]
German version: Angew. Chem. *84*, 543 (1972)

[1] Photoelectron Spectra of Organic Compounds, Part 1.

[2] *P. Bischof, E. Heilbronner, H. Prinzbach*, and *H. D. Martin*, Helv. Chim. Acta *54*, 1072 (1971).

[3] The hydrocarbons *(1)*—*(6)* were prepared by anodic bisdecarboxylation of the appropriate maleic acid adducts [4] and were purified by preparative gas chromatography.

[4] *H. Westberg* and *H. Dauben*, Tetrahedron Lett. *1968*, 1523.

[5] *A. D. Walsh*, Nature *159*, 167, 172 (1947); Trans. Faraday Soc. *45*, 179 (1949).

[6] Since there is also a combination of CH orbitals with the same symmetry behavior, this MO contains a small contribution from H-1s AO's.

[7] *L. Salem* and *I. S. Wright*, J. Amer. Chem. Soc. *91*, 5947 (1969).

[8] *J. A. Pople, D. L. Beveridge*, and *P. A. Dobosh*, J. Chem. Phys. *47*, 2026 (1967).

[9] The measurements were made with a PS 16 spectrometer from Perkin-Elmer Ltd. (Beaconsfield, England). The accuracy is ±0.03 eV.

[10] The value $\varepsilon_\pi(a')=-9.05$ eV from *(7)* was used for the π-bonds in *(2)* and *(5)*, and the mean of the π-orbital energies of *(8)* $[\varepsilon_\pi(a_1)+\varepsilon_\pi(b_1)]/2=-9.16$ eV for the π-bonds of *(3)*.

[11] *P. Bischof, E. Haselbach*, and *E. Heilbronner*, Angew. Chem. *82*, 952 (1970); Angew. Chem. internat. Edit. *9*, 953 (1970).

Ionization Potentials of Substituted Benzenes[1]

By *Martin Klessinger*[*]

Within the HMO approximation simple perturbation calculations quite often lead to surprisingly good agreement between theory and experiment (cf. *Dewar*'s PMO method[2]). Another impressive example is provided by the removal of the degeneracy of the highest occupied benzene π-orbital (e_{1g}) under the inductive influence of substituents, which is directly measurable by photoelectron spectroscopy (PES).

Assuming that in the HMO approximation the effect of a substituent X on the π-electron system is given by a change $\delta\alpha_\mu(X)$ in the Coulomb integral α_μ of the substituted C atom μ, one obtains for the change of the orbital energy ε_i[2]

$$\delta\varepsilon_i = \sum_\mu c_{\mu i}^2 \delta\alpha_\mu(X) \qquad (1)$$

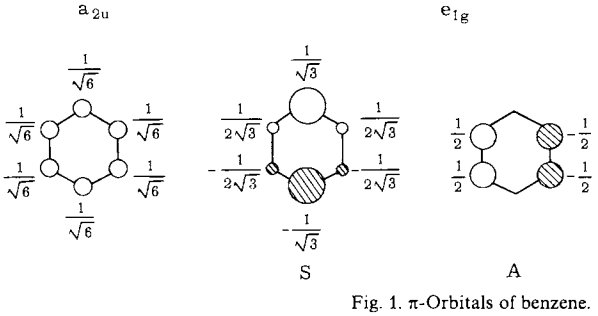


Fig. 1. π-Orbitals of benzene.

In Fig. 1 the occupied π-MO's $\Phi_i=\sum_\mu c_{\mu i}\varphi_\mu$ of benzene are shown diagrammatically; they belong to the irreducible representation A_{2u} and E_{1g} of the point group D_{6h} and have the orbital energies $\varepsilon(a_{2u})=\alpha+2\beta$ and $\varepsilon(e_{1g})\alpha+\beta$. According to *Koopmans*' theorem[3] the negative orbital energies are set equal to the vertical ionization potentials or the band maxima in the PE spectrum respectively:

$$-\varepsilon_i = I_v(i) \qquad (2)$$

In Fig. 2 the experimental PE spectra of some methyl- and fluoro-benzenes are compared with the negative orbital energies $-\varepsilon_i$ calculated according to eqn. (1) with the coefficients $c_{\mu i}$ shown in Fig. 1 and $\delta\alpha_\mu(CH_3)=+1.0$ eV and $\delta\alpha_\mu(F)=-1.2$ eV.

The almost quantitative agreement between HMO predictions and experiment, which is not limited to mono- and

[*] Prof. Dr. M. Klessinger
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

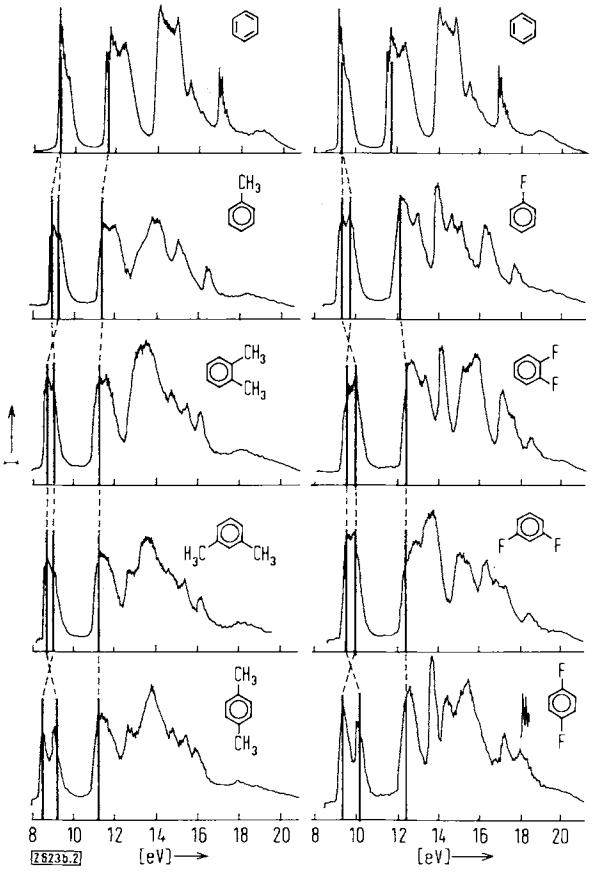


Fig. 2. PE spectra of methyl- and fluoro-benzenes, and correlation diagrams of the π-MO's derived from eqn. (1).

di-substituted benzene derivatives, can be further slightly improved by dividing the inductive effect of the substituents into the π-contribution given by eqn. (1) and a σ-contribution $\Delta I_\sigma(X)$ which is proportional to the number n of substituents[4].

This is made clear in Table 1 in which the experimental π-ionization potentials[5] are compared with the values calculated from the relation

$$I_v(i) = I_v(i)_{benzene} - \delta\varepsilon_i - n\Delta I_\sigma(X) \quad (3)$$

where $\delta\varepsilon_i$ is calculated from eqn. (1) with $\delta\alpha_\mu(CH_3) = 0.85$ eV and $\delta\alpha_\mu(F) = -1.10$ eV and the σ inductive effect is given by $\Delta I_\sigma(CH_3) = 0.05$ eV and $\Delta I_\sigma(F) = -0.10$ eV.

The fact that for $I_v(3)$ the same correlation exists in the HMO data as for $I_v(1)$ and $I_v(2)$ can be regarded as support for the assignment, proposed by *Turner et al.*[8], of these bands to an ionization from the lowest occupied π-MO (a_{2u})[9]. If eqn. (1) is valid for substituted polyenes in a way analogous to that for benzene derivatives, the two π-ionization potentials in fluorinated butadienes should be at higher energies than in unsubstituted butadienes. That, however, is not the case if, according to *Brundle* and *Robin*[10] $I_v(2) = 11.47$ eV is assigned to σ-ionization for butadiene, so that the bands $I_v(1) = 9.06$ eV and $I_v(3) = 12.23$ eV must correspond to π-ionizations, whereas in 1,1,4,4-tetrafluorobutadiene these π-ionizations are unambiguously correlated with $I_v(1) = 9.38$ eV and $I_v(2) = 12.04$ eV.

Further investigations of the influence of substituents on the PE spectra of aromatic and conjugated systems are in progress; the results reported here give hope that they will lead to more detailed information about the ordering of orbitals in benzene and similar systems.

Received: February 2, 1972 [Z 623b IE]
German version: Angew. Chem. *84*, 544 (1972)

Table 1. Vertical ionization potentials of substituted benzenes (calculated values in parentheses) [5].

Substitution	$I_v(1)$	$I_v(2)$	$I_v(3)$
X = CH_3			
— (D_{6h})	9.2_5 (—) e_{1g}	9.2_5 (—) e_{1g}	11.6 (—) a_{2u}
1- (C_{2v})	9.0 (8.92) b_1(S) [a]	9.3 (9.20) a_2(A)	11.4 (11.41) b_1
1,2- (C_{2v})	8.7_5 (8.73) b_1(A)	9.0 (9.01) a_2(S)	11.2_5 (11.22) b_1
1,3- (C_{2v})	8.7_5 (8.73) a_2(A)	9.0_5 (9.01) b_1(S)	11.2 (11.22) b_1
1,4- (D_{2h})	8.6 (8.58) b_{1g}(S)	9.1_5 (9.15) b_{3g}(A)	11.2_5 (11.22) b_{2u}
1,2,3- (C_{2v})	8.6 (8.68) a_2(A)	8.6 (8.68) b_1(S)	10.9_5 (11.03) b_1
1,2,4- (C_{1h})	8.5 (8.46) a″(A)	8.9_5 (8.89) a″(S)	11.0 (11.03) a″
1,3,5- (D_{3h})	8.6_5 (8.68) e″(A)	8.6_5 (8.68) e″(S)	11.0 (11.03) a_2''
1,2,3,5-(C_{2v})	8.3 (8.34) b_1(S)	8.6 (8.63) a_2(A)	10.9 (10.83) b_{1u}
X = F			
1- (C_{2v})	9.3_5 (9.35) a_2(A)	9.7_5 (9.72) b_1(S)	12.1_5 (11.88) b_1
1,2- (C_{2v})	9.6 (9.63) a_2(S)	9.9_5 (10.00) b_1(A)	12.4_5 (12.17) b_1
1,3- (C_{2v})	9.6 (9.63) b_1(S)	10.0 (10.00) a_2(A)	12.4_5 (12.17) b_1
1,4- (D_{2h})	9.4 (9.45) b_{3g}(A)	10.2 (10.19) b_{1g}(S)	12.6 (12.17) b_{2u}

[a] S and A denote the symmetry of those benzene MO's from which the MO of the stated symmetry derives.

[1] Photoelectron Spectra of Organic Compounds, Part 2. — Part 1: Angew. Chem. *84*, 544 (1972); Angew. Chem. internat. Edit. *11*, 524 (1972).

[2] *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.

[3] *T. Koopmans*, Physica *1*, 104 (1934).

[4] That corresponds approximately to the field effects α_S and α_E in the FCT theory of *M. Godfrey*, J. Chem. Soc. *B 1971*, 1534.

[5] The measurements were made with a PS 16 spectrometer from Perkin-Elmer Ltd. (Beaconsfield, England). Within the experimental error of ±0.03 eV the values agree with those quoted in the literature for mono- and *p*-di-substituted benzenes [6, 7].

[6] *A. D. Baker, D. P. May*, and *D. W. Turner*, J. Chem. Soc. *B 1968*, 22.

[7] *I. D. Clark* and *D. C. Frost*, J. Amer. Chem. Soc. *89*, 244 (1967), give adiabatic ionization potentials for some fluorobenzenes.

[8] *A. D. Baker, C. R. Brundle*, and *D. W. Turner*, Int. J. Mass. Spectrom. Ion. Phys. *1*, 327 (1968).

[9] For a literature review on assignments of the benzene spectrum see *S. D. Worley*, Chem. Rev. *71*, 295 (1971).

[10] *C. R. Brundle* and *M. B. Robin*, J. Amer. Chem. Soc. *92*, 5550 (1970).

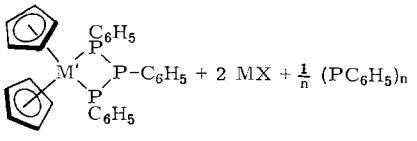
Bis(π-cyclopentadienyl)(1,2,3-triphenyltriphosphanato-P^1,P^3)-titanium and -zirconium[1]

By *Kurt Issleib, Grete Wille,* and *Frieder Krech*[*]

The treatment of 1,4-dialkali-1,2,3,4-tetraphenyltetraphosphanes with bis(π-cyclopentadienyl)-titanium or -zirconium dihalides leads, not as in the case of lithium dialkylphosphides[2] to compounds of the type $[(C_5H_5)_2MPR_2]_2$, but (contrary to statements by *H. Köpf*[3]) to bis(π-cyclopentadienyl)(1,2,3-triphenyltriphosphanato)-metal complexes *(1)* and *(2)*.

$$M_2P_4(C_6H_5)_4 + (C_5H_5)_2M'X_2 \rightarrow$$

M = Li, Na; X = Cl, Br



$$+ 2\,MX + \tfrac{1}{n}\,(PC_6H_5)_n$$

(1), M' = Ti

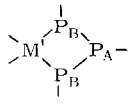
(2), M' = Zr

The four-membered metal-phosphorus ring structure of *(1)* and *(2)* is proved by determination of molecular masses and by ^{31}P-NMR data.

(1) forms dark violet and *(2)* orange crystals that are diamagnetic in the solid state and in solution [χ_g at 295 °K $= -0.60$ and $-0.62 \cdot 10^{-6}$ cm^3 g^{-1} for *(1)* and *(2)*, respectively]; in the solid state they are relatively stable to air, but in solution are readily oxidized, *(2)* more easily than *(1)*. The complexes dissolve as monomers in dioxane (cryoscopic by *Beckman*'s method), are readily soluble in THF, dioxane, benzene, or toluene but difficultly so in light petroleum or *n*-hexane, and decompose in water or alcohols.

The mass spectra (70 eV) of *(1)* show the molecular ion ($m/e = 502$) and, *inter alia*, fragments $(C_5H_5)_2M(PC_6H_5)_2^+$, $(PC_6H_5)_3^+$, $P(C_6H_5)_3^+$, $(PC_6H_5)_2^+$, $P(C_6H_5)_2^+$, $(C_5H_5)_2M^+$, $C_5H_5M^+$, and $C_6H_5^+$ ($m/e = 394$, 324, 262, 216, 185, 178, 113, 77), M = Ti.

The ^{31}P-NMR spectra of *(1)* and *(2)* (in THF, 85% H_3PO_4 as external standard) are of AX_2 type, as the Table shows.



	δ (ppm)	J_{PP} (Hz)
(1)	$P_A = +180.9 \pm 1$ $P_B = -184.9 \pm 1$	323.0 ± 10
(2)	$P_A = -181.4 \pm 1$ $P_B = -\ 90.7 \pm 1$	338.5 ± 10

The lower chemical shift δP_B of *(1)* than of *(2)* is to be ascribed to a larger electron delocalization $P_B \rightarrow Ti^{IV}$, which accords with the easier reducibility of $(C_5H_5)_2Ti^{2+}$.

(1) and *(2)* were characterized by degradative reactions in dioxane with ethereal HCl and iodine; the decomposition is instantaneous, with a color change from violet to red or from orange to colorless:

$$(1),\,(2) + 2\,HCl \rightarrow (C_5H_5)_2M'Cl_2 + C_6H_5PH_2 + \tfrac{2}{n}(PC_6H_5)_n$$

The metal:phosphorus ratio can be determined by treatment with iodine, hydrolysis of the oxidation product, $C_6H_5PI_4$, and back-titration of the iodine.

$$(1),\,(2) + 7I_2 \rightarrow (C_5H_5)_2M'I_2 + 3C_6H_5PI_4$$

Experimental

$(C_5H_5)_2TiCl_2$ or $(C_5H_5)_2ZrBr_2$ in dioxane is added dropwise during 30 min to a hot suspension of an equimolar amount of $Na_2P_4(C_6H_5)_4 \cdot 6$ Dioxane, $Li_2P_4(C_6H_5)_4 \cdot 4$ Dioxane, $Na_2P_3(C_6H_5)_3 \cdot 2$ Dioxane or $K_2(PC_6H_5)_3 \cdot 2$ THF in dioxane. There is an immediate color change to dark violet or orange, respectively. The reaction mixture is boiled under reflux for 30 min, then freed from solvent in a vacuum. The residue is treated with toluene. After separation of the alkali halide on a G4 frit, the solution is concentrated to about 10 ml, then kept in a refrigerator, whereupon *(1)* or *(2)* crystallizes. The crystals are filtered off, washed twice with ether and dried in a vacuum. M.p. under argon 243—245 °C for *(1)* and 233—235 °C for *(2)*; yield 43—60% according to the batch. All manipulation is done under argon. The amount of solvent is suited to the ratio and amounts of the components. Example: $Na_2P_4(C_6H_5)_4 \cdot 6$ Dioxane 12.1 g in 80 ml dioxane, $(C_5H_5)_2TiCl_2$ 3 g in 100 ml dioxane and 80 ml toluene. In this case $(C_6H_5P)_n$ is isolated from the filtrate after concentration.

Received: February 29, 1972 [Z 624 IE]
German version: Angew. Chem. *84*, 582 (1972)

[1] Alkali-Phosphorus Compounds and Their Reactions, Part 66.—Part 65: *K. Issleib* and *F. Krech*, Z. Anorg. Allg. Chem. *385*, 47 (1971).

[2] *K. Issleib* and *H. Häckert*, Z. Naturforsch. *21b*, 519 (1966).

[3] *H. Köpf*, Angew. Chem. *83*, 914 (1971); Angew. Chem. internat. Edit. *10*, 840 (1971).

[*] Prof. Dr. K. Issleib, Dr. G. Wille, and Dr. F. Krech
Sektion Chemie der Universität
DDR-402 Halle, Weinbergweg

Cationic γ-Oxo-isocyano Complexes of Iron, Ruthenium, and Osmium(II)[1]

By *Matthias Schaal* and *Wolfgang Beck*[*]

Alkylation of cyano complexes, leading to isocyanide compounds, has long been known[2]. In an attempt to prepare isocyano complexes by treating potassium hexacyanoferrate(II) with oxonium salts in acetone, we found new, hexacoordinated, cationic cyano complexes in which a keto group was in position 3 relative to the isocyanide group. Analogous ruthenium and osmium complexes are formed similarly in good yields (*ca.* 80%). These complexes are apparently formed by acid-catalyzed aldol addition of the acetone, in which it can be assumed that the carbonium ion of the dimeric acetone is trapped by nucleophilic attack of the coordinated cyano ligand. In fact, the iron(II) complex *(1)* is obtained in almost quantitative yield also from diacetone alcohol or mesityl oxide and

[*] Prof. Dr. W. Beck and Dipl.-Chem. M. Schaal
Institut für Anorganische Chemie der Universität
8 München 2, Meiserstrasse 1 (Germany)

$$[M(CN)_6]^{4-} + 12\ CH_3\text{-}CO\text{-}CH_3 + 6\ R_3O^+BF_4^- \xrightarrow[(CH_3)_2CO]{20\,^\circ C}$$

$$[M(C{\equiv}N\text{-}C(CH_3)_2\text{-}CH_2\text{-}CO\text{-}CH_3)_6]^{2+}(BF_4^-)_2 + 4\ BF_4^- + 6\ R_2O + 6\ ROH$$

(1)

M = Fe^{II}, Ru^{II}, Os^{II}; R = C_2H_5, n-C_3H_7)

$K_4[Fe(CN)_6]$ (or $K_3[Fe(CN)_6]$) with 35% aqueous HBF_4 solution.

The structure of the complexes follows from the IR and ^{1}H-NMR data (Tables 1 and 2). Only one νCN band of the isocyanide ligands appears in the IR spectrum; the keto absorption corresponds in its position to that of the saturated ketone. The ^{1}H-NMR spectrum of the complexes, like that of diacetone alcohol, shows three singlets with the intensity ratio 6[$C(CH_3)_2$]:2[CH_2]:3[—OC—CH_3].

Table 1. ^{1}H-NMR spectra of the γ-oxo-isocyano complexes (solutions in CH_2Cl_2 with TMS as internal standard).

M(II)	$\tau_{C(CH_3)_2}$	τ_{CH_2}	τ_{-OC-CH_3}
Fe	8.38	6.97	7.82
Ru	8.42	6.98	7.81
Os	8.40	6.97	7.82

Table 2. IR absorptions (cm^{-1}) of the γ-oxo-isocyano complexes (solid, in KBr).

M(II)	νC≡N	νC=O	νBF_4	M. p. (°C)
Fe	2215	1725	1058	149
Ru	2214	1720	1055	133
Os	2206	1718	1053	136–137

The keto group of the isocyanide ligand shows typical carbonyl reactions, *e.g.* with 2,4-dinitrophenylhydrazine it gives a hydrazone derivative.

Analogous reactions of cyano complexes can be effected with other organic carbonyl compounds. Thus iron(II) complexes were obtained by treating $K_4[Fe(CN)_6]$ with ethyl methyl ketone *(2a)*, cyclohexanone *(2b)* or acetophenone *(3)* in the presence of an oxonium salt. In the case of acetophenone only five cyano ligands were alkylated *(3)*.

$$[Fe(C{\equiv}N\text{-}C(R^1R^2)\text{-}CHR^3\text{-}CO\text{-}R^4)_6]^{2+}(BF_4^-)_2$$

(2a) $R^1 = CH_3$; $R^3 = H$; $R^2 = R^4 = C_2H_5$

(2b) R^1, $R^2 = -(CH_2)_5-$; R^3, $R^4 = -(CH_2)_4-$

$$[Fe(C{\equiv}N\text{-}C(CH_3)(C_6H_5)\text{-}CH_2\text{-}CO\text{-}C_6H_5)_5CN]^+(BF_4)^-$$

(3)

Experimental

Triethyloxonium tetrafluoroborate (5.7 g, 30 mmol) is added in small portions with stirring to a suspension of $K_4[Mn(CN)_6]$ (M = Fe, Ru or Os) (3 mol) in a ketone. Stirring is continued at room temperature until $[M(CN)_6]^{4-}$ ions are no longer detectable. The solution is then filtered and the residue is washed with much methylene chloride. The complex is carefully precipitated from the filtrate by light petroleum. Purification is by recrystallization from CH_2Cl_2 or $CHCl_3$, giving colorless crystals.

Received: March 6, 1972 [Z 625 IE]
German version: Angew. Chem. *84*, 584 (1972)

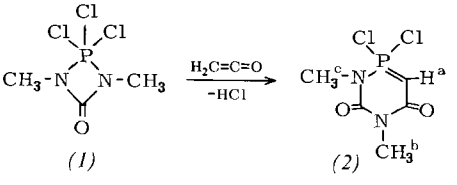
[1] Part 37 of Pseudohalogen-Metal Compounds. — Part 36: *B. Kreutzer, P. Kreutzer,* and *W. Beck,* Z. Naturforsch. *27b*, 461 (1972).

[2] *L. Malatesta* and *F. Bonati:* Isocyanide Complexes of Metals. Wiley, London 1969; *I. Ugi:* Isonitrile Chemistry. Academic Press, New York 1971.

Synthesis of 2,2-Dichloro-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydro-1,5,2λ^5-diazaphosphorine

By *N. Singh* and *H. P. Latscha*[*]

In previous work we expanded the four-membered ring system of compound *(1)*[1] to a six-membered ring system by treatment with isocyanate derivatives[2]. We have now achieved an analogous ring expansion by means of ketene. A variety of products is obtained according to the reaction conditions[3]. At −20 to −25 °C a compound is formed to which we assign the structure 2,2-dichloro-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydro-1,5,2λ^5-diazaphosphorine *(2)* on the basis of its molar mass (228, mass spectrometry) and ^{1}H-NMR spectrum [in $CDCl_3$, δ = 5.77 (H^a, J_{HP} = 7.0 Hz), 3.55 (H^b), 3.25 ppm (H^c, J_{HP} = 7.5 Hz)]. *(2)* represents one of the limiting formulas whose various contributions cannot be estimated.



(1) *(2)*

The new compound throws some light on the ylene-ylide problem since the hydrogen of its methine group is firmly attached and therefore gives a split signal in the ^{1}H-NMR spectrum (cf. Ref. [4]).

(2) exists as a yellow powder or yellowish-brown crystals, is moderately sensitive to hydrolysis, and decomposes between 98 and 106 °C. It dissolves in, *e.g.* chloroform, methylene chloride, 1,2-dichloroethane, or tetrachloroethane; it is insoluble in, *e.g.* ether, light petroleum, or carbon tetrachloride. The results of elemental analysis and the IR spectrum accord with the assigned structure.

Experimental:

Ketene, completely freed from acetone, is passed into an ethereal solution of *(1)*[1] at −20 to −25 °C until the solution is yellow and viscous; the reaction can be followed by disappearance of the signal of *(1)* from the ^{31}P-NMR spectrum. The reaction time and the yield depend on the amount of ketene that can be made to react with *(1)*. The ketene generator that we used delivered *ca.* 40 g per hour (from acetone). The ketene was passed into the solution as gas through the stirrer plate of a vibro mixer. With this arrange-

[*] N. Singh, M. Sc. and Doz. Dr. H. P. Latscha
Institut für Anorganische Chemie der Universität
69 Heidelberg, Im Neuenheimer Feld 7 (Germany)

ment the average reaction time was 5 h and the yield of *(2)* was *ca.* 5 g from a 0.2 molar batch.

(2) can be freed from by-products by digestion of the viscous reaction mixture with warm benzene; about half of the mixture dissolves. If the filtrate is concentrated to one-third volume, analytically pure yellowish-brown crystals separate within a few days. If these are dissolved in, *e.g.* chloroform, and then precipitated by ether, the product, when dry, forms a yellow powder.

Received: March 16, 1972 [Z 626 IE]
German version: Angew. Chem. *84*, 585 (1972)

[1] *H. Ulrich* and *A. A. R. Sayigh*, Angew. Chem. *76*, 647 (1964); Angew. Chem. internat. Edit. *3*, 585 (1964).

[2] *H. P. Latscha*, Z. Anorg. Allg. Chem. *346*, 166 (1966); *P. B. Hormuth* and *H. P. Latscha*, *ibid. 365*, 26 (1969); *369*, 59 (1969); *H. P. Latscha* and *W. Klein*, Angew. Chem. *81*, 291 (1969); Angew. Chem. internat. Edit. *8*, 278 (1969).

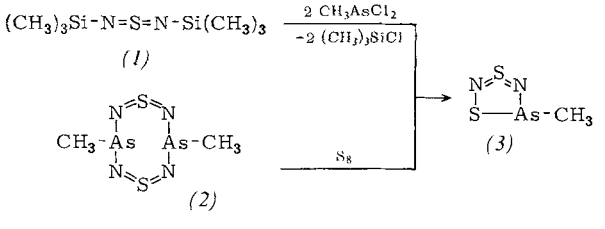
[3] *N. Singh*, Dissertation, Universität Heidelberg 1972.

[4] *L. Siekmann*, *H. O. Hoppen*, and *R. Appel*, Z. Naturforsch. *23b*, 1156 (1968).

$CH_3AsS_2N_2$, a Five-membered Arsenic-Sulfur-Nitrogen Ring

By *Otto J. Scherer* and *Reinhard Wies*[*]

If sulfur bis[(trimethylsilyl)imide] *(1)* is treated with dichloro(methyl)arsane in the molar ratio 1:2, and not as before in the molar ratio 1:1[1], a poor yield is obtained of 3-methyl-1,4-dithia-2,5-diazaarsole *(3)*. The same compound is formed in minimal yield if *(2)* is treated with S_8 in absence of a solvent.



The product can be regarded as an arsenic analog of S_3N_2, the still missing member of the series of sulfur nitrides, S_4N_4[2a], S_4N_2[2a,b], and S_2N_2[2a]. It is a wine-red liquid that is readily hydrolyzed, extremely volatile, and readily soluble in ether or benzene, moderately so in carbon tetrachloride, but incompletely in pentane. It can be distilled without decomposition at 33—35 °C/0.05 torr and solidifies to a glass at low temperature. One hour's warming at 100 °C leads to irreversible darkening but not to decomposition.

Compound *(3)* was characterized by complete elemental analysis, cryoscopic determination of molecular weight (in benzene: found 187, calc. 182) as well as by ^{1}H-NMR, mass, IR, and UV spectra. ^{1}H-NMR (60 MHz; 10% CCl_4 solution; TMS ext.): $\delta(CH_3As) = -72.0$ Hz (s). Mass spectrum (70 eV)[3]: $m/e = 182$ (molecular ion, 43), 167 (AsN_2S_2, 100), 136 (22), 121 (21), 107 (16), 104 (2), 90 (10), 89 (8), 88 (5), 78 (5), 46 (8); none of the other fragments has a relative intensity of >1. IR (capillary film between KBr plates): we assign bands at 1050 and 930 cm^{-1} provisionally to the NSN system. UV (in CCl_4), $\lambda_{max} = 261$ ($\varepsilon = 2680$), 300 (860), 432 (1610).

Experimental

Dichloro(methyl)arsane (18.6 g, 116 mmol) is added to sulfur bis[(trimethylsilyl)imide] (12.0 g, 58 mmol) under nitrogen at room temperature. The original yellow color changes to wine-red within a short time without noticeable alteration in temperature. Chloro(trimethyl)silane, which separates as an upper layer, is distilled off in 2 h at atmospheric pressure (external temperature 80—85 °C). The residue is then fractionally distilled at oil-pump vacuum; b.p. 40—95 °C/2 torr (bath temperature up to *ca.* 130 °C). Redistillation gives a liquid of b.p. 33—35 °C/0.05 torr (2.2 g, 21% calculated on the imide used). As residue remains a voluminous foam of a still unidentified solid substance.

Received: March 23, 1972 [Z 627 IE]
German version: Angew. Chem. *84*, 585 (1972)

[1] *O. J. Scherer* and *R. Wies*, Angew. Chem. *83*, 882 (1971); Angew. Chem. internat. Edit. *10*, 812 (1971).

[2] a) *E.g., M. Goehring*: Ergebnisse und Probleme der Chemie der Schwefelstickstoffverbindungen. Akademie Verlag, Berlin 1957; b) *J. Nelson* and *H. G. Heal*, J. Chem. Soc. *A 1971*, 136.

[3] We thank *N. Pelz* for the measurement.

A Rapid Method for Determination of the Optical Purity of Amino Acids[**]

By *Wolfgang Parr* and *Patrick Y. Howard*[*]

Determination of small amounts of D-amino acids in the presence of a large excess of L-isomers (or *vice versa*) is still one of the most difficult exercises in analytical chemistry. However, since *Corrigan*[1] recently proved the widespread occurrence of D-amino acids in nature, a method for rapid and reliable determination of these "unnatural" amino acids is highly desirable.

We showed earlier that enantiomeric amino acids could be separated as TFA-amino acid isopropyl esters (TFA = trifluoroacetyl) by gas chromatography on optically active stationary phases[2, 3], but overlapping then occurred, *e.g.* of D-serine and L-leucine.

On the basis of our theoretical investigations of the diastereomeric association complex[4–6] responsible for the separation of chiral amino acids, we have synthesized a new, optically active, stationary dipeptide phase—cyclohexyl *N*-TFA-L-α-aminobutyryl-L-α-aminobutyrate.

First, the two necessary derivatives [*N*-Boc-L-α-aminobutyric acid (Boc = *tert*-butyloxycarbonyl) and cyclohexyl L-α-aminobutyrate hydrochloride] were prepared from L-α-aminobutyric acid. The peptide bond was formed by use of dicyclohexylcarbodiimide in presence of 1-hydroxybenzotriazole[7]. After removal of the Boc group with 5N HCl in dioxane the dipeptide was acylated with tri-

[*] Prof. Dr. O. J. Scherer and Dr. R. Wies
Universität Trier-Kaiserslautern, presently at
Institut für Anorganische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[*] Prof. Dr. W. Parr and Dr. P. Y. Howard [***]
Chemistry Department, University of Houston
Houston, Texas 77004 (USA)

[**] This work was supported by the National Science Foundation.

[***] Present address: Texas Research Institute for Mental Sciences, Houston, Texas 77004 (USA).

fluoroacetic anhydride. The new phase was then crystallized as white needles (yield 79%; m.p. 110—112°C; elemental analysis, calc.: C 52.45, H 6.88, N 7.59, F 15.56; found: C 52.44, H 6.90, N 7.62, F 15.66; homogeneous on thin-layer chromatography with various solvents and on gas chromatography-mass spectrometry on an SE-30 column).

The gas-chromatographic investigations with the new stationary phase were carried out on a Varian 1200-1 gas chromatograph equipped with an FID detector, modified for capillary columns. A stainless steel capillary column (122 m × 0.508 mm) was coated with a 10% solution of cyclohexyl *N*-TFA-L-α-aminobutyryl-L-α-aminobutyrate in methylene chloride and conditioned in the usual way[2, 3]. At 120°C with a carrier gas (He) pressure of 1.76 kp/cm², enantiomeric mixtures of the isopropyl esters of the TFA derivatives of D,L-alanine, D,L-valine, D,L-threonine, D,L-isoleucine, D,L-leucine, D,L-serine, D,L-proline, and D,L-aspartic acid could be completely separated, but glycine and L-threonine were not wholly separable. This resolution was achieved, however, at 110°C (Fig. 1). Separation of the higher-boiling isopropyl esters of *N*-TFA-amino acid esters on a 30 m capillary column has been previously described by us[2].

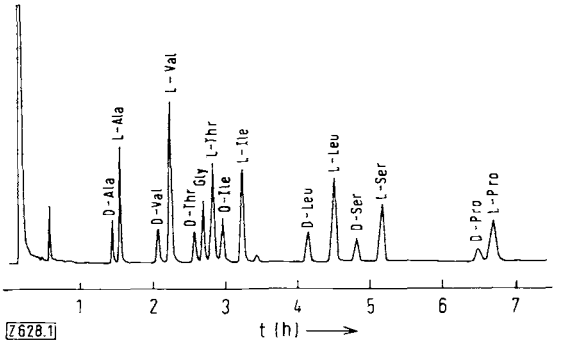


Fig. 1. Chromatogram of isopropyl esters of TFA-amino acids on cyclohexyl *N*-TFA-L-α-aminobutyryl-L-α-aminobutyrate as the stationary phase. Chromatographic conditions: 122 m × 0.508 mm capillary column 110°C isothermal; entry block 190°C, detector temperature 290°C; carrier gas helium at 1.76 kp/cm².

With this new, optically active, stationary phase the more volatile amino acid derivatives can now be separated unambiguously from one another. In this way, 16 of the naturally occurring amino acids can be investigated relatively rapidly (6 h) and with great precision (1%) to a limiting detection range of 0.1%. Since, unlike the separation of diastereomers on *optically inactive* stationary phases, nonasymmetric reagents were used for derivatization of the amino acids and correction of the results for antipodic impurities is unnecessary.

Received: March 23, 1972 [Z 628 IE]
German version: Angew. Chem. *84*, 586 (1972)

[1] *J. J. Corrigan*, Science *164*, 142 (1969).
[2] *W. Parr, J. Pleterski, C. Yang*, and *E. Bayer*, J. Chromatogr. Sci. *9*, 141 (1971).
[3] *W. Parr* and *P. Y. Howard*, Chromatographia *4*, 162 (1971).
[4] *K. Grohmann* and *W. Parr*, Chromatographia *5*, 18 (1972).
[5] *W. Parr* and *P. Y. Howard*, J. Chromatogr. *67*, 227 (1972).
[6] *P. Y. Howard*, Dissertation, University of Houston 1971.
[7] *W. König* and *R. Geiger*, Chem. Ber. *103*, 788 (1970).

Phase Transfer Catalysis in the Hofmann Carbylamine Reaction[**]

By *William P. Weber, George W. Gokel*, and *Ivar K. Ugi*[*]

The Hofmann carbylamine synthesis[1] is one of the two classical methods for the preparation of isocyanides *(1)*[1-3] but has never enjoyed popularity because of low yields and experimental difficulties.

$$R{-}NH_2 \xrightarrow[\text{Base}]{CHX_3} R{-}N{\equiv}C \qquad (1)$$

The many procedural modifications proposed over the years have not improved the method substantially[3]. The one case where very high yields are reported[4] appears non-reproducible[5].

We wish to report a carbylamine synthesis utilizing the phase transfer catalysis method[6] of generating dihalocarbene from chloroform or bromoform and 50% aqueous sodium hydroxide which constitutes a very effective and convenient method for the direct one-step conversion of a primary amine into the corresponding isocyanide. In particular, we have applied this method to the synthesis of methyl and ethyl isocyanides utilizing commercially available aqueous amine solutions.

In comparable cases the overall yields of the present method are only slightly less than those of the phosgene method, which has been the method of choice for preparation of isocyanides[7]. Since the phase transfer carbylamine reaction is a one-step method *versus* the two-step phosgene method it may be preferable in many cases.

We have employed two basic procedures: one applies to low boiling amines, *e.g.*, methyl and ethyl (Procedure A), and the second to the higher boiling amines (Procedure B). Procedure A utilizes aqueous amine solutions and solid sodium hydroxide and because of the low boiling point of methyl and ethyl isocyanides, bromoform is used as the

Table 1. Preparation of isocyanides by the phase transfer carbylamine reaction.

Isocyanide	Yield (%) [a]	Method
Methyl	24	A
Methyl	50	B [b]
Ethyl	47	A
n-Butyl	60	B
n-Dodecyl	41	B
Cyclohexyl	48	B
tert-Butyl	50	B [10]
Phenyl	57	B
α-Naphthyl	20	B
Benzyl	40	B

[a] Based on bromoform or chloroform.
[b] Contamined by chloroform.

[*] Prof. Dr. W. P. Weber, Dr. G. W. Gokel, and Prof. Dr. I. K. Ugi [***]
Department of Chemistry, University of Southern California
Los Angeles, California 90007 (USA)

[**] This research was partially supported by the Caltech President's Fund and NASA Contract NAS 7—100. A Biomedical Sciences Support Grant FR-07012-04 from the National Institutes of Health is also gratefully acknowledged.

[***] New address: Laboratorium für Organische Chemie der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

carbene source [residual chloroform can be separated from the product only by very careful fractionation (*e.g.*, spinning band)] instead of chloroform which is used in method B. The isocyanides prepared by the phase transfer carbylamine reaction are listed in Table 1.

Caution: All isocyanide preparations should be conducted in a fume hood.

Procedure A[8]:

A 500-ml flask equipped with a magnetic stirring bar and dry ice-acetone reflux condenser is charged with 33% aqueous ethylamine solution (40 ml), water (12 ml), benzyltriethylammonium chloride (0.6 g), sodium hydroxide (35 g), and finally bromoform (50.3 g, 0.2 mol). The mixture is stirred overnight at 20 °C and then distilled directly. The distillate contains ethylamine, water, and ethyl isocyanide. Drying over KOH pellets followed by distillation gives pure ethyl isocyanide, 5.2 g (47% based on bromoform), b. p. 65 °C.

Procedure B:

Aniline (18.6 g, 0.2 mol) is allowed to react with 50% aqueous sodium hydroxide (60 ml), chloroform (16 ml, 0.2 mol), and benzyltriethylammonium chloride (0.5 g) in dichloromethane (50 ml). After a short induction period (≈10 min), the flask warms and dichloromethane reflux maintains the reaction temperature close to 40 °C. After the exothermic reaction subsides, the reaction is stirred for an additional hour and then diluted with water (200 ml)[9]. The organic phase is separated off, washed with water and brine, and dried over K_2CO_3. Distillation affords 11.7 g (57% based on starting amine) of phenyl isocyanide b. p. 52—53 °C/12 torr.

Received: March 27, 1972 [Z 629 IE]
German version: Angew. Chem. *84*, 587 (1972)

[1] *A. W. Hofmann*, C. R. Acad. Sci. Paris *65*, 484 (1867); Liebigs Ann. Chem. *144*, 114 (1867); *146*, 107 (1868); Ann. Chim. (Paris) [4], *17*, 210 (1869); Chem. Ber. *3*, 766 (1870).

[2] *A. Gautier*, Liebigs Ann. Chem. *142*, 289 (1867).

[3] See: *P. Hoffmann, G. Gokel, D. Marquarding*, and *I. Ugi* in *I. Ugi*: Isonitrile Chemistry. Academic Press, New York 1971, p. 9.

[4] *L. Malatesta*, Gazz. Chim. Ital. *77*, 238 (1947).

[5] *R. H. Baker* and *D. Stanonis*, J. Amer. Chem. Soc. *73*, 699 (1951).

[6] *M. Makosza* and *M. Wawrzyniewicz*, Tetrahedron Lett. *1969*, 4659; *C. M. Starks*, J. Amer. Chem. Soc. *93*, 195 (1971).

[7] *I. Ugi, U. Eholzer, H. Knupfer*, and *K. Offermann*, Angew. Chem. *77*, 492 (1965); Angew. Chem. internat. Edit. *4*, 472 (1965).

[8] 25 ml of *o*-dichlorobenzene may be added as co-solvent.

[9] Residual amine may be removed by washing with phosphate buffer (pH 4—5).

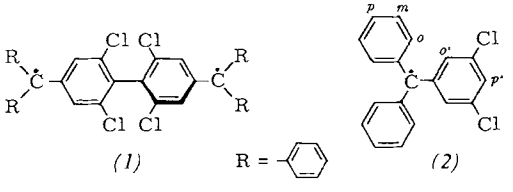
[10] In the case of *tert*-butylamine a 2:1 ratio of amine to chloroform was used.

ESR Measurements for the 2,2',6,6'-Tetrachloro Derivative of Chichibabin's Hydrocarbon[**]

By *Rolf Sartorius* and *Hans-Dieter Brauer*[*]

The tetrachloro derivative *(1)* of *Chichibabin*'s hydrocarbon[11] is considered to be a typical diradical[2]. This is based on the assumption that the two phenyl rings of the central biphenyl system are twisted under the influence of the four chlorine atoms in *ortho*-positions to make an angle of *ca.* 90°, and that the halves of the molecule thus present two independent radical centers of trityl type. If the two halves of the molecule are exactly perpendicular, theory requires their complete optical and magnetic independence; according to *Seel*'s quantum-theoretical calculations[3], the lowest singlet and triplet states are degenerate for such a conformation of *(1)*.

There has not yet been an unambiguous proof of this interpretation. Investigation of *(1)* is difficult because of its association which leads, *inter alia*, to the formation of open-chain dimeric or oligomeric diradicals[1,4]. Thus, for instance, *Gouy*'s method cannot be used to decide whether the monomers of *(1)* are really true diradicals. Examination of space-filling models, however, does not exclude the possibility that the two halves of the molecule *(1)* may make an angle of $<90°$ to one another; in that case the lowest singlet and triplet states would no longer have the same energy, so that a singlet state must also be considered for the ground state of monomeric *(1)*. To obtain more precise information we have carried out ESR measurements for *(1)* in both the solid state and in solution. For comparison, the monoradical *(2)* was also investigated by this method. Both compounds were prepared by the method described by *Müller* and *Neuhoff*[1].



(1) *(2)*

In the ESR spectrum of solid *(1)* a very intense doublet signal was observed at $H_0 = 3400$ G ($g = 2.0028$), probably due mainly to dimeric or oligomeric diradicals. In the half-field region, at $H_{min} = 1699$ G, a further signal of lower intensity was found that could be caused by either intra- or inter-molecular spin-spin coupling[5].

To clarify this, we studied dilute, glassy, solidified solutions of *(1)* in toluene. To suppress association as far as possible, the solutions (10^{-2} M, calc. on monomers) were first warmed to 60 °C and then rapidly cooled in liquid nitrogen. Fig. 1 shows an ESR spectrum of *(1)* measured at −120 °C. This contains, besides an intense doublet, several ($\Delta m = 1$) signals characteristic of molecules in the triplet state. The resonance field strength H_{min} of the outermost weak transition with $\Delta m = 2$ could not be measured under the conditions used. We ascribe the triplet spectrum found in the high-field region to monomeric *(1)*. This assignment is supported by the observation that the ESR spectrum of the monoradical *(2)*, measured under the same conditions, consists only of a doublet signal; intermolecular spin-spin coupling leading to formation of triplet systems can thus be excluded as the cause of the triplet spectrum observed for *(1)*. The zero-field splitting parameters calculated from the ($\Delta m = 1$) signals[6], have the values: $|D| = 0.0072$, $|E| \leq 0.0003\ cm^{-1}$.

In the region −150 to −110 °C the intensity of the ($\Delta m = 1$) signal increases with increasing temperature; the temperature-dependence of the signal amplitudes leads, by the known relation[7], to a triplet-singlet splitting of $\Delta E = 1.0 \pm 0.3$ kcal/mol.

[*] Prof. Dr. H.-D. Brauer and Dipl.-Chem. R. Sartorius
Institut für Physikalische Chemie der Universität
6 Frankfurt 1, Robert-Mayer-Strasse 11 (Germany)

[**] We are grateful to the Deutsche Forschungsgemeinschaft for financial support of this work.

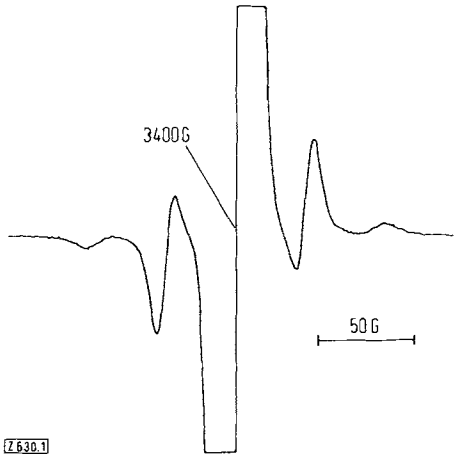


Fig. 1. ESR spectrum of 3,3',5,5'-tetrachloro-4,4'-bi(β,α'-diphenylbenzyl) *(1)* in glassy solidified toluene at −120°C.

The proved existence of monomeric triplet molecules indicates a clear magnetic interaction between the halves of the molecules *(1)*. This applies also to optical considerations, as can be derived from a comparison of the electron spectra of *(1)* and *(2)*: unlike *o,o'*-tetrasubstituted biphenyl derivatives, whose absorption spectra contain a maximum at almost the same wavelength as for the corresponding halved benzene derivatives[8, 9], the longest-wave absorption band ($\lambda_{max}=592$ nm) of *(1)* is found to be shifted by 65 nm to longer wavelengths in comparison with *(2)* ($\lambda_{max}=527$ nm). Whereas for biphenyl derivatives it is assumed that the two halves of the molecule are twisted to provide an angle of substantially 90°, there is for *(1)* evidently an increased tendency for the two halves of the molecule to become as nearly coplanar as possible, which may be derived from the concomitant, comparatively large increase in mesomerism energy.

The ESR spectra of compounds *(1)* and *(2)* in benzene at room temperature contain signals with clearly defined hyperfine structure. The HFS spectrum of *(1)* consists of *ca.* nineteen lines with individual line widths of about 550 mG. Appreciably more lines are found in the HFS spectrum of *(2)*, where the width of a single line is about 120 mG. From the line broadening that occurs on transition from the single-spin system *(2)* to the two-spin system *(1)* it can be concluded that there is considerable dipole-dipole coupling between the unpaired electrons in the two-spin system. It is not possible to make any unambiguous statement about the nature of the species causing the HFS spectrum of *(1)* because the spectrum could not be analyzed. The spectrum of *(2)* could, however, be analyzed: the coupling constants a^H have the following values: $a^H(p')=3.08$, $a^H(o')=2.78$ or 2.76, $a^H(p)=2.76$ or 2.78, $a^H(m)=1.15$ and $a^H(o)=2.54$ G.

From the results of our measurements it can be concluded that *(1)* is not a true diradical. Rather, there is considerable interaction between the two halves of the molecule in the equilibrium conformation of *(1)*, a fact evidently explicable by their twisting through an angle of $<90°$. The ground state of the equilibrium conformation is a singlet state lying about 1 kcal/mol below the lowest corresponding triplet state. However, the present results do not exclude the possibility that at medium temperatures there are diradicals (*i.e.* conformations with a torsion angle of $\approx 90°$) among the monomers in *(1)* which might be considered as the cause of the ESR hyperfine-structure spectrum.

Received: January 4, 1972 [Z 630 IE]
revised: January 28
German version: Angew. Chem. *84*, 546 (1972)

[1] *E. Müller* and *H. Neuhoff*, Ber. Dtsch. Chem. Ges. *72*, 2063 (1939).

[2] *E. Müller, A. Rieker, K. Scheffler*, and *A. Moosmayer*, Angew. Chem. *78*, 98 (1966); Angew. Chem. internat. Edit. *5*, 6 (1966).

[3] *F. Seel*, Z. Elektrochem., Angew. Phys. Chem. *52*, 182 (1948).

[4] *R. K. Waring jr.* and *G. J. Sloan*, J. Chem. Phys. *40*, 772 (1964).

[5] *P. Biloen, P. Prins, J. D. W. van Voorst*, and *G. J. Hoytink*, J. Chem. Phys. *46*, 4149 (1967).

[6] *E. Wasserman, L. C. Snyder*, and *W. A. Yager*, J. Chem. Phys. *41*, 1763 (1964).

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

[8] *L. W. Pickett, S. F. Walter*, and *H. France*, J. Amer. Chem. Soc. *58*, 2296 (1936).

[9] *E. Müller*, Fortschr. Chem. Forsch. *1*, 325 (1949).

Chemical Syntheses with Metal Atoms: Preparation of Bis(butadiene)iron Complexes and Butadienetetracarbonylchromium

By *Ernst Koerner von Gustorf, Ottmar Jaenicke*, and *Oskar E. Polansky*[*]

Wilke introduced the term "naked nickel atom" into organometallic chemistry. That means "nickel in complexes whose ligands can all be replaced by butadiene"[1].

"Completely naked" metal atoms are obtained by evaporation of metals in a high vacuum[2]. It is well known that atomic and oligoatomic species are much more reactive than condensed phases—one can refer, *e.g.* to *Skell*'s work[3] with C_1 and C_3. This has led us to attempt to synthesize organometallic compounds by reacting metal atoms with organic substrates.

A first, largely unsuccessful, experiment in this direction was an attempt to obtain ferrocene by exploding iron wires in liquid, in gaseous or over solid cyclopentadiene[4]. The density of metal vapor in wire explosions is obviously too high to permit sufficiently rapid attack by cyclopentadiene in competition with formation of polyatomic iron species. Therefore, we have developed during the last two years an apparatus that makes it possible to evaporate metals in a high vacuum and to co-condense them with organic compounds, *e.g.* at the temperature of liquid nitrogen (see Fig. 1).

The metal to be evaporated is put into a water-cooled copper block[5] which is placed in a steel reaction vessel at 10^{-3} to 10^{-4} torr in the focus (diameter 1—3 mm) of a laser beam[6]. The evaporated metal is condensed on the cooled walls of the vessel simultaneously, or intermittently, with an excess of the organic substrate. At the end of the experiment the warming up of the products can, if necessary, be carried out in the presence of further components that convert the primary products and stabilize them.

In a first, exploratory experiment 42 mg of iron were evaporated by irradiation of pieces of iron wire[7] for 30 min at intervals of 1 min, butadiene being condensed in intermittently. Before thawing, the reaction mixture[8] was treat-

[*] Dr. E. Koerner von Gustorf, O. Jaenicke, and Prof. Dr. O. E. Polansky
Max-Planck-Institut für Kohlenforschung
Abteilung Strahlenchemie
433 Mülheim-Ruhr, Stiftstrasse 34—36 (Germany)

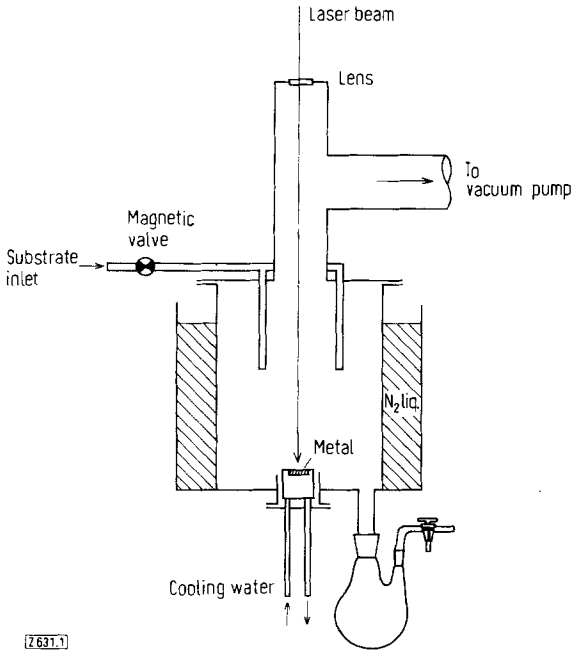
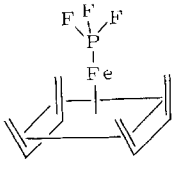


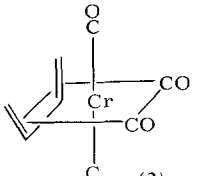
Fig. 1. Apparatus for evaporation and co-condensation of metals with organic substrates (scale 1:4).

ed with CO. Chromatography on silica gel/pentane afforded 45 mg (0.23 mmol) of bis(butadiene)monocarbonyliron (yield 31%, based on Fe evaporated), that proved identical in melting point and spectroscopic properties with a product already previously obtained by us photochemically[9, 10].

By this method other ligands also can be introduced in place of CO in the axial position of bis(butadiene)iron complexes. Intermittent evaporation of 385 mg of iron (6.9 mmol) in 55 min[5], co-condensation of butadiene, and subsequent treatment with PF_3 afforded a reaction mixture, from which 295 mg (1.2 mmol) of bis(butadiene)trifluorophosphaneiron *(1)* was obtained by crystallization from pentane as yellowish-brown needles (sublime at 73 °C; yield 17%, based on Fe evaporated). The structure of *(1)* follows from elemental analysis, the mass spectrum [*m/e*: 252 (M), 164 (M − PF_3), 110 (FeC_4H_6), 88 (PF_3), 56 (Fe)], and the ^{1}H-NMR spectrum (in C_6D_6) which shows three symmetrical multiplets, each for 2H, at 5.75, 9.1 and 10.5 τ. Since the chemical shifts are very similar for the protons in bis(butadiene)monocarbonyl iron and in *(1)*, it can be reasonably assumed that the butadiene units in *(1)* have the spatial arrangement that is proved for the monocarbonyl complex.



(1)



(2)

Chromium is more volatile than iron. On intermittent irradiation (each of 2 seconds duration), we were able to evaporate 530 mg (10 mmol) of chromium in 11.5 min[11]. Intermittent condensation of butadiene into the vessel and subsequent treatment with CO afforded a dark brown oil, from a solution of which in pentane at −70 °C 95 mg (0.44 mmol, yield 4.4%, based on Cr evaporated) yellow crystals separated; they decomposed above 0 °C. The composition $C_4H_6Cr(CO)_4$ follows from elemental analysis and the mass spectrum [*m/e*: 218 (M), 190 (M—CO), 162 (M—2CO), 134 (M—3CO), 106 (M—4CO), 52 (Cr)]. The formulation as butadienetetracarbonylchromium *(2)* is supported by the IR spectrum (in CCl_4), which shows four metal-carbonyl stretching vibrations at 2040, 1977, 1946, and 1932 cm^{-1}, and by the ^{1}H-NMR spectrum (in $C_6D_5CD_3$) at −10 °C, which shows three multiplets, each for 2 H, at 5.65, 8.3 and 9.45 τ. *(2)* is the first example of 1,3-dienetetracarbonylchromium complexes, which are apparently appreciably more labile than the relatively stable tetracarbonylchromium complexes of cyclic 1,5-dienes[12]. Complexes such as *(2)* have been postulated as intermediates in the photochemical hydrogenation of 1,3-dienes with $Cr(CO)_6/H_2$ but could then not be isolated, for reasons that can now be appreciated[13].

We are now investigating the general applicability of our method to the synthesis of labile transition-metal complexes.

Two other laboratories are at present carrying out studies on organometallic syntheses with metal atoms. *Timms*[14] succeeded in synthesizing ferrocene, dibenzenechromium and π-allylhalonickel complexes; he heats the metals electrically; but his apparatus is not suitable for investigation of relatively involatile, air-sensitive compounds[15]. *Skell* has carried out orienting experiments by similar methods with a variety of metals[16, 17].

Received: February 10, 1972 [Z 631 IE]
German version: Angew. Chem. *84*, 547 (1972)

[1] *G. Wilke*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

[2] Cf. *e. g. D. M. Mann* and *H. P. Broida*, J. Chem. Phys. *55*, 84 (1971).

[3] *P. S. Skell, L. D. Wescott, J. P. Goldstein*, and *R. R. Engel*, J. Amer. Chem. Soc. *87*, 2830 (1965); *P. S. Skell* and *R. F. Harris, ibid. 91*, 4440 (1969) and lit. there cited.

[4] *E. Koerner von Gustorf, I. J. Russell*, and *J. R. Driscoll*, unpublished work, Boston College, Summer 1969.

[5] We have constructed an addition to the apparatus by means of which it is possible to move the metal continuously and directly into the focus of the laser beam.

[6] We have so far used a 1.2 kW cw CO_2 laser (500—550 W output) of the Battelle-Institut, Frankfurt/Main. We thank Dr. *K. Gürs* for help with the evaporation experiments.

[7] 2 mm diameter, puriss., Balzers.

[8] To make it easier to remove the products from the wall, *ca.* 100 ml of pentane was condensed on to the walls of the reaction vessel before commencing the irradiation.

[9] *E. Koerner von Gustorf, J. Buchkremer, Z. Pfajfer*, and *F.-W. Grevels*, Angew. Chem. *83*, 249 (1971); Angew. Chem. internat. Edit. *10*, 260 (1971); *E. Koerner von Gustorf, Z. Pfajfer*, and *F.-W. Grevels*, Z. Naturforsch. *26b*, 66 (1971).

[10] We assume that CO displaces one C_4H_6 ligand from a bis(1,2,3,4-*tetrahapto*-butadiene)(1,2-*dihapto*-butadiene)iron first formed.

[11] Granulate, Balzers.

[12] Gmelins Handbuch der anorganischen Chemie, Vol. 3, Chromorganische Verbindungen. Verlag Chemie, Weinheim 1971, p. 141.

[13] *J. Nasielski, P. Kirsch*, and *L. Wilputte-Steinert*, J. Organometal. Chem. *27*, C 13 (1971); *L. Wilputte-Steinert* and *P. Kirsch*, V. Int. Conf. Organometal. Chem., Moscow 1971, Abstr. 165.

[14] *P. L. Timms*, Chem. Commun. *1969*, 1033; *M. J. Piper* and *P. L. Timms*, J. C. S. Chem. Commun. *1972*, 50.

[15] *P. L. Timms*, J. Chem. Soc. *A 1970*, 2526.

[16] *P. S. Skell*, XXIII. Int. Congr. Pure Appl. Chem., Boston 1971, Special Lectures. Butterworths, London 1971, Vol. 4, p. 215; *P. S. Skell* and *J. J. Havel*, J. Amer. Chem. Soc. *93*, 6687 (1971).

[17] Note added in proof: The reaction of zinc atoms with fluoroalkyl iodides has been reported by *K. T. Klabunde, M. S. Key*, and *J. Y. F. Low*, J. Amer. Chem. Soc. *94*, 999 (1972).

Reversible N_2 Fixation by Dicarbonyl-π-cyclopentadienyl(tetrahydrofuran)manganese(I)[1]

By *Dieter Sellmann*[*]

Metal complexes that fix N_2 are of particular interest if, at the site of N_2 fixation, other ligands can also be introduced reversibly. Such a ligand exchange is required for the mechanism of N_2 reduction in nitrogenase systems, where replacement of complex-bound H_2O or NH_3 must occur:

$$M{-}OH_2 + N_2 \rightarrow M{-}N_2 + H_2O \quad (1)$$

$$M{-}NH_3 + N_2 \rightarrow M{-}N_2 + NH_3 \quad (2)$$

M = central metal atom

Eq. (1) describes the beginning of the reaction chain if a nitrogenase system interacts with N_2 for reduction, while eq. (2) describes the liberation of the end product. NH_3 is used for synthesis of amino acids, the N_2 complex re-entering the reduction chain.

A study of the reactions of $C_5H_5Mn(CO)_2N_2$ *(1)*[2] has made it possible to simulate such replacement reactions.

First it was shown that *(1)* is unstable in tetrahydrofuran (THF) at room temperature, being converted into the THF complex $C_5H_5Mn(CO)_2OC_4H_8$ *(2)* with evolution of N_2:

$$(1) + THF \rightarrow (2) + N_2\uparrow \quad (3)$$

The evolution of nitrogen stops after some time, although small amounts of *(1)* are still detectable by IR spectroscopy in the THF solution. The fact that the reaction leading to *(2)* does not procede to completion, in spite of the large excess of THF, led to the assumption of an equilibrium that is shifted largely to the side of *(2)* owing to the low N_2 concentration. If such an equilibrium exists it should be possible to synthesize *(1)* also by reaction of *(2)* with N_2 in a reaction that is the reverse of eq. (3):

$$(2) + N_2 \rightarrow (1) + THF \quad (4)$$

This could in fact be done, either by reducing the concentration of THF relative to that of N_2 or by raising the N_2 concentration by pressure. In the first case N_2 was bubbled through a freshly prepared solution of *(2)*[3] until the THF had volatilized completely in the gas stream. In the second case N_2 was pressed at 150 atm into a solution of the same kind for 24 h and the THF was then removed at room temperature *in vacuo*. At 20 °C and $\approx 10^{-3}$ torr a mixture of *(1)* and $C_5H_5Mn(CO)_3$ *(3)* sublimed from the residues of each reaction. *(1)* can be easily identified in the mixture by means of its characteristic IR bands. These findings prove the assumed equilibrium and thus the competition between N_2 and THF for the central metal in the complex fragment $\{C_5H_5Mn(CO)_2\}$ *(4)*:

$$(1) + THF \rightleftharpoons (2) + N_2 \quad (5)$$

When a CO/N_2 mixture is bubbled through a solution of *(2)*, the complex *(3)* is the only product. Thus, as in most N_2-fixing systems, *(2)* is inactivated for uptake of N_2 by absorption of CO.

It is, however, not possible from these facts to decide the important question whether the preferential formation of the CO complex is based on kinetic or thermodynamic grounds. Nevertheless, a kinetic cause is favored by the fact that spectroscopic data indicate N_2 to be a stronger electron donor than CO in *(1)*[2].

Comparing eq. (1) and (5) shows clearly the analogy to nitrogenase systems. Alongside $[Ru(NH_3)_5H_2O]^{+2}$[4] and $\{C_5H_5Fe[(CH_3)_2P(CH_2)_2P(CH_3)_2]OC(CH_3)_2\}BF_4$[5], *(2)* is the third system known in which N_2 is able to replace an oxygen-donor ligand at atmospheric pressure.

Received: January 24, 1972 [Z 632 IE]
German version: Angew. Chem. *84*, 549 (1972)

[*] Dr. D. Sellmann
Anorganisch-chemisches Laboratorium der
Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[1] Reactions of Complexed Ligands, Part 6. — Part 5: *D. Sellmann*, J. Organometal. Chem. *36*, C 27 (1972).

[2] *D. Sellmann*, Angew. Chem. *83*, 1017 (1971); Angew. Chem. internat. Edit. *10*, 919 (1971).

[3] *W. Strohmeier, C. Barbeau*, and *D. von Hobe*, Chem. Ber. *96*, 3254 (1963).

[4] *D. F. Harrison, E. Weissberger*, and *H. Taube*, Science *159*, 320 (1968).

[5] *W. E. Silverthorn*, Chem. Commun. *1971*, 1310.

Methyl Hydrogen Carbonate[1]

By *Gerhard Gattow* and *Werner Behrendt*[*]

Continuing our studies of carbonic acid[2] we have now concerned ourselves with the half esters, which have not previously been prepared.

Methyl hydrogen carbonate *(1)* is formed on treatment of a suspension of $Na[CH_3OCO_2]$ (obtained by reaction of $NaOCH_3$ dissolved in methanol with CO_2) in dimethyl ether with a solution of HCl(g) in dimethyl ether at −50 °C. After filtration from the NaCl formed and removal of the dimethyl ether by distillation at −80 °C, the half ester remains as a solid.

$CH_3OCO(OH)$ is a colorless material that melts at −36 °C; decomposition ($\rightarrow CO_2 + CH_3OH$) at temperatures above the melting point. The half ester is only moderately soluble in dimethyl or diethyl ether; it decomposes immediately in water. The dissociation constant, determined by way of the hydrolysis constant of $Na[CH_3OCO_2]$, at 25 °C in H_2O is: $K_a = 2.44 \cdot 10^{-6}$. By measurement of the CO_2 pressure of the solid (−70 to −36 °C), the heat of formation of *(1)* was found to be: $\Delta H_f = -155.5 \pm 1$ kcal/mol.

The IR spectrum of a solution of *(1)* in $(C_2H_5)_2O$ at −70 °C contains, besides the ether bands, the following absorption bands that can be unambiguously assigned to the half ester: 3484 [s; ν(OH)], 1779 [m; ν_{as}(CO)], 1730 [s; ν_{as}(CO)], 1277 [s; $\delta_s(CH_3)$], 1255 [s, $\delta_s(CH_3)$], 823 [s, $\pi(OCO_2)$], 665 [m; ?], 652 [m; ?], 567 [w; $\delta_s(OCO_2)$] cm^{-1}.

[*] Prof. Dr. G. Gattow and Dipl.-Chem. W. Behrendt
Institut für Anorganische Chemie und Kernchemie der Universität
65 Mainz, Johann-Joachim-Becher-Weg 24 (Germany)

The substance with a melting range of -57 to -60 °C described by *Hempel* and *Seidel*[3] as methyl hydrogen carbonate probably consisted of a mixture of solid carbon dioxide and methanol (m.p. -56.6 °C at 5.28 atm.).

Received: February 11, 1972 [Z 633 IE]
German version: Angew. Chem. *84*, 549 (1972)

[1] Part 60 of Chalogenolates. – Part 59: *M. Dräger* and *G. Gattow*, Z. Anorg. Allg. Chem., in the press.

[2] *G. Gattow* and *U. Gerwarth*, Angew. Chem. *77*, 132 (1965); Angew. Chem. internat. Edit. *4*, 149 (1965); Z. Anorg. Allg. Chem. *357*, 78 (1968).

[3] *W. Hempel* and *J. Seidel*, Ber. Dtsch. Chem. Ges. *31*, 2997 (1898).

2,3:3,4:4,2-Tri-μ-carbonyl-2,2,3,3,4,4-hexacarbonyl-1-aluminotricobalt: Preparation and Spectroscopic Findings[**]

By *Karl E. Schwarzhans* and *Hans Steiger*[*]

$AlCo_3(CO)_9$, a metal cluster containing aluminum-cobalt bonds, has been obtained by reaction of sublimed aluminum trichloride with an excess of sodium tetracarbonylcobaltate(-1) in dry benzene under an inert gas (N_2).

$$3\,Na[Co(CO)_4] + AlCl_3 \rightarrow AlCo_3(CO)_9 + 3\,NaCl + 3\,CO$$

$$[(18\ mmol) + (2\ mmol) \xrightarrow[30\,°C;\,3\,d]{250\ ml\ C_6H_6}]$$

This crystalline compound (yield 25—30% calc. on $AlCl_3$) is deep red, sensitive to moisture, and not very stable thermally, but can be sublimed at room temperature and 0.1 mm. Its composition is proved by elemental analysis and by IR and mass spectra.

In the mass spectrum (50 eV) the molecular ion ($I_{rel} = 5.4$) is accompanied by the following characteristic fragments:

$AlCo_3(CO)_8^+$ (16.3), $AlCo_3(CO)_7^+$ (5.2), $AlCo_3(CO)_6^+$ (3.6), $AlCo_3(CO)_5^+$ (18.2), $AlCo_3(CO)_4^+$ (34.6), $AlCo_3(CO)_3^+$ (18.3), $AlCo_3(CO)_2^+$ (18.2), $AlCo_3(CO)^+$ (14.5), $AlCo_3^+$ (31.1), $Co_2(CO)_3^+$ (20), $Co(CO)_3^+$ (14.4), $CoCO^+$ (3.7), Co^+ (100). The relatively high intensity of the $AlCo_3^+$ fragment is striking.

The ν_{CO} region of the IR spectrum is to a large extent comparable with that of dodecacarbonyltetracobalt[1] in respect of the positions, number, and intensities of the bands:

$AlCo_3(CO)_9$, ν_{CO} in benzene: 2100 (w), 2066 (m), 2053 (s), 2032 (m), 1893 (w), 1858 (m-s) cm^{-1};—$Co_4(CO)_{12}$, ν_{CO} in *n*-hexane: 2104 (w), 2063 (m-s), 2054 (s), 2037 (w), 2027 (w), 1898 (w), 1867 (m) cm^{-1}.

The IR spectra show that the structure of the metal skeleton is similar in the two clusters. A structure is therefore proposed for $AlCo_3(CO)_9$ that differs from that of $Co_4(CO)_{12}$ (for which several X-ray investigations are available[2–4]) in that the apical $Co(CO)_3$ group of $Co_4(CO)_{12}$ is replaced by the aluminum ion, as shown in Figure 1. The agreement of the IR spectra further indicates that $Co_4(CO)_{12}$ has this structure also in solution, contrary to a previous structural proposal[5] that was based on IR spectroscopic findings.

[*] Doz. Dr. K. E. Schwarzhans and H. Steiger
Anorganisch-chemisches Laboratorium der
Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

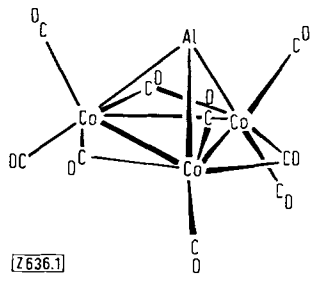


Fig. 1. Structure proposed for $AlCo_3(CO)_9$.

Metal clusters with the compositions $(C_5H_5)_2TiCo_2(CO)_8$ and $(C_5H_5)_4Zr_2Co_2(CO)_5$ have also been obtained analogously to the reaction mentioned above.

Received: March 3, 1972 [Z 636 IE]
German version: Angew. Chem. *84*, 587 (1972)

[1] *G. Bor*, Spectrochim. Acta *19*, 1209 (1963).

[2] *P. Corradini*, J. Chem. Phys. *31*, 1676 (1959).

[3] *L. F. Dahl* and *C. H. Wei*, J. Amer. Chem. Soc. *88*, 1821 (1966).

[4] *C. H. Wei*, Inorg. Chem. *8*, 2384 (1969).

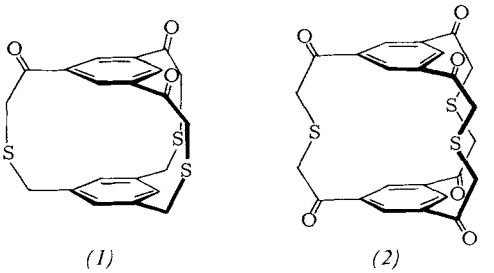
[5] *D. L. Smith*, J. Phys. Chem. *42*, 1460 (1965).

Cyclophanes Possessing Cavities[1][**]

By *Fritz Vögtle* and *Rainer G. Lichtenthaler*[*]

We wish to report the planned synthesis of a new heterocyclic system in which approximately parallel benzene rings joined by three bridges enclose a cavity.

Using a method that had been optimized for the metacyclophane series[2] and applying the dilution principle we treated 1,3,5-tris(bromoacetyl)benzene with 1,3,5-tris(mercaptomethyl)benzene and with sodium sulfide ($\times 9\,H_2O$) in *tert*-butanol as solvent. We obtained the crystalline [4.4.4]-(1,3,5)cyclophane *(1)* [m.p. >360 °C, dec.; from $(CH_3)_2SO$] and the [5.5.5](1,3,5)cyclophane *(2)*[3] [m.p. >360 °C, dark coloration; from $(CH_3)_2SO$], respectively, in reproducible yields of 10 and 0.16%.



(1) *(2)*

The molecular weights of the two cyclophanes and the presence of three sulfur atoms were initially confirmed by mass spectrometry. Compound *(1)*, which was obtained

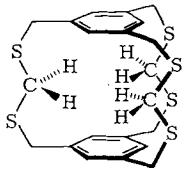
[*] Prof. Dr. F. Vögtle and Dipl.-Chem. R. G. Lichtenthaler
Institut für Organische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

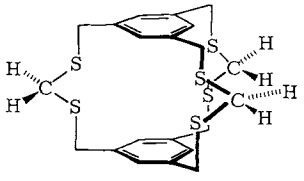
in larger quantities, gave a correct CHS elemental analysis. Determination of S in *(2)* was supplemented by a high-resolution mass spectrum.

The structures of *(1)* and *(2)* are proved by their ^{1}H-NMR spectra [$(CD_3)_2SO$]: *(1)* gives two singlets of equal intensity for the aromatic protons ($\tau = 2.0$ and 3.2 ppm) and, as expected, another two singlets of equal intensity for the methylene protons ($\tau = 6.0$ and 6.2 ppm). The proton resonance of *(2)* is made up of only two singlets at $\tau = 1.7$ (6 aromatic protons) and 6.0 ppm (12 CH_2 protons). Remarkably, the last-named peak is not shifted relative to the corresponding signal of an acyclic reference compound (diphenacyl sulfide).

These proton resonance findings are in agreement with model considerations which show that largely unhindered rotational movement is possible in the bridges of both compounds. However, only compound *(2)* can modify its cavity in a bellows-like manner by mutual approach of the two benzene rings without rotation about the threefold symmetry axis.



(3a)



(3b)

We attempted to shed some light on the question whether the conformation shown for *(2)* having three inwardly directed sulfur atoms is actually preferred in the [5.5.5]-(1,3,5)cyclophane system[4] by synthesis of 2,4,13,15,24,26-hexathia[5.5.5](1,3,5)cyclo-2-phane *(3)*. If the conformation *(3a)* were to predominate, as suggested by molecular models, an S—CH_2—S absorption would result at comparatively high field since the inwardly directed methylene protons would be exposed to the anisotropic effects of both benzene rings. In contrast, no significant shift of the signals relative to those of the open-chain reference compound bis(benzylthio)methane would be expected for the conformation *(3b)*.

We obtained compound *(3)* [almost colorless crystals, m.p. >380°C, dec.; from $(CH_3)_2SO$] in 10% yield on reaction of 1,3,5-tris(mercaptomethyl)benzene with methylene bromide in the molar ratio 2:3 according to the dilution principle in *tert*-butanol as solvent. The structure *(3)* given is based provisionally on the S analysis and the molecular weight as determined by mass spectrometry.

Here too the ^{1}H-NMR spectrum is highly informative: It contains [in $(CD_3)_2SO$] three singlets: $\tau = 3.2$ (6 aromatic protons), 6.5 (12 benzyl protons), 6.9 ppm (6 S—CH_2—S protons). A comparison with the analogous signals of bis-(benzylthio)methane [$\tau = 6.8$ (2 S—CH_2—S protons) and 6.4 ppm (4 benzyl protons), in $(CD_3)_2SO$] reveals no significant upfield shift. Synthesis of further representatives of this type of compound should establish whether the above finding is due to a low contribution of conformation *(3a)* to the time-averaged structure or whether the benzene rings are too far displaced from the inwardly directed protons owing to the large C—S bond length. The possibility of inserting metal atoms or ions into the cavities will also be studied.

Received: March 27, 1972 [Z 638 IE]
German version: Angew. Chem. *84*, 588 (1972)

[1] Multiply bridged aromatic compounds, Part 5. — Part 4: *F. Vögtle* and *R. G. Lichtenthaler*, Tetrahedron Lett. *1972*, in press.

[2] *F. Vögtle* and *R. G. Lichtenthaler*, to be published.

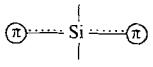
[3] The full name of compound *(1)* according to the phane system of nomenclature is 4,11,24-trioxo-2,13,22-trithia[4.4.4](1,3,5)cyclo-2-phane, and that of *(2)* is 1,5,12,16,23,27-hexaoxo-3,14,25-trithia[5.5.5]-(1,3,5)cyclo-2-phane.

[4] Cf. *A. J. Hubert*, J. Chem. Soc. *C 1967*, 6.

Evidence for Conjugation through a Saturated Silicon Atom[1]

By *Ulrich Weidner* and *Armin Schweig*[*]

One of the focal points of organosilicon chemistry[2] is the question whether two π systems separated by a tetrahedrally coordinated Si atom are conjugatively coupled through this atom:



We have now succeeded in detecting this kind of conjugation ("through-conjugation"[2]) in the photoelectron (PE) spectrum of dimethyldivinylsilane *(1)*, $(CH_3)_2Si(CH{=}CH_2)_2$.

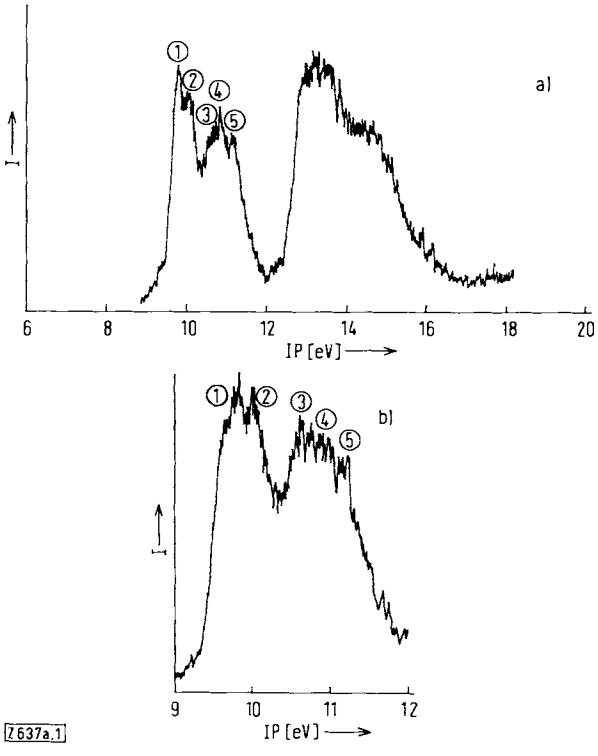


Fig. 1. Photoelectron spectrum (a) [7] of dimethyldivinylsilane *(1)*. The spectrum (b) shows the first two peaks on an expanded scale. The vertical ionization potentials (in eV), corrected relative [8] intensities, and the assignments (symmetries) of the bands ① to ⑤ are: ① 9.8/1.0/$\pi_1(b_1)$; ② 10.0/1.0/$\pi_2(a_2)$; ③ 10.6/1.0/$\sigma_1(b_2)$; ④ 11.0/0.9/$\sigma_2(a_1)$; ⑤ 11.2/1.0/$\pi_3(b_1)$.

[*] Dipl.-Chem. U. Weidner and Prof. Dr. A. Schweig
Physikalisch-chemisches Institut der Universität
355 Marburg, Biegenstrasse 12 (Germany)

Theoretically through-conjugation can arise by participation of a π-type Si bonding MO (Si—C hyperconjugation[3]) or the d_π AOs ($p_\pi d_\pi$ conjugation[2,4]) on the silicon atom in π conjugation. If *(1)* has C_{2v} symmetry then, provided that through-conjugation is a real phenomenon, three π MOs of different energy are to be expected: the $\pi_1(b_1)$ HOMO having a node in each Si—C bond, the next lower $\pi_2(a_2)$ MO having one node at Si, and finally the $\pi_3(b_1)$ MO without a node. π_1 corresponds to the antibonding π_1 MO and π_3 to the bonding π_2 MO in trimethylvinylsilane *(2)*[5]; the $\pi_2(a_2)$ MO in *(1)* is new and has no analog in *(2)*[5].

$\pi_2(a_2)$ is expected to lie a little lower than $\pi_1(b_1)$ since the above conjugation mechanisms of the saturated silicon atom should only exert a slight effect. Such arguments would predict that the first peak in the PE spectrum of *(1)* consist of two bands ① and ② in contrast to that of *(2)*[5]. The spectrum of *(1)* is reproduced in Figure 1. The intensity ratio of the first two peaks is 2:3[6] (the corresponding intensity ratio in the spectrum of *(2)* is 1:3[6]).

The expanded spectrum (Fig. 1 b) clearly shows the splitting of the first peak into two bands ① and ② separated by 0.2 eV. This finding demonstrates that a saturated Si atom between two π systems cannot be regarded as performing an isolating function.

Received: February 18, 1972 [Z 637a IE]
German version: Angew. Chem. *84*, 550 (1972)

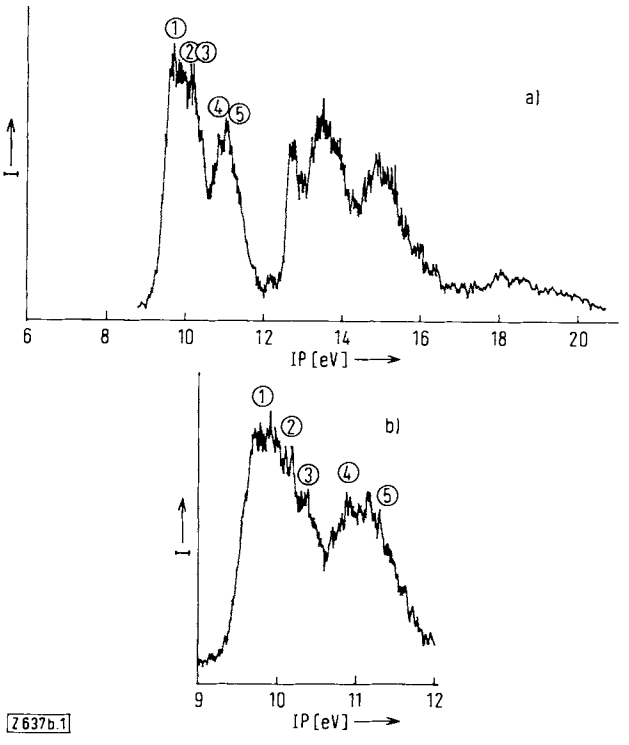


Fig. 1. Photoelectron spectrum (a) of tetravinylsilane *(1)*. The spectrum (b) shows the first two peaks on an expanded scale.

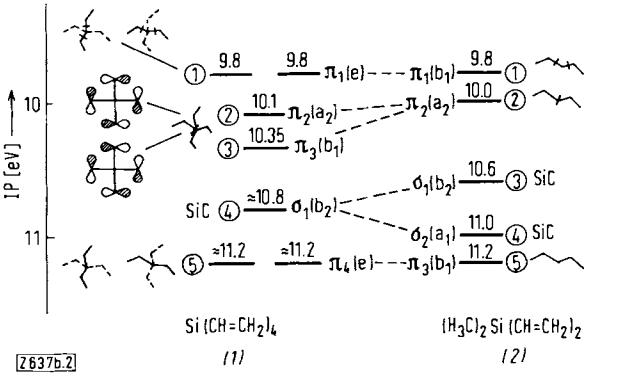


Fig. 2. Comparison of the MO and energy-level diagrams of tetravinylsilane *(1)* (D_{2d} symmetry) and dimethyldivinylsilane *(2)* (C_{2v} symmetry). The spiroantibonding and spirobonding interaction in the MOs $\pi_2(a_2)$ and $\pi_3(b_1)$ of *(1)* are illustrated with the aid of the $2p_\pi$ AOs on the four C atoms adjacent to the Si atom drawn looking down the S_4 axis.

[1] Theory and application of photoelectron spectroscopy, Part 8. We are indebted to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support of this work, and to the Deutsches Rechenzentrum, Darmstadt, for carrying out the calculations. — Part 7: Ref. [9].

[2] *C. J. Attridge*, Organometal. Chem. Rev. *A 5*, 323 (1970).

[3] *C. Eaborn* and *S. H. Parker*, J. Chem. Soc. *1954*, 939; *C. Eaborn*, *ibid. 1956*, 4858; J. Organometal. Chem. *20*, 49 (1969); *W. Hanstein*, *H. J. Berwin*, and *T. G. Traylor*, J. Amer. Chem. Soc. *92*, 829 (1970); *C. G. Pitt*, J. Organometal. Chem. *23*, C 35 (1970); *J. M. Jerkunica* and *T. G. Traylor*, J. Amer. Chem. Soc. *93*, 6278 (1971); *U. Weidner* and *A. Schweig*, Angew. Chem. *84*, 167 (1972); Angew. Chem. internat. Edit. *11*, 146 (1972).

[4] *E. A. V. Ebsworth* in *A. G. MacDiarmid*: Organometallic Compounds of the Group IV Elements, Vol. 1. Dekker, New York 1968.

[5] *U. Weidner* and *A. Schweig*, Angew. Chem. *84*, 167 (1972); Angew. Chem. internat. Edit. *11*, 146 (1972); *U. Weidner* and *A. Schweig*, J. Organometal. Chem., in press.

[6] The intensity value of 3 for the second peak in the PE spectra of *(1)* and *(2)* is attributable to ionization of two Si—C σ MOs in addition to the bonding π MOs (π_3 for *(1)* and π_2 for *(2)*).

[7] The HeI (584 Å) photoelectron spectra were recorded with a PS 16 spectrometer produced by Perkin-Elmer Ltd. Beaconsfield (England).

[8] *O. Klemperer*: Electron Optics. University Press, Cambridge 1953, p. 414.

[9] *U. Weidner* and *A. Schweig*, J. Organometal. Chem., in press.

Estimation of Spiro-Interaction (Spiroconjugation) in Tetravinylsilane[1]

By *Ulrich Weidner* and *Armin Schweig*[*]

The term "spiroconjugation"[2] denotes the interaction between two mutually perpendicular π systems separated by a tetrahedral atom. Such a system is present in tetravinylsilane *(1)*[3]. By comparison of the photoelectron (PE) spectra of *(1)* and dimethyldivinylsilane *(2)*[4] we have now been able to detect a spiro-interaction in *(1)* and to estimate its magnitude.

The PE spectrum[5] of *(1)* is reproduced in Figure 1 a, and the first two peaks of this spectrum are shown on an expanded scale in Fig. 1 b. The ratio of the corrected[6] intensities of the first two peaks is 4:3; the corresponding ratio for *(2)* is found to be 2:3[4]. These intensity ratios are readily understandable in the light of Figure 2 which demonstrates how the energy-level and MO diagrams of *(1)* can be derived from those of *(2)*[4]. The Si—C antibonding and bonding MOs $\pi_1(b_1)$ and $\pi_3(b_1)$ in *(2)* correspond to the degenerate MOs $\pi_1(e)$ and $\pi_4(e)$ in *(1)*. Instead of the antisymmetric and symmetric Si—C combination $\sigma_1(b_2)$ and $\sigma_2(a_1)$ in *(2)* the single Si—C MO $\sigma_1(b_2)$ is retained in *(1)*. The $\pi_2(a_2)$ MO unequivocally established in *(2)* splits into the spiroantibonding and spirobonding MOs $\pi_2(a_2)$

[*] Dipl.-Chem. U. Weidner and Prof. Dr. A. Schweig
Physikalisch-chemisches Institut der Universität
355 Marburg, Biegenstrasse 12 (Germany)

and $\pi_3(b_1)$ in *(1)*. Particular interest attaches to the magnitude of the splitting. We estimate a value of 0.2—0.3 eV for the spiro-splitting in *(1)* from the structure and width of the first peak in Figure 1b. To the best of our knowledge, this is the first spiro-splitting to be measured by PE spectroscopy and, in particular, the first detection of spiroconjugation both in a non-spiro compound and in an organosilicon compound.

Received: February 21, 1972 [Z 637b IE]
German version: Angew. Chem. *84*, 551 (1972)

[1] Theory and application of photoelectron spectroscopy, Part 9. We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for their support of this work, and to the Deutsches Rechenzentrum for carrying out the calculations. — Part 8: ref. [4].

[2] *H. E. Simmons* and *T. Fukunaga*, J. Amer. Chem. Soc. *89*, 5208 (1967); *R. Hoffmann, A. Imamura*, and *G. D. Zeiss, ibid. 89*, 5215 (1967); *R. Bosche, A. S. Dreiding*, and *E. Heilbronner, ibid. 92*, 123 (1970); *A. Tajiri* and *T. Nakajima*, Tetrahedron *27*, 6089 (1971); *M. J. Goldstein* and *R. Hoffmann*, J. Amer. Chem. Soc. *93*, 6194 (1971).

[3] According to definition (IUPAC: Nomenclature of Organic Chemistry, Sect. A. Butterworths, London 1966) spiro compounds consist of two rings with one common atom (spiro atom). Hence *(1)* is not a spiro compound. However, *(1)* possesses two mutually perpendicular π systems separated by a tetrahedral atom, thereby fulfilling the requirements (cf. ref. [2]) for spiro conjugation.

[4] *U. Weidner* and *A. Schweig*, Angew. Chem. *84*, 550 (1972); Angew. Chem. internat. Edit. *11*, 536 (1972).

[5] The HeI (584 Å) photoelectron spectra were recorded with a PS 16 spectrometer produced by Perkin-Elmer Ltd., Beaconsfield (England).

[6] *O. Klemperer*: Electron Optics. University Press, Cambridge 1953, p. 414.

The Photoelectron Spectra of Benzenoid Hydrocarbons $C_{18}H_{12}$ [1]

By *Franz Brogli* and *Edgar Heilbronner*[*]

While there has been an abundance of calculations of π-orbital energies, particularly those of fused benzenoid hydrocarbons, since the fundamental publications by *Erich Hückel* in the 1930's, experimental verification of the theoretical values obtained for large systems (more than 14 C atoms) has been lacking. The low vapor pressure of these compounds precludes measurement of their high-resolution photoelectron spectra with spectrometers of conventional construction. However, recent advances have now rendered even highly involatile compounds accessible to study by photoelectron spectroscopy.

[*] Dipl.-Chem. F. Brogli and Prof. Dr. E. Heilbronner
Physikalisch-Chemisches Institut der Universität
CH-4056 Basel, Klingelbergstrasse 80 (Switzerland)

The preceding communication in this series[1] showed that for unsaturated benzenoid and nonbenzenoid hydrocarbons the π-orbital energies $\varepsilon_J(\pi) = -I_{v,J}$ calculated on the basis of Koopmans' theorem from the ionization potentials $I_{v,J}$ can be parametrized by a simple HMO model when first-order bond localization[2] is accounted for by a perturbation method[3]. The relevant regression function is

$$I'_{v,J} = -(\alpha + \beta x_J) + b \sum_{\mu\nu} (p^+_{\mu\nu,J} - p_{\mu\nu})(p_0 - p_{\mu\nu}) \qquad (1)$$

where

a) $\alpha + \beta x_J = \varepsilon_J^{HMO}$ is the orbital energy of the π orbital ψ_J in the usual Hückel approximation;

b) $p_{\mu\nu}$ is the bond order between the bonding centers μ,ν of the neutral hydrocarbon M;

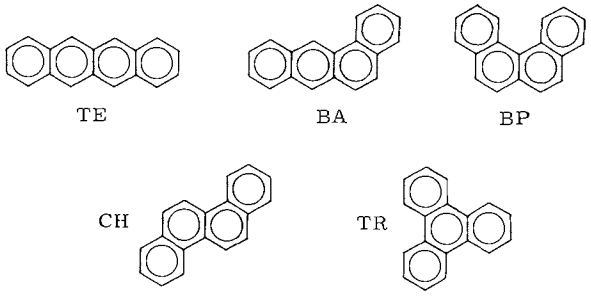
c) $p^+_{\mu\nu,J} = p_{\mu\nu} - c_{J\mu}c_{J\nu}$ is the corresponding bond order in the radical cation $M^+(\psi_J^{-1})$, *i.e.* M^+ in the configuration in which ψ_J is only singly occupied;

d) $p_0 = 2/3$ is the standard bond order in benzene;

e) b is a factor dependent upon the force constants of the π and σ bonds and upon the derivative $d\beta/dR$ of the resonance integral β with respect to the length R of the π bond.

Summation is performed over all bonds.

An impressive test of the quality of the ionization potentials $I'_{v,J}$ calculated from equation (1) is provided by a photoelectron spectroscopic investigation of the five isomeric benzenoid hydrocarbons of molecular formula $C_{18}H_{12}$: tetracene (TE), 1,2-benzanthracene (BA), 3,4-benzophenanthrene (BP), chrysene (CH), and triphenylene (TR).



The PE spectra were recorded with a PS 16 spectrometer (Perkin-Elmer, Beaconsfield, England) whose specifications correspond to those given by *Turner*[4]. Table 1 lists the vertical π-ionization potentials $I_{v,J}$, their assignments to the corresponding π orbitals (cf. Ref. [5]) and the values

Table 1. Vertical ionization potentials of the five isomeric benzenoid hydrocarbons $C_{18}H_{12}$. $I_{v,J}(\pi)$ = measured vertical ionization potentials in eV; $I'_{v,J}$ = calculated according to (1) with $-\alpha = 5.782$ eV, $-\beta = 3.199$ eV, $b = 5.106$ eV. The designation of the orbitals ψ_J refers to the following symmetry groups: TE, D_{2h}; BA, C_s; BP, C_{2v}; CH, C_{2h}; TR, D_{3h} (cf. ref. [5]). Values in parentheses refer to shoulders and are therefore accurate to one decimal place only.

	TE			BA			BP			CH			TR		
PE Band	ψ_J	$I_{v,J}$	$I'_{v,J}$	ψ_J	$I_{v,J}$	$I'_{v,J}$	ψ_J	$I_{v,J}$	$I'_{v,J}$	ψ_J	$I_{v,J}$	$I'_{v,J}$	ψ_J	$I_{v,J}$	$I'_{v,J}$
1	a_u	7.01	6.88	a″	7.42	7.40	b_1	7.62	7.71	a_u	7.61	7.60	e″	7.86	7.98
2	b_{1g}	8.41	8.34	a″	8.03	8.14	a_2	8.00	8.00	a_u	8.10	8.19	a_1''	8.63	8.68
3	b_{1u}	(8.6)	8.59	a″	8.82	8.78	a_2	8.96	8.93	b_g	8.68	8.64	e″	9.66	9.67
4	a_u	9.56	9.53	a″	9.34	9.29	b_1	(9.13)	9.05	b_g	9.44	9.41	a_2''	10.05	9.93
5	b_{2g}	(9.7)	9.78	a″	9.90	9.87	b_1	9.95	10.04	a_u	9.73	9.69			
6	b_{1g}	10.25	10.31	a″	10.40	10.38	a_2	10.26	10.25	b_g	10.52	10.58			

$I'_{v,J}$ calculated from (1). The close correlation between $I_{v,J}$ and $I'_{v,J}$ may be seen from Figure 1.

The residual variance of the regression plotted in Figure 1 amounts to $V(I'_{v,J})=0.00483\ eV^2$ at $\phi = 22$ degrees of freedom. A corresponding value of $V(I^{HMO}_{v,J})=0.01128\ eV^2$ ($\phi=23$) is obtained for a simple HMO model which does not include bond localization (all $\beta_{\mu\nu}=\beta$). The variance

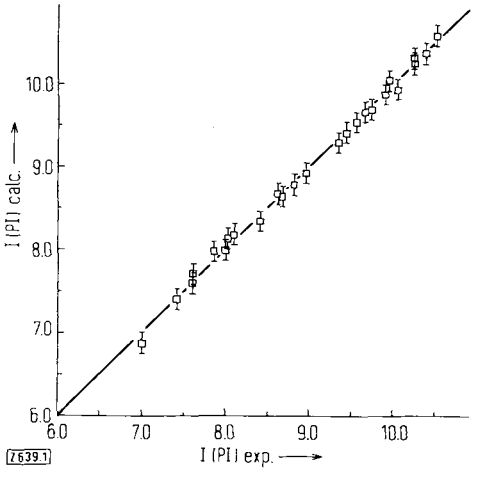


Fig. 1. Correlation between the vertical ionization potentials calculated from (1) ($I'_{v,J}\equiv I$(PI) calc.) and the experimental values ($I_{v,J}\equiv I$(PI) exp.). The confidence limits shown refer to 90% security.

ratio $F=0.01128/0.00483=2.36$ is greater than the critical value $F=2.03$ for 95% security, corresponding to degrees of freedom $\phi_1=23$ and $\phi_2=22$. This means that the regression (1) yields significantly better agreement with experiment than that based on orbital energies ε_j^{HMO} calculated from an unperturbed HMO model.

However, it should be borne in mind that the improvement of the correlation due to the perturbation term in (1), *i.e.* the significant reduction in residual variance, is smaller in the present case than for the smaller π systems studied in the preceding communication[1]. This was to be expected since the perturbation of the π-bond lengths due to removal of an electron will become smaller with increasing size of the π system.

The regression shown in Figure 1 supports the assumption that the first six bands (four bands for TR) in the PE spectra of the hydrocarbons $C_{18}H_{12}$ should be assigned to π orbitals. This assignment is also consistent with the band shapes and relative band intensities, as will be reported elsewhere.

Received: March 6, 1972 [Z 639 IE]
German version: Angew. Chem. *84*, 551 (1972)

[1] Applications of Photoelectron Spectroscopy, Part 36. This work is part of Project No. SR 2. 477. 71 of the Schweizerischer Nationalfonds. — Part 35: *F. Brogli* and *E. Heilbronner*, Theoret. Chim. Acta, in press.

[2] *G. Binsch, E. Heilbronner*, and *J. N. Murrell*, Mol. Phys. *11*, 305 (1966); *G. Binsch* and *E. Heilbronner* in *A. Rich* and *N. Davidson*: Structural Chemistry and Molecular Biology. Freeman, San Francisco 1968, p. 815.

[3] *H. Götz* and *E. Heilbronner*, Helv. Chim. Acta *44*, 1365 (1961).

[4] *D. W. Turner*, Proc. Roy. Soc. *A 307*, 15 (1968).

[5] *A. Streitwieser Jr.* and *J. I. Brauman*: Supplemental Tables of Molecular Orbital Calculations. Pergamon Press, Oxford 1965, Vol. 1.

Complex Shift Reagent for ^{13}C-NMR Studies on Carbohydrates

By *Wolfgang Voelter, Claus Bürvenich*, and *Eberhard Breitmaier*[*]

Application of the pulse Fourier transform technique has raised the sensitivity of NMR spectroscopy[1]. ^{13}C-NMR is consequently being employed increasingly for determination of configuration and conformation of carbohydrates[2] and nucleosides[3, 4].

The ^{13}C signals of carbohydrates are assigned by comparison of spectra of analogous compounds and on the basis of the following, experimentally well-substantiated rules[1–5]:

1. The resonances of deoxy carbon atoms appear at highest field.

2. The peaks of anomeric carbon atoms lie at lowest field.

3. A pyranose carbon atom having an axial hydroxyl group is generally more strongly shielded than a corresponding one with an equatorial hydroxyl group.

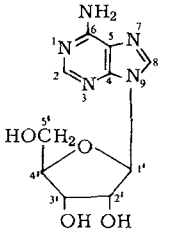
4. On changing a pyranose hydroxyl group from an equatorial to an axial position the signals of γ carbon atoms having an axial hydrogen atom on the same side of the ring are shifted upfield.

5. Replacement of a hydroxyl hydrogen by a methyl group shifts the signal of the ring carbon atom closest to the oxygen downfield by 6 to 12 ppm.

In the case of mutarotating sugars, recording the spectra before and after mutarotational equilibration has proved particularly valuable in signal assignment of anomeric pairs[4, 5].

A new means of investigating conformations and configurations of sugars or sugar residues has been found in comparison of the ^{13}C spectra of the sugar and its borate complex. (Circular dichroism of molybdenum and copper complexes can be employed for similar purposes[6, 7].)

The use of borate as a complex shift reagent will be demonstrated for adenosine and 2′-deoxyadenosine.



(1)

As with molybdate ion[6], complex formation with borate is pH dependent. In order to detect complex formation between borate and the sugar, the ^{13}C signals of adenosine *(1)* are recorded with and without borate at various pH values (cf. Figs. 1a and 1b).

The signals are assigned as in previous publications[3].

Figure 1a shows that the ^{13}C signals of C-1′ to C-5′ change by less than 0.5 ppm between pH 1 and pH 10. More pronounced shifts are observed for C-5 and for the signals of the remaining adenyl-C atoms at low pH. In

[*] Doz. Dr. W. Voelter, Dipl.-Chem. C. Bürvenich, and Doz. Dr. E. Breitmaier
Chemisches Institut der Universität
74 Tübingen, Wilhelmstrasse 33 (Germany)

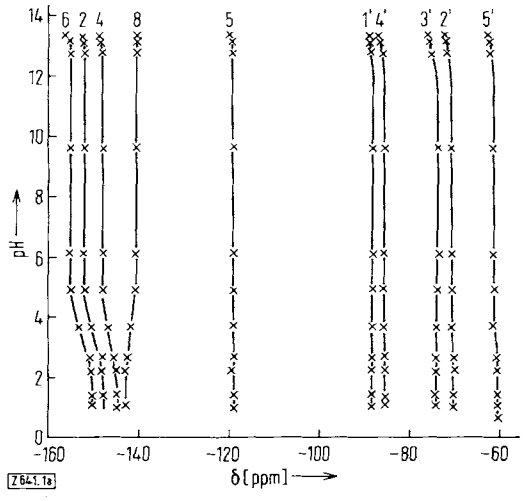


Fig. 1a. pH dependence of ^{13}C signals of adenosine solutions. The solution contained 30—270 mg of adenosine per 5 ml depending upon solubility.

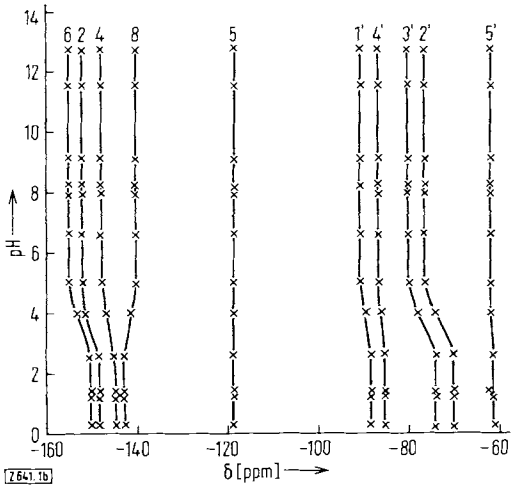


Fig. 1b. pH dependence of ^{13}C signals of adenosine-borate solutions. The solutions contained 30—270 mg of adenosine per 5 ml and 100 mg of boric acid.

6-substituted purines protonation occurs initially at N-1 (p*K* 2—4)[8]. Proton addition hardly affects the electron density on C-5; the resonances of C-2, C-4, and C-6 are shifted upfield and that of C-8 downfield (Figs. 1a and 1b). The upfield shift of the C-2 and C-6 signals on monoprotonation can be explained in terms of the rule found by *Pugmire* and *Grant*[9] for six-membered heterocyclics. The pH dependence of the ^{13}C resonances observed with pyrimidine does not apply to C-5 of the purine system.

Figure 1b represents the pH dependence of the ^{13}C signals of adenosine-borate solutions. The resonances of the adenyl-C atoms are almost identical with those in Figure 1a. The signals of C-2′ and C-3′, however, are shifted downfield by about 6 ppm in the presence of borate at pH > 6. Complex formation of neighboring *cis*-hydroxyl groups on C-2′ and C-3′ with borate can thus be unequivocally detected by ^{13}C-NMR spectroscopy. Whereas the signal of C-5′ is hardly affected by complex formation, the signals of C-1′ and C-4′ adjacent to C-2′ and C-3′ exhibit a slight but readily detectable downfield shift.

In the absence of a hydroxyl group on C-2′ the ribose residue can no longer form chelates with borate. The ^{13}C chemical shifts of 2′-deoxyadenosine solutions with and without borate are almost equal.

It may be seen from the above ^{13}C study that borate is particularly suitable as a complex shift reagent for the detection of neighboring *cis*-hydroxyl groups in carbohydrate chemistry. The requisite information is obtained without great experimental effort by measurement of sample solutions adjusted to pH 10, once with addition of borate and once without. Moreover, the method can be used for elucidation of hitherto debatable structures in this class of compounds[10].

The ^{1}H-broad band decoupled Fourier transform ^{13}C-NMR spectra were recorded with a Bruker HFX 90 multinuclear spectrometer. The (deoxy)-adenosine and (deoxy)-adenosine-borate solutions were adjusted to the desired pH values by addition of sodium hydroxide or hydrochloric acid of various molarities.

Received: April 10, 1972 [Z 641 IE]
German version: Angew. Chem. *84*, 589 (1972)

[1] *E. Breitmaier, G. Jung,* and *W. Voelter,* Angew. Chem. *83*, 659 (1971); Angew. Chem. internat. Edit. *10*, 673 (1971).

[2] *D. E. Dorman* and *J. D. Roberts,* J. Amer. Chem. Soc. *92*, 1355 (1970); *A. S. Perlin, B. Casu,* and *H. J. Koch,* Can. J. Chem. *48*, 2596 (1970); *E. Breitmaier, G. Jung,* and *W. Voelter,* Chimia *25*, 362 (1971); *E. Breitmaier, W. Voelter, G. Jung,* and *C. Tänzer,* Chem. Ber. *104*, 1147 (1971).

[3] *A. J. Jones, D. M. Grant, M. W. Winkley,* and *R. K. Robins,* J. Amer. Chem. Soc. *92*, 4079 (1970); *E. Breitmaier, G. Jung,* and *W. Voelter,* Chimia *26*, 136 (1972).

[4] *E. Breitmaier* and *W. Voelter,* Hoppe-Seylers Z. Physiol. Chem., in press.

[5] *W. Voelter, E. Breitmaier,* and *G. Jung,* Angew. Chem. *83*, 1011 (1971); Angew. Chem. internat. Edit. *10*, 935 (1971).

[6] *W. Voelter,* Hoppe-Seylers Z. Physiol. Chem. *350*, 15 (1971); *W. Voelter, E. Bayer, R. Records, E. Bunnenberg,* and *C. Djerassi,* Chem. Ber. *102*, 1005 (1969); *W. Voelter, G. Kuhfittig,* and *E. Bayer,* Angew. Chem. *82*, 985 (1970); Angew. Chem. internat. Edit. *9*, 964 (1970).

[7] *H. Bauer,* Diplomarbeit, Universität Tübingen 1972; *H. Vergin, H. Bauer, G. Kuhfittig,* and *W. Voelter,* Z. Naturforsch., in press.

[8] *A. M. Fiskin* and *M. Beer,* Biochemistry *4*, 1289 (1965).

[9] *R. J. Pugmire* and *D. M. Grant,* J. Amer. Chem. Soc. *90*, 697 (1968).

[10] *E. W. Malcolm, J. W. Green,* and *H. A. Swenson,* J. Chem. Soc. *1964*, 4669.

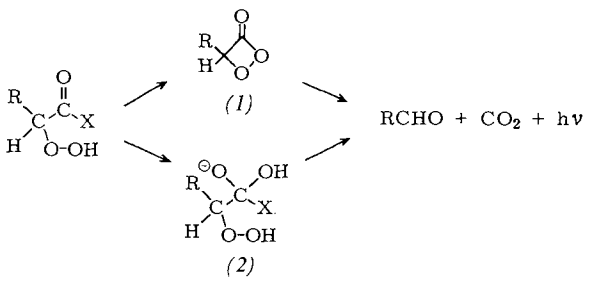
(1-Adamantyl)-α-peroxylactone: Synthesis, Kinetics, and Luminescence[**][1, 2]

By *Waldemar Adam* and *Hans-Christian Steinmetzer*[*]

Five years ago α-peroxylactones *(1)* were postulated for the first time as active precursors in the bioluminescence of the firefly[3] and of *Cypridina hilgendorfii*[3a]. This was confirmed in the latter case by ^{18}O labeling[4]. In the firefly[5] and in *Renilla*[6], however, an α-hydroperoxide *(2)* is responsible for bioluminescence. α-Peroxylactones are also suspected as luminescence-initiating species in the reaction of acridinium salts with H_2O_2[7] and of ketenes with singlet oxygen[8].

[*] Prof. Dr. W. Adam and Dr. H.-Chr. Steinmetzer
Chemistry Department, University of Puerto Rico
Rio Piedras, Puerto Rico 00931 (USA)

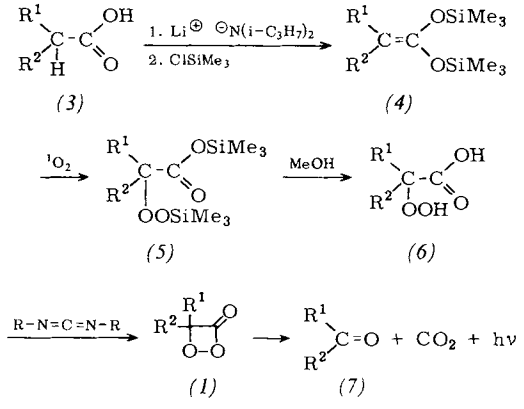
[**] Cyclic peroxides, Part 26.—Part 25: *W. Adam* and *L. Szendrey,* Tetrahedron Lett., in press. This work was supported by the National Science Foundation, the Petroleum Research Fund of the American Chemical Society, the Research Corporation, and the A. P. Sloan Foundation. *H.-Chr. St.* is indebted to the Deutsche Forschungsgemeinschaft for a traveling grant.



Our research team has recently succeeded in synthesizing the α-peroxylactone 4-*tert*-butyl-1,2-dioxetan-3-one *(1a)*, the chemiluminescence and decomposition kinetics of which were also recorded[1,2]. The instability of this first authentic α-peroxylactone at room temperature has hitherto prevented its isolation.

The present aim of our synthetic efforts is to substitute *(1)* in such a manner as to raise its stability or improve the possibilities for its isolation (increased volatility or ready crystallization).

We first attempted to obtain *(1b)* in a manner already described[1]. Unfortunately, compound *(5b)*, and even



a, R^1 = H, R^2 = *tert*-Butyl[1,2]
b, R^1 = R^2 = Phenyl
c, R^1 = H, R^2 = 1-Adamantyl
Me = CH_3

more so *(6b)*, decompose even at room temperature to give benzophenone *(7b)*, which would suggest a drastic reduction in stability on going from *(1a)* to *(1b)*.

In contrast, the synthesis of *(1c)* was completely devoid of problems. Compound *(4c)* (in analogy to those in ref. [9]) can be obtained in 92% yield as a colorless oil, b. p. 122 to 125 °C/0.01 torr. Its IR spectrum in CCl_4 exhibits characteristic bands at 1670 (C=C) and 1275, 1255 cm^{-1} (Si—O); the ^{1}H-NMR spectrum in CCl_4 is also in agreement with the structure: δ = 0.20 ($OSiMe_3$), 1.57—2.23 (aliph. H), and 3.27 ppm (olef. H).

The dye-sensitized photooxygenation of *(4c)* to *(5c)* proceeds with a not unexpected methylsilyl group migration similar to that found in the ene reaction[1,2]. An analogous shift in the photooxygenation of trimethylsilyl enol ethers[10] indicates a general reaction pattern. The reaction *(4c)* → *(5c)* can be followed by means of IR spectroscopy. The characteristic IR bands of *(5c)* lie at 1730, 1710 (C=O), and 1250 cm^{-1} (Si—O). The NMR spectrum of *(5c)* contains two signals for O—$SiMe_3$ at δ = 0.20 and 0.32, and a singlet at 3.87 ppm (C—H) alongside the almost unchanged multiplet of the adamantyl protons. Iodometric titration shows the oil to be 95 ± 1% pure.

Methanolysis of *(5c)* at *ca.* −20 °C gives a quantitative yield of the α-hydroperoxy acid *(6c)* [90% after recrystallization from cyclohexane, dec. point 114—115 °C, 97.8 ± 1% pure (iodometric titration). IR ($CHCl_3$): 3500—2400 (OOH and COOH) and 1715 cm^{-1} (C=O); NMR ([D_6]-acetone): δ = 1.50—2.40 (m/15H), 4.00 (s/1H), 9.25 ppm (s, broad/2H)]. *(6a)* and *(6c)* are the first authentic α-hydroxyperoxy acids[11]. Reduction of *(6c)* with H_2/Pd on active charcoal gives a quantitative yield of the α-hydroxy acid, m. p. 153—155 °C. The structure of the compound is confirmed by spectral data.

Ring closure of *(6c)* to *(1c)* proceeds best in CCl_4 at −20 °C with equimolar amounts of dicyclohexylcarbodiimide. The rapidly disappearing C=O absorption of the α-peroxylactone *(1c)* is seen at 1875 cm^{-1}. This instability of the highly water-sensitive compound has so far hindered its isolation in pure form. Apart from CO_2, adamantane-1-carbaldehyde *(7c)*[11] was identified as a decomposition product by its 2,4-dinitrophenylhydrazine adduct[11,12] (m. p. 224—225 °C, 218.1 °C[11], 225 °C[12]) and by a band at 1720 cm^{-1} (1720 cm^{-1}[11]).

The kinetics of decomposition of *(1c)* can readily be followed by observing the decay of the band at 1875 cm^{-1} when the sample is kept in a thermostated IR cell. Figure 1 shows the reaction to be of first order. The activation parameters resulting from the Eyring equation have the following values at 300 K [values for *(1a)* given in parentheses[2]]: $\Delta H^{\neq}$ = 13.7 ± 0.3 (18.8) kcal/mol, $\Delta S^{\neq}$ = −24.1 ± 1.0 (−8.9) e. u., and $\Delta G^{\neq}$ = 20.9 ± 0.5 (21.5) kcal/mol.

Since the decomposition kinetics of *(1c)* were followed in the reaction solution, the effect of external factors on the decomposition rate cannot be entirely ruled out in spite of strict first order behavior. It may, however, be regarded as probable that *(1c)* is less stable than *(1a)* owing to substituent effects that are still obscure. The large negative value of $\Delta S^{\neq}$ indicates not only a concerted, sterically very demanding rate-determining step but also that the adaman-

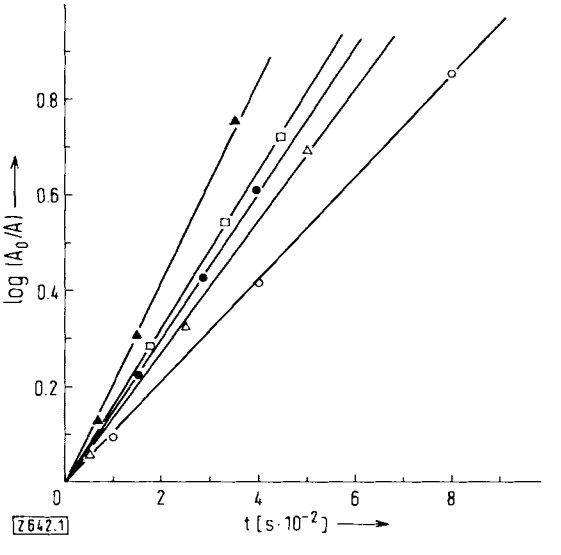


Fig. 1. First order kinetics of the thermal decomposition of α-peroxylactone *(1c)*. Decay of the 1875 cm^{-1} band at 295.1 K (-○-○-), at 301.7 K (-△-△-), and at 303.5 K (-□-□-). Decay of the emission band at 425 nm of *(1c)* (-●-●-) and decay of the emission band at 560 nm of *(1c)* and R (-▲-▲-).

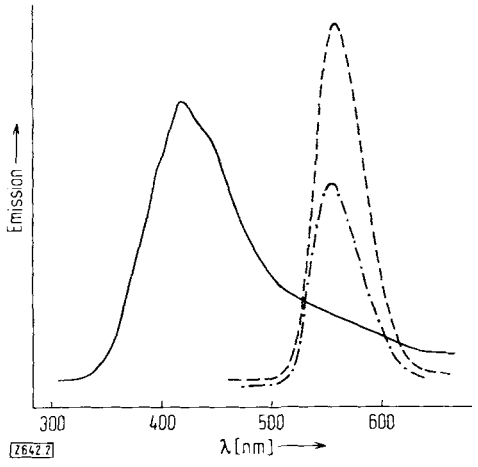


Fig. 2. Chemiluminescence of *(1c)* alone (——), chemiluminescence of *(1c)* and rubrene (– – –), fluorescence of rubrene alone (–·–·–).

tyl substituted molecule can only reach this stage in a state of increased order in comparison with its *tert*-butyl analog *(1a)*[2].

According to *McCapra*[13], α-peroxylactones should decarboxylate to the aldehyde or ketone with emission of light. Figure 2 reproduces the chemiluminescence spectrum of *(1c)* in CCl_4 with a maximum at 415 nm and a broad end emission up to about 650 nm. Excited di-*tert*-butyl ketone, which fluoresces at 405 nm[14], can serve as a model for *(1c)*.

The presence of a fluorescence acceptor like rubrene (R) enhances chemiluminescence by a factor of about 10^3, but only the fluorescence spectrum of R ($\lambda_{max} = 560$ nm) is seen, as is apparent from Figure 2. Since the chemiluminescence in the presence of R and the fluorescence spectrum of R are superimposable, energy transfer from electronically excited *(7c)* to R is established. The decrease in intensity of chemiluminescence also corresponds to a first order decomposition rate. Surprisingly, the presence of R causes a considerable increase in the K value for *(1c)* too [c.f. *(1a)*[2]] (Fig. 1). We cannot, as yet, offer an explanation for this observation.

Received: April 11, 1972 [Z 642 IE]
German version: Angew. Chem. *84*, 590 (1972)

[1] *W. Adam* and *J. C. Liu*, J. Amer. Chem. Soc. *94*, 2894 (1972).

[2] *W. Adam* and *J. C. Liu*, unpublished results.

[3] *T. A. Hopkins, H. H. Seeliger, E. H. White*, and *M. W. Cass*, J. Amer. Chem. Soc. *89*, 7148 (1967); *F. McCapra, Y. C. Chang*, and *V. P. Francois*, Chem. Commun. *1968*, 22.

[3a] *F. McCapra* and *Y. C. Chang*, Chem. Commun. *1967*, 1011.

[4] *O. Shimomura* and *F. H. Johnson*, Biochem. Biophys. Res. Commun. *44*, 340 (1971).

[5] *M. Deluca* and *M. E. Dempsey*, Biochem. Biophys. Res. Commun. *40*, 117 (1970).

[6] *M. Deluca, M. E. Dempsey, K. Hori, J. E. Wampler*, and *M. J. Cormier*, Proc. Nat. Acad. Sci. USA *68*, 1658 (1971).

[7] *F. McCapra, D. G. Richardson*, and *Y. C. Chang*, Photochem. Photobiol. *4*, 1111 (1965).

[8] *L. J. Bollyky*, J. Amer. Chem. Soc. *92*, 3230 (1970).

[9] *Y. N. Kuo, F. Chen, C. Ainsworth*, and *J. J. Bloomfield*, Chem. Commun. *1971*, 135.

[10] *G. R. Rubottom* and *M. Lopez*, 11th Latin-American Chemistry Congress, Santiago/Chile, 1972.

[11] *D. A. Applequist* and *L. Kaplan*, J. Amer. Chem. Soc. *87*, 2194 (1965).

[12] *H. Stetter* and *E. Rauscher*, Chem. Ber. *93*, 1161 (1960).

[13] *F. McCapra*, Chem. Commun. *1968*, 155.

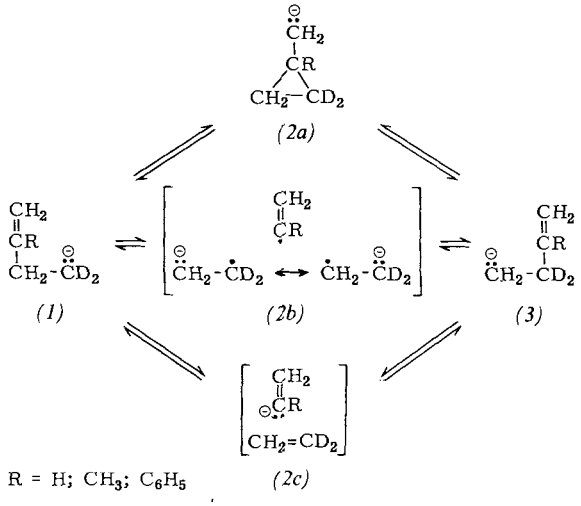
[14] *M. O'Sullivan* and *A. C. Testa*, J. Amer. Chem. Soc. *92*, 5842 (1970).

Rearrangement of 3-Butenyl Grignard Reagents: Anionic or Radical?[**]

By *Adalbert Maercker* and *Werner Streit*[*]

Dedicated to Professor G. Wittig on the occasion of his 75th birthday

The rearrangement of 3-butenide anions *(1)*, R = H, discovered by *Roberts* and his co-workers[1], during which the α- and β-carbon atoms exchange places *(1)* ⇌ *(3)*, has a special position among 1,2-shifts inasmuch as its mechanism may involve an intramolecular nucleophilic substitution according to an addition-elimination mechanism *(2a)*, whereas for the shift of saturated alkyl groups in accord with the *Woodward-Hoffmann* rules[2] only a cleavage-recombination mechanism can become operative. A decision between heterolysis according to an elimination-addition mechanism *(2c)* and homolysis to a radical pair *(2b)* with subsequent recombination within the solvent cage was achieved by the CIDNP method[3] in numerous cases in favor of the radical mechanism *(2b)*[4].

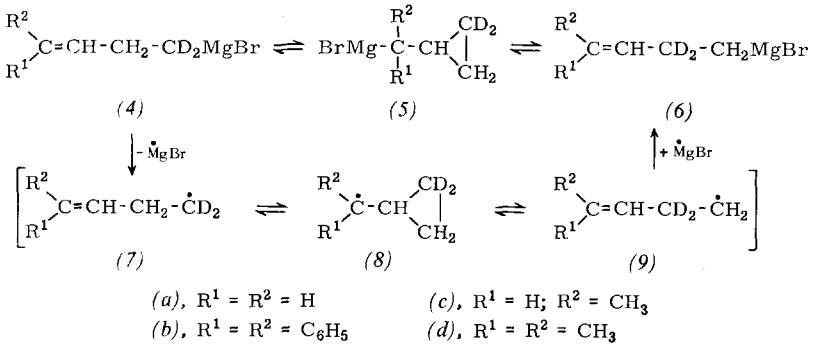


The starting point of our investigations was the question whether rearrangement of 3-butenide anions *(1)* occurs *via* an anionic cyclopropylmethanide intermediate[5] *(2a)* or whether homolytic processes are involved here too. An elimination-addition by way of *(2c)* was also conceivable. The strong retardation of isomerization[6] by methyl or phenyl groups in the γ-position to the carbanionic center *(1)*, R = CH_3 or C_6H_5, contraindicates a cleavage-recombination mechanism *via (2b)* or *(2c)*. On the other hand, acceleration of the rearrangement[7] by phenyl groups in the δ-position *(4b)* makes a cyclopropylmethanide intermediate *(5b)* probable. However, Grignard compounds contain mainly covalent carbon-metal bonds, so that homolysis by way of the radical intermediates *(7)* ⇌ *(8)* ⇌ *(9)* must also be taken into account inasmuch as the radical *(8b)* would also be stabilized.

After CIDNP experiments[3] with unsubstituted 3-butenylmagnesium bromide up to 120 °C had proved negative, we synthesized the compounds *(4c)* (*cis*:*trans* = 42:58) and *(4d)* in diethyl ether (1.1 and 1.3 mol/liter, respectively)

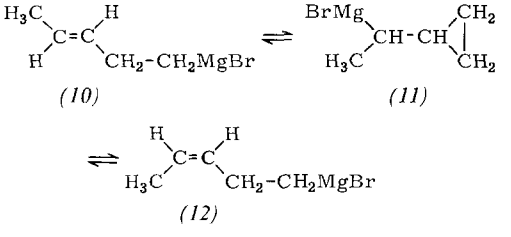
[*] Priv.-Doz. Dr. A. Maercker and Dipl.-Chem. W. Streit
Institut für Organische Chemie der Universität
852 Erlangen, Henkestrasse 42 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



(a), $R^1 = R^2 = H$ (c), $R^1 = H$; $R^2 = CH_3$
(b), $R^1 = R^2 = C_6H_5$ (d), $R^1 = R^2 = CH_3$

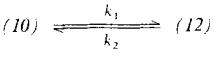
and studied the kinetics of the rearrangement *(4)*⇌*(6)* by NMR spectroscopy. While the unsubstituted compound *(4a)* had rearranged at room temperature with a half-reaction time of 30 h[1], the equilibrium *(4c)*⇌*(6c)* (*cis*:*trans* = 22:78) was established only after 775 hours at 100 °C. A still greater deceleration was brought about by introduction of a second methyl group in the δ-position: the Grignard compound *(4d)* was only 20% rearranged after 900 hours at 100 °C. This finding contraindicates a radical mechanism. Admittedly, according to recent views[8] the stability of *(8c)* and *(8d)* is not expected to be greater than that of *(8a)*, but the deceleration of the rearrangement cannot be brought into accord with formation of the radical intermediates *(7)*⇌*(8)*⇌*(9)*, but only with a carbanion mechanism[6] involving *(5)*.



(10) *(11)*

(12)

In order to determine whether the cyclopropylmethanide intermediate *(5)*, which cannot be detected in the equilibrium mixture, is a true intermediate or only a transition state, we studied the kinetics of the *cis-trans* isomerization



by gas-chromatographic determination of the carboxylation products as methyl esters. Independently of whether the starting material was *(10)* [98% + 2% of *(12)*] or *(12)* [60% + 40% of *(10)*], a reaction of the first order gave always the same *cis-trans*-mixture (21:79) ($K = k_1/k_2 = 0.266$) with $k_1 + k_2 = 14.5$ or $13.2 \times 10^{-3}\ h^{-1}$, respectively. Since this value is of the same order of magnitude as $k_1 + k_2$ for establishment of the equilibrium *(4c)*⇌*(6c)*, *(5)* and *(11)* are probably true intermediates in which the single bond between the carbanionic center and the cyclopropane ring has sufficient time for free rotation. The *cis-trans* isomerization *(10)*⇌*(12)* thus probably occurs by the same mechanism[6] as equilibration *(4)*⇌*(6)* of the α- and β-positions.

Received: March 29, 1972 [Z 648 IE]
German version: Angew. Chem. *84*, 531 (1972)

[1] *M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Rüchardt*, and *J. D. Roberts*, J. Amer. Chem. Soc. *82*, 2646 (1960).

[2] Review: *R. B. Woodward* and *R. Hoffmann*, Accounts Chem. Res. *1*, 17 (1968); Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[3] Review: *H. Fischer* and *J. Bargon*, Accounts Chem. Res. *2*, 110 (1969).

[4] Review: *U. Schöllkopf*, Angew. Chem. *82*, 795 (1970); Angew. Chem. internat. Edit. *9*, 763 (1970).

[5] *A. Maercker* and *J. D. Roberts*, J. Amer. Chem. Soc. *88*, 1742 (1966).

[6] *A. Maercker* and *K. Weber*, Liebigs Ann. Chem. *756*, 43 (1972).

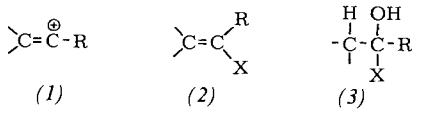
[7] *M. E. H. Howden, A. Maercker, J. Burdon*, and *J. D. Roberts*, J. Amer. Chem. Soc. *88*, 1732 (1966).

[8] *C. Rüchardt*, Angew. Chem. *82*, 845 (1970); Angew. Chem. internat. Edit. *9*, 830 (1970).

Formation and Detection of Vinyl Cations

By *C. A. Grob*[*]

Vinyl cations *(1)*, unknown and rejected a few years ago, are now the subject of an increasing number of investigations. In these cations the formal positive charge resides on the carbon atom of an olefinic double bond. With two—presumably linearly—attached ligands they belong to the group of disubstituted carbenium ions.

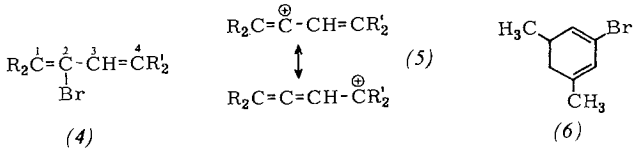


(1) *(2)* *(3)*

(a), R = Aryl
(b), R = Alkenyl
(c), R = Cyclopropyl

The objections which have frequently been raised against the existence of vinyl cations are justifiable inasmuch as simple vinyl halides *(2)* (X = halogen) resist hydrolysis and do not precipitate silver halide from aqueous silver nitrate as is observed with alkyl halides. However, an electron donating aryl substituent in the α-position, as in *(2a)*, can promote ionization under relatively mild conditions, as was first shown in 1964[1]. Thus α-halo styrenes *(2a)* react in aqueous alcohol to form ketones (*via* the enol), enol ethers, and acetylene derivatives by the S_N1—E1 mechanism. α-Alkenyl *(2b)*[2] and α-cyclopropyl substituents *(2c)*[3] likewise increase reactivity.

The reaction rates of α-aryl substituted vinyl bromides of the type *(2a)* depend on substituents in the benzene ring in a predictable manner. Since they are not influenced by the hydrogen ion concentration of the medium a mechanism involving acid-catalyzed hydration to the intermediate *(3)*[4] can be excluded.



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

It is noteworthy that the solvolysis rates of 2-bromodienes *(4)* are hardly influenced by the presence of one or two methyl groups on C-1 [*(4)*, R = CH_3]. However, two methyl groups on C-4 [*(4)*, R′ = CH_3] accelerate the reaction by more than five powers of ten, as expected on the basis of the electron distribution in the mesomeric vinyl cation *(5)*. However, charge delocalization can only occur if C-1, C-2, and C-3 have a linear arrangement, as required by the limiting allenic form. If this alignment is prevented, as in the cyclic bromodiene *(6)*, the negligible solvolytic reactivity characteristic of vinyl halides returns[5]. Vinyl cations have many features in common with ordinary carbenium ions, such as the tendency to isomerize[6] or to rearrange by way of ion pairs. Detailed mechanistic studies are in progress in several laboratories.

Lecture at Leverkusen, April 19, 1972 [VB 338 IE]
German version: Angew. Chem. *84*, 592 (1972)

[*] Prof. Dr. C. A. Grob
Institut für Organische Chemie der Universität
CH-4056 Basel, St.-Johanns-Ring 19 (Switzerland)

[1] *C. A. Grob* and *G. Cseh*, Helv. Chim. Acta *47*, 194 (1964).
[2] *C. A. Grob* and *R. Spaar*, Tetrahedron Lett. *1969*, 1439; Helv. Chim. Acta *53*, 2119 (1970).
[3] *M. Hanack* and *T. Bässler*, J. Amer. Chem. Soc. *91*, 2117 (1969); *S. A. Sherrod* and *R. G. Bergmann*, *ibid.* *91*, 2115 (1969).
[4] *C. A. Grob* and *H. R. Pfaendler*, Helv. Chim. Acta *54*, 2060 (1971).
[5] *C. A. Grob* and *H. R. Pfaendler*, Helv. Chim. Acta *53*, 2130 (1970).
[6] *C. A. Grob* and *R. Nussbaumer*, Helv. Chim. Acta *54*, 2528 (1971).

Energy Coupling and Electron Transport

By *Britton Chance*[*]

In recent years titrations of redox potentials of the redox components of respiration chains (flavoproteins, ubiquinones, cytochromes) have led to a new classification of the components of respiration chains. In this scheme four groups of redox systems are differentiated, within each of which the potential is approximately the same and fixed:

1. Flavoproteins and iron-sulfur proteins in the region −300 mV;

2. Flavoproteins, iron-sulfur proteins, ubiquinones and cytochrome b_K in the region 0 mV;

3. Cytochrome c_1, c and a, as well as copper- and iron-sulfur proteins in the region +240 mV; and

4. Oxygen in the region +840 mV.

Electrons are moved from one of these groups to another by means of electron transport components of alternating redox potential. They adjust their potentials to those of the acceptor or donor groups in the redox systems of fixed potential which function as redox buffers; the energy loss is minimal[1]. The transport systems are called energy transducer components. The nature of the transducer components of the first and second groups is unclear, but cytochrome b_T was recognized by redox potential titrations and kinetically as the transducer component between the second and the third group, and cytochrome a_{3T} spectrophotometrically as the linking compound between the third group and oxygen.

This classification has been supported by analysis of the kinetic models by computer simulation and by optimization of the kinetic constants for suitable mechanisms. In particular it was possible to differentiate cytochromes a and a_{3T} by measuring the kinetics of the reaction with oxygen at low temperatures (in presence of ethylene glycol down to −30 °C)[2]. In these experiments reaction of the respiratory system of intact mitochondria with oxygen was initiated by using a laser flash to decompose a preparation

[*] Prof. Dr. B. Chance
Johnson Research Foundation,
University of Pennsylvania, Medical School
Philadelphia, Pennsylvania (USA)

saturated with carbon monoxide. It proved possible to measure directly the initial reaction of cytochrome a_3 with oxygen by the usual disappearance of absorption at 444 nm and, further, by hitherto unobserved disappearance of the absorption at 600 nm together with appearance of a small but significant absorption band at 428 nm[3]; in that work a new intermediate compound of oxygen and cytochrome a_3, formed extremely rapidly, was identified, whose spectral properties indicated the presence of an oxygenated cytochrome a_3-Fe^{2+} compound. Reaction kinetics at room temperature, redox titrations and computer analysis of the kinetics indicate that the reaction product of cytochrome a_3 and oxygen achieves a potential below that of cytochrome a prior to electron transfer between the two. By analogy with the behavior of hemoglobin it is probably to be expected that drastic changes in the conformation of hemin will occur on alteration of the redox potential of the components and of their spectral properties.

[Lecture at Dortmund on February 22, 1972] [VB 337 IE]
German version: Angew. Chem. *84*, 553 (1972)

[1] *D. F. Wilson* and *P. L. Dutton*, Biochem. Biophys. Res. Commun. *39*, 59 (1970); Arch. Biochem. Biophys. *136*, 583 (1970); *B. Chance, D. F. Wilson, P. L. Dutton*, and *M. Erecinska*, Proc. Nat. Acad. Sci. USA *66*, 1175 (1970); *D. F. Wilson* and *P. L. Dutton* in *T. E. King* and *M. Klingenberg*: Electron and Coupled Energy Transfer in Biological Systems. Dekker, New York 1971, Vol. 1, p. 221; *D. F. Wilson, P. L. Dutton, M. Erecinska, J. G. Lindsay*, and *N. Sato*, Accounts Chem. Res., in press; *T. Ohnishi, D. F. Wilson, T. Asakura*, and *B. Chance*, Biochem. Biophys. Res. Commun. *46*, 1631 (1972); *M. Erecinska, B. Chance*, and *D. F. Wilson*, FEBS-Lett. *16*, 284 (1971); *M. Erecinska, D. F. Wilson, Y. Mukai*, and *B. Chance*, Biochem. Biophys. Res. Commun. *41*, 386 (1970); *P. L. Dutton, D. F. Wilson*, and *C. P. Lee*, Biochemistry *9*, 5077 (1970); *B. Chance*, FEBS-Lett., in press; *D. DeVault*, Biochim. Biophys. Acta *225*, 193 (1971).

[2] *B. Chance* and *M. Erecinska*, Fed. Proc. *31*, 416 (1971), Abstr. 1113; *M. Erecinska* and *B. Chance*, Arch. Biochem. Biophys., in press.

[3] *D. F. Wilson, J. G. Lindsay*, and *J. Brocklehurst*, Biochim. Biophys. Acta, in press.

REVIEW ABSTRACTS

Formation of alkali metal complexes in solution is the subject of a review by *R. Winkler*. General characteristics of complex formation reactions are outlined in the introduction, and specific properties of alkali metal complexes are then described. Several techniques are mentioned for measuring rate and equilibrium constants for complexation reactions of alkali ions with the indicator and model ligand murexide in methanol. The article closes with a detailed discussion of the properties of biological substances with specific alkali ion carrier function, *e. g.* antibiotics with cyclopeptide, cyclodepsipeptide, or macrolide structure. [Kinetics and Mechanism of Alkali Ion Complex Formation in Solution. Structure and Bonding *10*, 1—24 (1972); 38 references]

[Rd 503 IE –H]

The bonding properties of inorganic pseudohalides with the triatomic groups azide, fulminate, cyanate, and thiocyanate are discussed by *Z. Iqbal*. Data about molecular and lattice geometries, vibrational and electronic spectra, lattice energies, and energies of formation are used for comparisons of these types of compounds. A special chapter is devoted to the exotic thermal behavior of azides and fulminates. [Intra- and Inter-Molecular Bonding and Structure of Inorganic Pseudohalides with Triatomic Groupings. Structure and Bonding *10*, 25—55 (1972); 86 references]

[Rd 504 IE –H]

Current views of bonding in carbonylmetal compounds are treated by *P. S. Braterman*. The review provides a qualitative description of the metal-carbon bond in terms of molecular orbital theory and of bonding in polynuclear compounds without or with direct metal-metal interaction. In a second (smaller) section theoretical attempts at quantitative evaluation of energy states of carbonyls are discussed. [Spectra and Bonding in Metal Carbonyls, Part A: Bonding. Structure and Bonding *10*, 57—86 (1972); 110 references]

[Rd 505 IE –H]

The theory of the magnetic properties of polynuclear transition metal compounds is reviewed by *J. S. Griffith*. The treatment of anisotropic g tensor interaction leads to a closed expression for the susceptibility of binuclear compounds. For the treatment of three (or more) coupled magnetic moments the Racah and Wigner irreducible tensor method is used. Three-body interactions and the fine structure of degenerate ground states are also considered. As an example, the magnetic properties of proteins with two sulfur-bridged iron ions (spinach ferredoxin) are discussed. [On the General Theory of Magnetic Susceptibilities of Polynuclear Transition-metal Compounds. Systems with Two or Three Spins. Structure and Bonding *10*, 87 to 126 (1972); 93 references]

[Rd 506 IE –H]

The thermochemistry of the chemical bond is discussed by *V. Gutmann* and *U. Mayer*. Starting from a critical evaluation of *Pauling*'s concept of bond energy, electronegativity, and ionicity a new approach is suggested to describe the ionic character of a bond (valid only for that bond in a specified molecule) with the aid of thermochemical data. The new values of ionic character appear in some cases to be more reasonable than *Pauling*'s values, but they require a knowledge of the bond energies of the homoatomic molecules. A concept to circumvent this difficulty in the treatment of metal compounds is outlined. [Thermochemistry of the Chemical Bond. Structure and Bonding *10*, 127—151 (1972); 6 references]

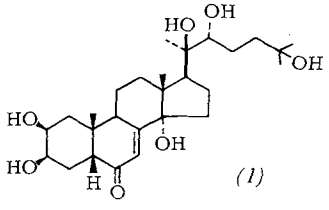
[Rd 507 IE –H]

Spectra and structural properties of complex tetracyanides of platinum, palladium, and nickel are reviewed in two papers by *S. Jerome-Lerutte* and *M. L. Moreau-Colin*. The former is concerned with the vibrational spectra of this group of compounds and with the force constants derived from them; the latter discusses their electronic spectra. A distinction is made between the spectra of "free" ions (in solutions) and the spectra of crystalline compounds. Finally, the luminescence of the tetracyanoplatinates is mentioned. [Vibrational Spectra and Structural Properties of Complex Tetracyanides of Platinum, Palladium, and Nickel. Structure and Bonding *10*, 153—166 (1972); 35 references.—Electronic Spectra and Structural Properties of Complex

Tetracyanides of Platinum, Palladium, and Nickel. *Ibid.* *10*, 167—190 (1972); 33 references]

[Rd 508 IE -H]

Arthropod molting hormones of plant origin are considered by *H. Hikino* and *T. Takemoto*. These phytoecdysones were isolated from *Achyranthes* and *Cyathula* species (Amaranthaceae, Centrospermae) where they are probably formed from cholesterol: β-ecdysone *(1)*; inokosterone; epiecdysterone; rubrosterone; amarasterone A and B; capitasterone; precyasterone; cyasterone; epicyasterone; isocyasterone; sengosterone; poststerone. 2β,3β-Dihydroxyl, 14α-hydroxy-7-en-6-one, and 20(*R*),22(*R*)-dihydroxyl partial structures are common to all these compounds. The article describes their isolation, chemistry, structure determination, synthesis and metabolism, physiological effects

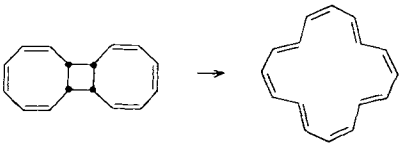


(1)

of ecdysterols in higher animals, as well as physiological activity in arthropods (particularly insects). [Arthropod Moulting Hormones from Plants, Achyranthes, and Cyathula. Naturwissenschaften *59*, 91—98 (1972); 55 references]

[Rd 500 IE -M]

The annulenes form the subject of a review by *F. Sondheimer*. Particularly familiar members of this series are [6]annulene (benzene) and the nonaromatic [8]annulene (cyclooctatetraene). Recent years have seen the synthesis of additional, higher annulenes. Two general methods are available for their preparation: 1. oxidative coupling of a terminal diacetylene to a macrocyclic polyacetylene, conversion into a dehydroannulene, catalytic hydrogenation of



(1) *(2)*

the triple to double bonds; 2. photolytic ring opening of a polycyclic valence isomer, *e.g. (1)* → *(2)*. NMR spectroscopy proved indispensable in the study of the aromaticity (π-electron delocalization) of annulenes. Configurationally isomeric annulenes undergo ready interconversion. Several annulenes are susceptible to thermal and photochemical valence isomerization. Some substitution products are accessible from the parent system, others by independent synthesis. Annulene systems having an uneven number of C atoms are present in the completely conjugated monocyclic annulenones which may be aromatic [(4*n*+3)-membered ring] or nonaromatic [(4*n*+1)-membered ring]. Heteroannulenes are also accessible. Future progress of annulene chemistry will require simple and productive methods of synthesis, the extension of heteroannulene syntheses, and the synthesis of organometal-annulene complexes. [The Annulenes. Accounts Chem. Res. *5*, 81 to 91 (1972); 74 references]

[Rd 502 IE -M]

Transition states as acids and bases is the title of a review by *J. L. Kurz*. It can be shown that the pK_a value of an acidic activated complex ($pK_a(\ddagger)$) is derivable from observable reaction rates. The expressions are particularly simple for H^+ or OH^- catalysis. Far-reaching conclusions of a qualitative nature can be drawn from the $pK_a(\ddagger)$ values; a concept is also available for quantitative interpretation of the $pK_a(\ddagger)$ values. This is illustrated for a nucleophilic displacement reaction, *viz.* hydrolysis of methyl chloride, as example. [Transition States as Acids and Bases. Accounts Chem. Res. *5*, 1—9 (1972); 40 references]

[Rd 501 IE -M]

BOOK REVIEWS

The Chemistry of Nonaqueous Solvents. Vol. 3. Edited by *J. J. Lagowski*. Academic Press, New York–London 1970. 1 st edit., 408 pp., 28 tables, bound, 196 s.

In this third volume of the series[1] the authors *(D. F. Burow, M. Macclean Davis, F. Fehér, R. C. Paul, A. I. Popov,* and *S. S. Sandhu)* have provided considerable help in the development of preparative inorganic chemistry and have produced a handbook which shows the very latest state of the art.

The book deals with sulfur dioxide, hydrogen sulfide, some acyl halides, acetic acid, and other carboxylic acids in their capacity as solvents. One section, on the behavior of Brønstedt acids and bases in "inert" organic solvents *(Marion Macclean Davis)*, should provide valuable information to workers in a very wide range of fields, for example through the interesting survey of solvent mixtures and the good summary of hydrogen bonding.

In most cases the literature references are arranged in the text in such a way that one can rapidly gain access to the reference in question. It is up to the user to make his own evaluation of the numerous references given, and we should not hold it against the authors if occasionally they have paid more attention to complete coverage than to critical selection.

From the viewpoint of the pragmatic user, the contributions of *Feher* (H_2S) and the two chapters by *Popov* (acetic acid and other carboxylic acids) merit special attention. The methodological hints given in these chapters are in many cases also useful when working with other nonaqueous solvents.

H. D. Hardt [NB 21 IE]

[1] Cf. Angew. Chem. internat. Edit. 7, 557, 962 (1968).

Lehrbuch der analytischen und präparativen anorganischen Chemie (Textbook of Analytical and Preparative Inorganic Chemistry). By *G. Jander* and *E. Blasius*. S. Hirzel Verlag, Stuttgart 1970. 9th edit., xxv, 497 pp., 68 figs., 6 tables, bound, DM 28.—.

Recent editions of this book have shown a tendency toward the introduction of new theoretical chapters or the updating and extension of existing ones; this tendency is continued in the present edition. It is thus not surprising that the chapters on "The law of mass action and ionic theory" and on "The chemistry of complexes" have been reformulated and amplified.

However, the continual increase in the theoretical chapters is making it more and more difficult for the beginner to use the work as a textbook at the start of his studies, for too many topics are treated too briefly and with insufficient clarity. One might be forgiven for wondering whether students in their first year would, for example, gain much by working through the chapter on "Chemical bonding", especially since there is no obvious relationship to qualitative analysis. Again, it would require considerable effort to understand the concept of Lewis acids and bases (to which only a single sentence is devoted) or the completely isolated treatment of the Grimm hydride shift.

The analytical section is very good and comprehensive, and the separation procedures are well thought out and reproducible; however, it is so complicated that one cannot see the picture as a whole, and thus it is unsuitable as teaching material for chemistry students. It would only be required in this form in establishments where the topic of inorganic chemistry is represented solely by qualitative analysis. On the other hand, the preparative section is dealt with in far too brief and classical a manner; for example, not a single synthesis of a π-complex is given. This is regrettable, since preparative work is also a way in which information on compounds can be conveyed.

For these reasons, this imposing-looking work can only by recommended with reservations to chemistry students. The authors have written another book, "Einführung in das anorganisch-chemische Praktikum (Introduction to Practical Inorganic Chemistry)"; this book contains sufficient qualitative and quantitative analytical chemistry to provide the analytical training required for a chemist, and it is to be preferred to the book under review.

Alois Haas [NB 23 IE]

Physical Principles and Techniques of Protein Chemistry, Part B. From the series Molecular Biology. An International Series of Monographs and Textbooks. Edited by *S. J. Leach*. Academic Press, New York–London 1970. 1st edit., xiv, 491 pp., numerous figures, $ 11.20.

This volume[1] is a collection of further applications of physical methods in protein chemistry. It consists of the following chapters: 10. Ultracentrifugal analysis *(J. H. Coates)*; 11. Viscosity *(J. H. Bradbury)*; 12. Optical diffraction *(S. N. Timasheff* and *R. Townend)*; 14. Nuclear magnetic resonance spectroscopy *(J. C. Metcalfe)*; 15. Bonding of protons and other ions *(F. R. N. Gurd)*; 16. Differential thermal analysis *(H. Morita)*.

In most cases the authors place great weight on instructive hints. The reader is familiarized with the theoretical fundamentals of the method, and this is done both for methods which are not much used in protein chemistry (Chapters 14 and 16) and also for the well known methods (Chapter 10). Almost all the chapters are oriented toward practical applications. There are only a few errors to mar the high level of achievement; the most serious of these is the incorrect definition of the scale of chemical shifts. In some places an insufficiently clear distinction is made between "frequency" and "wave number". Selection of the methods and the arrangement of the chapters have already been discussed in the review of Part A[1].

It is to be hoped that the projected Part C will soon appear and complete this very useful survey. If it is still possible, I would recommend the inclusion of an informative chapter on electron spin resonance and spin labelling.

Karel Bláha [NB 24 IE]

[1] Cf. Angew. Chem. internat. Edit. *83*, 362 (1971).

The Chemistry of Synthetic Dyes. Volume III. Edited by *K. Venkataraman*. Academic Press, New York–London 1970. 1st Edit., xix, 485 pp., numerous illustrations and tables, bound, $ 27.50.

The first supplementary volume to the standard work on dye chemistry (Volumes I and II of *Venkataraman*'s "The Chemistry of Organic Dyes") has just been issued, recording the advances made in certain sectors over the past 20 years.

The decisive factor in the carefully balanced presentation of many of the chapters is certainly that the authors are all experts in their fields and work in large industrial research laboratories. Only in this way could the descriptive matter be so permeated with the knowledge and practical experience and the main lines of advance be traced out with the maximum of accuracy and clarity while working from a literature source often consisting of innumerable patents which are difficult to assess. As in the earlier volumes, the extremely high number of literature references ensures the practical usefulness of this book. In accordance with recent developments, the theoretical fundamentals receive a wider coverage than before, *e.g.* in the section on "Color and electronic state" by *Mason*, which will also be readily understood by the chemist. In almost all cases, care is taken to ensure a smooth transition (or occasionally an amplification) from the formerly used dyestuffs chemistry presented in the earlier volumes.

The volumes of this work correspond in content and price to a volume of *Houben-Weyl*, and wherever the latter work is found the former should also be present. The concept of the new volumes and the stimulus which the field of dyestuffs gives—or is capable of giving—to a large number of related fields raise this work to the same level. No dyestuffs chemist working in industry and research can manage without this book, and anyone who by his profession is predominantly concerned with the use of dyes will get useful information from relevant sections of the book.

Peter Dimroth [NB 35 IE]

Analytical Flame Spectroscopy—Selected Topics. Edited by *R. Mavrodineanu*. Macmillan and Co. Ltd., London–Basingstoke 1970, 1st Edit., xxii, 772 pp., numerous illustrations and tables, bound, £ 14.00.

According to the editor's foreword, this book, the result of a collaboration between 19 authors, is intended to present a consistent account of analytical flame spectroscopy, *i.e.* atomic emission, atomic absorption, and atomic fluorescence spectroscopy. Such a book, which covers the

whole complex field of flame spectroscopy and where possible enables comparisons to be made between the individual techniques, is indeed very welcome, because for years atomic absorption and atomic emission spectroscopy have been regarded as competitive rather than complementary techniques. A book of this kind should have been written a long time ago.

The monograph begins with an introduction to emission flame photometry, in which *C. Th. J. Alkemade* guides the reader in admirably clear form "from sample to signal".

In the following contribution on "Sensitivity, detection limit, precision, and accuracy in flame emission and atomic absorption spectrometry", the authors are unable to decide whether good limits of detection should be described as "high" or "low". In addition, the uncritical mention of such delicate matters as the multiple passes of the beam through the flame means that the statements on optimization of instrument components offer no genuine information to the analyst.

The next two sections are concerned with the optics and electronics of spectrophotometers. The first contribution certainly gives detailed descriptions of lenses, mirrors, prisms, and gratings, but does not go into the specific requirements of atomic absorption and fluorescence. In the second contribution the analyst who is interested in electronics will find a readily understandable explanation of various analog and digital circuits.

The fifth chapter is titled "Nonmetals" and provides a wealth of material. However, with its almost 200 pages and over 600 literature references, this "book within a book" almost bursts the boundaries of the present monograph, and the reader cannot escape the impression that a certain amount of tightening up would have increased the information content.

Next comes a brief, clear exposition of the relative advantages of atomic emission and absorption spectrometry for the determination of the rare earth elements in the fuel-rich oxyacetylene flame. This section is made particularly valuable for the analyst by the appendix giving emission spectra for this group of elements.

In contrast, "Spectroscopic investigations of low-pressure oxyacetylene flames" is a purely theoretical paper, and as such will arouse little interest in the analyst.

The eighth chapter is a report on the application of flame photometry to agricultural chemistry, with mention of rocks and soils, plants, water, and fertilizers. It is very regrettable that this section deals exclusively with emission analysis, since agricultural chemistry is one of the classical fields of application for atomic absorption spectroscopy.

The same is true of the next section, which is concerned with "Applications of flame photometry in biology and medicine". In this case, however, it is apparent that the author *(R. Herrmann)* is in no way to blame for this limitation, for he writes in his introduction "Since the application of atomic absorption and atomic fluorescence methods in biology and medicine will be described in a separate chapter . . .". The reader will look for this chapter in vain. This contribution begins with a pleasingly objective comparison between flame emission and atomic absorption spectroscopy, which I should have been only too happy to see continued in the practical section.

This series of contributions on the applications of the techniques is concluded by two introductions, to "Atomic absorption spectrometry" *(J. B. Willis)* and "Atomic fluorescence flame spectrometry" *(J. D. Winefordner* and *R. Smith)*. The qualifications of the authors are reflected in these two clear, brief, and readily understandable articles, which considerably raise the level of the entire work.

The topic of atomic absorption spectroscopy is rounded off with an article on the theory, manufacture, and applications of hollow cathode lamps, which gives many interesting details on these element-specific light sources.

The work ends with a "Bibliography on flame spectroscopy" prepared by the editor for the years 1966 and 1967 with over 2000 references, about two-thirds of which relate to flame emission spectroscopy, while atomic fluorescence spectroscopy is not mentioned.

The make-up of this bibliography is symbolic for the problems of the entire work, both in its over-emphasis of emission flame photometry in comparison with atomic absorption spectroscopy (this is not dictated by the subject matter) and its out of date nature. The book essentially deals with the position as it was in 1966: the only contribution that has any supplementary material is the one on atomic absorption spectrometry, and this supplement begins with the words "During the period of more than 18 months that has elapsed since writing this chapter...". The supplement includes the essential new work in this field up to and including 1968; this could have been repeated with advantage for some of the other contributions.

On the whole, however, this book (at least in certain chapters) provides a welcome supplement to other works and gives many useful details.

Bernhard Welz [NB 36 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften under the direction of *Margot Becke-Goehring*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 8th fully revised edition.

System No. 47. Lead, Part C, 4. Conclusion of compounds. Coordination compounds. Ligand index. Subject index for Part C. Principal editor: *Hubert Bitterer*. 1971. vi, xix, 639 pp., 235 figures, Balacron DM 756.—.

Following remarkably quickly on the earlier volumes of Part C of System No. 47 "Lead"[1], the present 4th volume concludes the description of lead compounds. It begins with compounds of lead and zinc (System No. 32), and then, in accordance with the Gmelin arrangement, describes compounds with the elements up to System No. 46, *i.e.* tin. The coordination compounds of lead are then discussed. The organic ligands are arranged in a formula index based on Hill's system (according to the number of C atoms, then of H atoms, and finally of the other elements in alphabetic order).

The volume closes with a comprehensive subject index (91 pages) listing all the compounds, groups of compounds, alloys, and facts from Volumes C1 to C4. The literature is evaluated up to, and in some cases beyond, 1969.

The present volume is primarily of interest to metallographers, metallurgists, and metal physicists, since large parts are concerned with alloy systems. The superconducting lead-thallium and lead-indium alloys have been particularly intensively studied. Corresponding to the importance

(theoretical as well as industrial) of lead-tin alloys, 32 pages are devoted to this subject and a further 67 pages to lead-tin alloys that also contain other components and are used *e. g.* as bearing metals, solders, type metals, cable sheaths, metal baths, *etc.* Among the oxide systems containing lead, glasses are particularly important; the technical significance of these glasses has been known for a long time, but like glasses in general, they are gaining in scientific importance.

The last chapter deals with the coordination compounds of lead with neutral and inner complex forming ligands, with the exception of organo-lead compounds. Though the arrangement of this material naturally presents great difficulties, an arrangement that is simple from the chemical point of view has been found. The many structural formulas in this part of the volume are particularly commendable, as they provide the chemist with a general picture at a glance. Together with the alphabetically listed ligands or classes of ligands in the subject index and a formula index for organic ligands they enable the desired information to be found quickly.

Ekkehard Fluck [NB 31 IE]

[1] Cf. Angew. Chem. internat. Edit. 9, 913 (1970).

Physical Surfaces. Volume 20 in the "Physical Chemistry" series. By *J. J. Bikerman*. Academic Press, New York–London 1970. 1st Edit., ix, 476 pp., numerous illustrations, bound, $ 25.00.

J. J. Bikerman's "Surface Chemistry", published in 1958, will already have brought his name to the attention of many of those interested in surface physics and chemistry. As its title implies, this new book is intended primarily as a discussion of the basic physical aspects of surfaces rather than matters of chemistry and application. A restriction of this kind is essential to a book which, in a single volume, aims to cover such diverse topics as the mechanics and physical chemistry of liquid surfaces, liquid-liquid interfaces, foams and emulsions, solid surfaces, wetting, adsorption, electric surface phenomena, and adhesion.

The author familiarizes the reader with the many phenomena that can be observed on surfaces and interfaces, deals with the experimental results obtained, and describes approaches to their theoretical interpretation. The subject is dealt with in a comprehensive manner, old established facts appear side by side with information on the most recent discoveries, the references (about 800) cover a period ranging from the first half of the last century to the closing years of the 1960's. Thus, the work should be regarded more as a textbook than a report on recent progress.

The book should be of particular value to any teacher or student looking for a sound review of the physical chemistry of surfaces and interfaces.

Gerd Wedler [NB 37 IE]

Introduction to Molecular Biology. By *S. E. Bresler*. Academic Press, New York–London 1971. 1st Edit., xv, 556 pp., numerous illustrations, bound, $ 17.50.

The revolution in physics in the form of atomic physics was followed in the forties by a revolution in biology in the form of atomic biology. One need hardly be an expert to see that within the space of one short human lifetime biology has changed from a descriptive science to one based on a theoretical foundation. The development of molecular biology is due not only to the invasion of the biologists' Elysian fields by theoretical physicists but also to the application of new physico-chemical techniques to characterize megamolecular structures. Under the stimulus of such techniques and by means of the skill involved, molecular biology has gained a key position in modern thought and research, and thus a textbook-style introduction to this field is highly desirable. One therefore approaches this book with eager expectation, especially as the book is distinguished by two other facts. In the first place, the author is a physical chemist who has worked in the field of high polymers, and he cannot help but give a practical cast to his account of the application of mathematical and physical methods to the structure and function of biopolymers. Secondly, the book comes from the USSR, and although the Russians have a considerable need to catch up in molecular biology, their education gives them a thorough mathematical background. The work should therefore be elementary but not superficial. Both these expectations are indeed partly fulfilled, though we are left with the feeling that molecular biology is still a very heterogeneous field; wide areas of collected descriptive matter are followed by brief stretches of laws capable of physico-chemical interpretation. Only in rare cases can a biological process be derived theoretically and mathematically, or even predicted.

The book is fairly obviously derived from a lecture manuscript, which appeared in the USSR in 1963 and 1966 and to which some supplementary material was added for the purposes of the translation to bring it up to 1969. This may explain the extreme care with which the reader is artificially led from one topic to another, and the introduction, without derivation, of various complicated concepts. Thus, in order to explain the mechanisms of enzyme action, the theory of absolute reaction rates is abruptly introduced in *deus ex machina* fashion, and similarly statistical thermodynamics are used to clarify the concept of allostery. But these are just words, which will leave the biology student (for whom the book is primarily intended) unsatisfied and disappointed. Interesting concepts are, however, opened up for the chemist.

On closer inspection, the book has much to offer to advanced students of both biology and chemistry. The clear layout embraces the structure of proteins and nucleic acids, with particular emphasis on the methods of investigation and the problems of transition between states of ordering. The functions of proteins, deoxyribonucleic acids, and ribonucleic acids are made comprehensible, and fundamental research results are described in detail. It is true that in every chapter one may search in vain for many recent results and hypotheses, and it would have been helpful to have omitted the standard presentation of basic chemical facts in favor of a carefully thought out discussion of the innermost secrets of the molecular world. But if many sections of the book are disappointing, they are balanced by chapters that come closest to the author's experience and interests. These are the physico-chemical relationships in the behavior of biopolymers, which scarcely get a mention in other textbooks. These sections (and they are the better half of the book) may be strongly recommended to students capable of further advance, provided they have sufficient background in physics to understand them; they may also be recommended to biochemists and biophysicists who wish to be better informed on the modes of thinking and methods of operation of their colleagues.

L. Jaenicke [NB 38 IE]

Die biologische Zukunft des Menschen (The Biological Future of Mankind). Umschau-Verlag, Frankfurt 1971. 1st Edit., 131 pp., DM 13.80.

This book with its very imposing title is the German translation of eight articles which appeared a year ago in the UNESCO journal "Impact of Science on Society". The topics are as follows: Sex, drugs, ethics; Modifications to the reproductive process; Genetic engineering: can we change the hereditary material?; Problems and prospects of organ transplantations; Extension of active life; Knowledge by injection; Biotechnology: the body as machine; Robots, an extension of the human arm.

The contributions are of very variable quality. The only articles which are really worth reading in the light of the book's title are the ones on modifications to the reproductive process, genetic engineering, and organ transplants. They are clearly written and present the reader with problems that have a solid basis in the present. They may well be of importance for the biological future of mankind (although mankind has hardly learned how to master its biological present); indeed, some of them definitely will be of importance. The other contributions are, in comparison, on a considerably lower plane with regard to clarity or contents. This is a pity, since on all the topics collected here, and a few others besides, there are important things to be said, even when we realize (and this is yet another distinguishing mark of the good contributions in this book) that the word "future" in such compilations is just a synonym for "present". This present requires extremely careful and imaginative attention, and it requires it in good time. The true problems of the biological future of mankind lie in the fact that every new development seems to have the nature of a boomerang; to our eyes it appears as moving in a straight line, and we do not notice its return—we tend to recognize the wood for the trees only when a forest fire is well on its way.

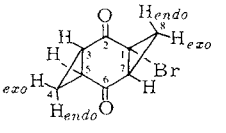
Helmut Grünewald [NB 40 IE]

Errata

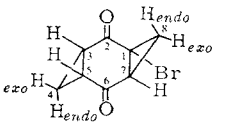
In the communication "Synthesis and X-Ray Structure Analysis of *anti*-1-Bromotricyclo[5.1.0.0^{3,5}]octane-2,6-dione (*anti*-1-Bromobishomoquinone)" by *Jürg Heller, André S. Dreiding, Rita Grieb*, and *Alfred Niggli*, Volume 11, March 1972, the following corrections should be made:

On page 236, right-hand column, lines 17 and 18 "*anti*-8,8-dibromo-1,4,4-trimethyltrichloro[5.1.0.0^{3,5}]octane" should read "*anti*-8,8-dibromo-1,4,4-trimethyltricyclo[5.1.0.0^{3,5}]-octane".

On page 236, right-hand column, the formula at the bottom of the column should not be



but



On page 238, left-hand column, line 15 "J. Chem. Soc." should read "J. Amer. Chem. Soc."

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 4036/4037, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (06201) 4031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 7
July 1972
Pages 551–652

International Edition in English

Structural Principles of Biomembranes[**]

By Werner Kreutz[*]

Dedicated to Professor O. Kratky on the occasion of his 70th birthday

The determination of the electron density distribution of the membrane cross sections of nerve myelin and the discs of the outer segments of retinal rods by a new X-ray evaluation method indicates, as in the case of the cross-sectional structure of the photosynthetic membrane, an "asymmetric" mass distribution. In connection with the detection of planar protein lattices in the membranes of photosynthetic bacteria, the chloroplasts of higher plants, erythrocytes, and retinal discs as well as the detection of a new category of lipid characteristics, comprising isothermal conformational and phase changes by specific ligand binding, a basis is established for the development of a general concept of biomembrane structure.

1. Introduction

The phenomenological capabilities of biomembranes comprise an impressive range of functions, such as nerve excitation, sensory transduction, gland functions, energy transformation (photosynthesis and respiration), osmotic regulation, *etc.* This quite apart from the fact that, as purely morphological elements, they are responsible for the compartmentation of "internal milieus" and thus create one of the essential prerequisites for life *per se*. For membranologists this fascinating complexity of biomembranes represents a great challenge, namely that of understanding this functional variety on the molecular level. It is this aspect as manifested in the dynamic molecular architecture, in the molecular characteristics, and in molecular interactions with which this progress report is concerned.

The following four questions outline the essential problems which confront us on the molecular level:

1. What is the steric state (conformation) of the proteins and what is their planar arrangement within the membrane? Are there variable protein states?

2. What is the conformation of the lipids and what is their planar distribution? Do variable lipid conformations exist?

3. What interactions occur between proteins and lipids? What is their steric relationship (coupling)?

4. What possibilities of structural variation and what physicochemical capabilities associated therewith are encountered in the molecular membrane architecture as a whole for the accomplishment of the various functions such as *e.g.*: ensuring a specific permeability, regulation of permeability changes, passive-, facilitated-, and active transport mechanisms and their control, generation of concentration gradients or potentials, regulation of potential changes (*e.g.* light-induced or

[*] Prof. Dr. W. Kreutz
Institut für Biophysik und Strahlenbiologie der Universität
78 Freiburg, Albertstrasse 23 (Germany)

[**] The following abbreviations have been used:
DGD = digalactosyl diglyceride
MGD = monogalactosyl diglyceride
PA = phosphatidic acid
PC = phosphatidylcholine
PE = phosphatidylethanolamine
PG = phosphatidylglycerol
PI = phosphatidylinositol
PS = phosphatidylserine

chemically induced changes), transmission of excitation, potential-linked chemical syntheses (phosphorylation), redox reactions, and probably also information storing capacities.

Our knowledge gained hitherto indicates that the extensive variability of membrane functions derives from a flexible "basis-membrane" whose versatile structural adaptability permits the association of various special functional proteins on both sides of the membrane and thus makes vectorial processes feasible in both directions. It therefore appears reasonable to distinguish between a "basis membrane" and a "function membrane". With this in mind, it will be our initial endeavor to develop a general concept of the basis-membrane structure. If we are to proceed in this manner, then the stereochemical and physicochemical characteristics of the basis-membrane proteins and of the lipids will have to be discussed as a first step. An exposition of the qualities of the two groups of substances will provide the pre-conditions essential for an examination of the possibilities of coupling, *i. e.* the joining of these substances to form a membrane. The second part of the paper pursues the conversion of the basis membrane into the function membrane and an attempt is made to explain some functional capabilities on the basis of this structural concept.

2. The "Basis Membrane"

2.1. The Intrinsic Dynamics of Lipids

Hitherto, in the assessment of membrane phenomenology functional predominance has been attributed to the proteins. The reason for this lies in the fact that the lipid characteristics so far established did not allow an appreciable functional variance. In this respect it will be necessary in future to make a fundamental adjustment.

The physico-chemical data available today are essentially the result of observations of *p,T*-phase transitions between laminar cubic and hexagonal lattices[1-3], of measurements of surface potentials, of surface pressure or surface tension[4, 5], as well as surface requirement of monomolecular lipid layers on an aqueous phase (summary: [6]). To these must be added the determination of permeability data and electrical qualities of bimolecular lipid layers[7-10] and also ESR-[11] and NMR measurements[12] with lipids. Furthermore, it has commonly been accepted that phospho- and galacto-lipid molecules occur in only one conformational state, *i. e.* the one shown in Figure 1 a. (There is only one exception: the lipid conformational state postulated by *Finean*[13] in his model of myelin-membrane structure.)

It is as the result of the following qualities that the lipids acquire actual functions:

1. In principle lipids are able to exist in two different conformational states[14] (Figs. 1 a and 1 b).

2. These conformational states can be transformed from one into the other by ligand binding. In other words, lipids can undergo chemically induced conformational changes[15].

3. Lipids can undergo phase transitions induced by ligand binding[15].

4. The miscibility of lipids with each other is highly selective[14, 15].

In view of these qualities one is led to speak of an intrinsic lipid dynamic behavior. In considering these intrinsic dynamics we must also allow for transverse and lateral lipid movements in lipid layers[16] as well as for cation-induced lipid-organization changes[17].

2.1.1. Conformational States and Micelle Types

The steric characteristics and the miscibility behavior of lipids can be examined by using low angle X-ray diffraction methods. Different conformational states and micelle types produce very distinct X-ray diffraction patterns. Further information can be obtained by quantitative titrations of the polar groups[18] in different conformational states, by ESR spin labeling[11], NMR measurements[12], enzymatic fragmentation, and measurements of calorimetric and kinetic data of conformational changes[2].

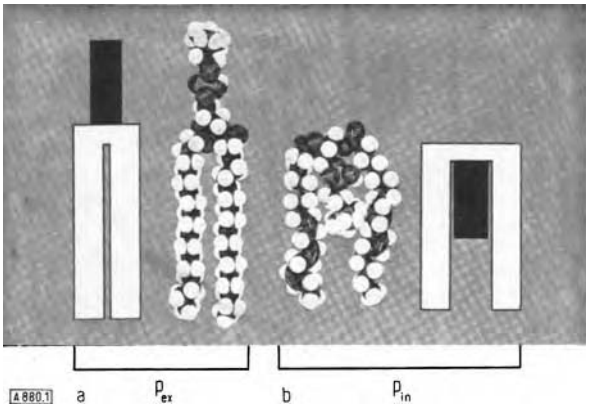


Fig. 1. a) p_{ex}-conformational state of lipids represented by a Stuart-Briegleb model and by the corresponding symbol used further on in this paper, b) representation of the p_{in}-conformational state.

The essential difference between the two conformational states of the lipids can most probably be ascribed to the fact that in the one case the polar group is located outside, and in the other it is incorporated in the fatty acid domains (Figs. 1 a and 1 b). In the following, the conformations shown in Fig. 1 will be referred to as the p_{ex}-conformation (polar group external conformation) and the p_{in}-conformation (polar group internal conformation). These two conformational states permit the formation of laminar and tubular-shaped lipid superstructures shown in Fig. 2. So far we have observed structures a, b, c, f of Fig. 2, but not e; d is questionable. It would appear that laminar micelles can be formed both by lipids in the p_{ex}-conformation and by lipids in the p_{in}-conformation, whereas the tubular structures, which are always arranged in hexagonal lattices, can only be formed by lipids in the p_{in}-conformation.

All saturated lipids, *i. e.* lipids comprising saturated fatty acids, occur at room temperature exclusively in the p_{ex}-conformation. This can be demonstrated very simply by

hydrogenating unsaturated natural lipids (n-lipids) thereby transforming them into saturated lipids (s-lipids). All lipids of this category so far studied[3] form laminar structures at room temperature, and accordingly reveal periods corresponding to twice the length of a fatty acid plus the polar groups in X-ray experiments (Fig. 2a)[14].

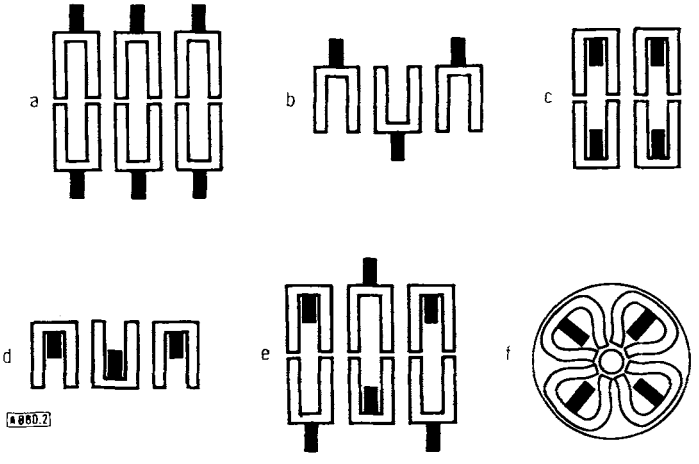


Fig. 2. a), b), c), d), e) conceivable laminar structures of lipids in the p_{in}- and p_{ex}-conformation, f) cross section of a tubular lipid superstructure formed by four lipid molecules in the p_{in}-conformation.

On the other hand the natural lipids which are partially or completely unsaturated exhibit a much more differentiated behavior. This category includes molecules of a static nature, *i.e.* which occur at room temperature invariantly in either the p_{ex}- or the p_{in}-conformation, and dynamic molecules which, depending upon physico-chemical parameters or ligand binding, acquire either the p_{ex}- or the p_{in}-conformation. Thus, for instance, PC (phosphatidylcholine) and DGD (digalactosyl diglyceride) represent typical static molecules, whereas PE (phosphatidylethanolamine), PA (phosphatidic acid), PS (phosphatidylserine), PG (phosphatidylglycerol), and PI (phosphatidylinositol) show a dynamic behavior.

2.1.2. Phase Transitions Caused by Ligand Binding

In this case the term "phase transition" signifies the cooperative transformation from one type of lipid lattice into another. Temperature-dependent phase transitions of lipids are well documented in the literature[1, 3] and since they take place at temperatures about 40 °C[11], they can scarcely play a significant role in physiological processes *in vivo*[*]. Of great physiological significance, however, could be the temperature-*in*dependent reversible phase transitions which can be performed by PE. The phospholipid PE possesses the unique quality of accomplishing temperature-independent phase transitions by bicarbonate and carbonic acid binding[15]. Since only bicarbonate and carbonic acid are bound in the ratio 1:1, this process also represents a pH-dependent phase transition. In other words, it constitutes a phase transition which is indirectly controlled *via* the auxiliary system:

$$H_2CO_3 \underset{+H^+}{\overset{+Na^+}{\rightleftharpoons}} NaHCO_3$$

According to the apparent p*K*-value of carbonic acid at pH = 6.3 the range of control extends from pH > 5.5 to pH < 7. In the pH range < 5.5 only tubular structures of PE in hexagonal arrangements are found (Fig. 3). In the range of regulation between pH = 5.5 and 7.0 the tubular structures are transformed into lamellae depending on the extent of bicarbonate and carbonic acid binding (max. at pH = 6.3). Our experiments also indicate that at pH > 8 the carbonic acid system no longer has any ligand function for PE, since in this pH-range PE again forms tubular micelles. It is an interesting fact that in the said pH-range PE mainly binds Ca^{2+}, its tubular micelles being transformed into laminar ones in the process (Fig. 3). Ca^{2+} and the carbonic acid system thus possess similar competing ligand functions; dominance of one over the other is in each case determined by a definite pH-range. Both in the case of bicarbonate (pH = 5.5—8) binding and in that of Ca^{2+} binding (pH > 7) PE occurs in the p_{in}-conformation and forms symmetrical bimolecular micelles of 44 Å or 45 Å thickness.

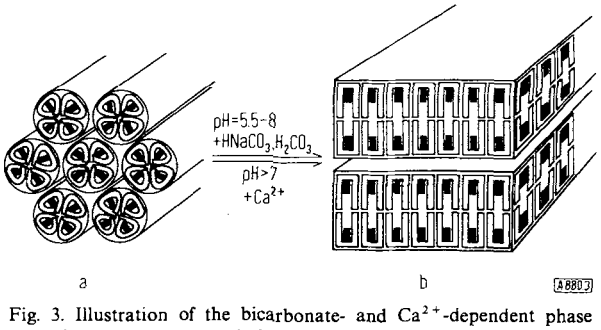


Fig. 3. Illustration of the bicarbonate- and Ca^{2+}-dependent phase transition of PE between tubular hexagonal lattices and laminar linear lattices.

A further significant characteristic is that Ca^{2+} is in part also bound in the acidic pH-range by PE, the PE undergoing transition from the p_{in}- to the p_{ex}-conformation and forming laminar bimolecular micelles that are 54 Å thick.

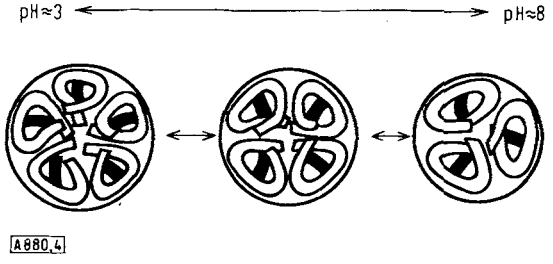


Fig. 4. pH-dependent cross-section construction of tubular PE-micelles consisting of five, four, and three PE molecules.

It is also noteworthy that in the absence of CO_2 and Ca^{2+} the diameter of the tubular structures decreases as the pH increases. It drops gradually from 48 ± 1 Å at pH ≈ 3, *via* 43 ± 1 Å, to 37 ± 1 Å at pH = 8. Since the tubular diameters are in a ratio of $\sqrt{5} : \sqrt{7} : \sqrt{3}$, the tubular cross sections apparently consist of 5, 4, or 3 PE molecules (Fig. 4)[15].

[*] The biological significance of the very well regulated body temperature of 36—37 °C in idiothermous animals could lie in the prevention of irregular thermal phase-transitions.

2.1.3. pH-Dependent and Ligand-Regulated Conformation Changes

In contrast to PE, which is outstanding for its ability to perform regulated phase transitions in which its conformational state essentially remains unchanged, PA is distinguished by the unique ability to undergo pH-, CO_2-, and Ca^{2+}-dependent conformational changes while maintaining the same laminar micelle type[15]. A decisive parameter in the conformational transition of PA is the p*K*-value of the second dissociation step of the phospho group at pH ≈ 7. In the acidic pH-range PA is found in the p_{in}-conformation, in the alkaline pH-range it exists in the p_{ex}-conformation (Fig. 5).

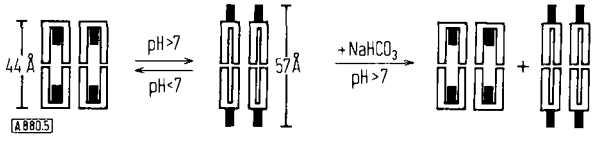


Fig. 5. pH-dependent conformational and micelle change of PA: The p_{in}-micelles are converted into p_{ex}-micelles. By the addition of bicarbonate at pH > 7 the p_{ex}-micelles are partly transformed into p_{in}-micelles.

In the presence of CO_2 both conformational states occur in about equal proportions in the alkaline range. On addition of Ca^{2+} throughout the entire pH scale, PA is quantitatively transformed from the p_{in}- into the p_{ex}-conformation (Fig. 6). In the acidic pH-range two different kinds of laminar micelle formation occur (Fig. 6a) (in varying proportions), whereas in the alkaline range only one laminar micelle type is formed (Fig. 6b). In conclusion it can be said that protonation of the secondary PO^- group of PA favors the p_{in}-conformation, whereas the binding of Na^+ and Ca^{2+} stabilizes the p_{ex}-conformation.

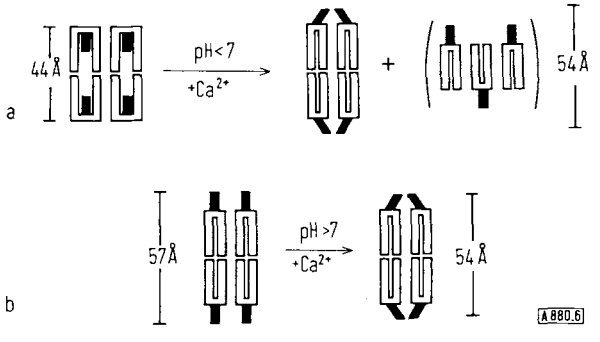


Fig. 6. Ca^{2+}-dependent conformational and micelle changes of PA: in the acidic range the p_{in}-micelles are converted into two types of p_{ex}-micelles, in the alkaline only one type of p_{ex}-micelle is formed.

PS shows neither the qualities of PE nor those of PA. Throughout the entire pH-scale, PS is found in the p_{ex}-conformation. Nor can this conformational state be modified by addition of Ca^{2+}-ions. However, PS is provided with another special property: The p_{ex}-conformation can be totally converted into the p_{in}-conformation by the addition of the amino acid alanine (Fig. 7a). This conversion cannot be achieved in such a perfect manner by other amino acids. Most amino acids are associated with the p_{ex}-conformation (Fig. 7b)[15].

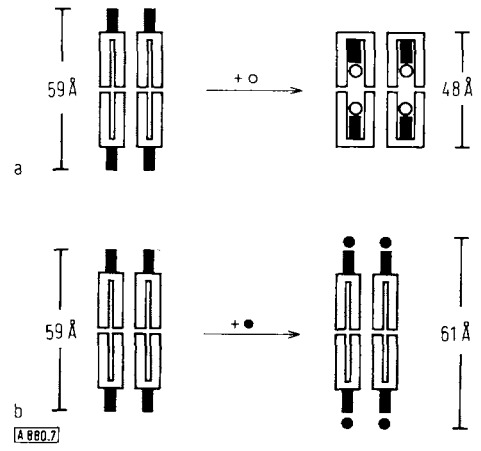


Fig. 7. Amino-acid induced conformational changes of PS. a) Alanine (○) transforms the p_{ex}-conformation quantitatively into the p_{in}-conformation, b) other amino-acids (●) are associated with the p_{ex}-conformation.

Comparable specific qualities are also to be anticipated in the case of PI and PG. However, in both instances no final results are yet available.

2.1.4. The Miscibility Behavior of Lipids

If phospholipids are mixed in organic solvents, dried by evaporation, and studied at room temperature by X-ray diffraction methods the following overall picture of lipid behavior is obtained: n-PC, n-PG, and sphingomyelin form laminar micelles, whereas n-PA, n-PE, and n-PS form tubular micelles. Tubular superstructures are also yielded by the combination PS/PA. A common characteristic of mixed micelle formation is that the mixing partners adapt their conformational state so that mixed micelles of homogeneous conformation are produced[14, 15].

In an aqueous environment, lipids show a far more complex behavior. This is already evident from the above description of the behavior of the pure lipids. The examination of aqueous lipid mixtures is rendered more difficult by the tendency of such aqueous suspensions to produce very diffuse X-ray diagrams, thus limiting evaluation possibilities. The data thus far obtained indicate that lipids are partly miscible and partly immiscible under such conditions. A decisive criterion for miscibility or immiscibility would appear to be an identical or divergent ligand-governed conformational state of the mixing partners. Immiscibility implies that the various lipid types are capable of forming separate domains within the lipid layer of biomembranes. Such a mosaic structure of the lipid layer may be regarded as an essential precondition for the possible performance of cooperative conformational and micellar transformations in lipid domains of identical population.

These viewpoints should be of particular interest with regard to the regulation of permeability in biomembranes. However, these problems cannot be considered exclusively from the lipid aspect. The lateral distribution of lipids must be decisively dependent upon the superstructure of the protein layer. A knowledge of the protein layer structure therefore seems to be indispensable for any further discussion of all these questions.

2.2. The Membrane Proteins

Each membrane is equipped with a special set of proteins according to its specific functional role. Some of these proteins are loosely associated with the membrane, whereas by far the larger part is firmly bound to the membrane or, in other words, actually constitutes part of the membrane itself. We do not propose to deal at this stage with the loosely attached proteins—they will be discussed in connection with the function membrane (Section 3)—but will limit ourselves to a consideration of the membrane-bound proteins. These have hitherto been referred to as "structural protein" in the literature. However, this general meaning of the term "structural protein" is too complex for the purpose of our discussion. At this point we only wish to deal with that part of the structural protein which can be defined by purely morphological physical criteria and which is distinguished by three main characteristics:

1. Its capability of forming two-dimensional lattices;
2. its particular solubility behavior;
3. its high volume occupancy.

The most notable quality is the first one. Therefore, we will henceforce designate this part of the structural protein "2d-lattice protein". The interrelationships between the "2d-lattice protein" and the structural protein will be established in Section 2.2.2.

2.2.1. The Tertiary Structure of the 2d-Lattice Protein

The best known 2d-lattice protein is that of the photosynthetic membrane. Moreover, this protein is the only one for which it has been possible to calculate a Gauss synthesis of the electron density distribution of the subunit (protomer) from X-ray data[14, 19]. For reasons which cannot be explained in detail here, this Gauss synthesis is still imperfect. Nevertheless, it is adequate to indicate certain basic structural features.

Fig. 8 illustrates the extent of our information so far gathered from the electron density maps[14, 19]. A possible interpretation is that two ring-like protein molecules, whose mass is unequally distributed between the upper and lower horizontal section, are arranged orthogonally to each other to form a subunit. Although the "ring" dimensions amount to 27 Å and 36 Å only, they cover the whole subunit plane of 42 × 93 Å; the only possible explanation is that linking side chains must be present between the two rings and between the subunits.

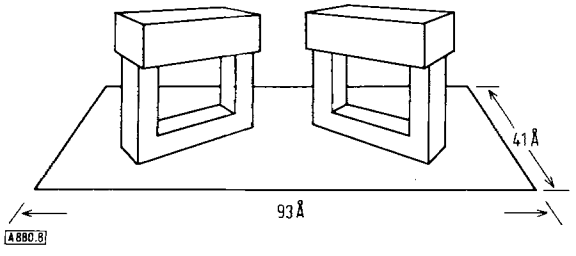


Fig. 8. Schematic representation of the mass distribution of the tertiary structure of the 2d-lattice protein subunit.

A clearer picture is obtained if the amino acid composition is taken into account. Based on the amino acid determinations of *Weber*[20], *Menke*[21], *Criddle*[22], and *Bailey*[23], the subunit should consist of 94 ± 2 amino acids (Table 1).

Table 1. Amino-acid composition of one lattice-protein subunit. The subunit consists of 94 ± 2 amino acids.

Amino acid	moles of amino acid per subunit
Asp-NH_2	7.45
Thr	4.07
Ser	4.80
Pro	5.08
Glu-NH_2	8.31
Gly	9.35
Ala	8.17
Val	7.0
Cys-SH	1.0
Met	1.46
Ile	3.76
Leu	9.25
Tyr	1.51
Phe	5.19
Lys	3.2
His	0.92
Arg	3.16
Trp	1.22
Amide	8.83

The sum of these amino acids represents a molecular weight of about 10000 for the subunit shown in Figure 8, *i.e.* 5000 per ring. The same result is obtained in estimating the molecular weight on the basis of the calculated mass distribution (Fig. 8).

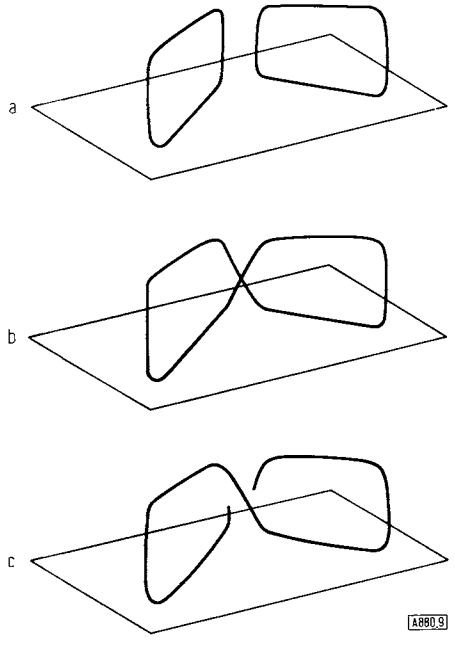


Fig. 9. Three possible conformations of a polypeptide chain consisting of 94 amino acids which are in agreement with the X-ray data.

In principle there are three conformational variations which might be in accordance with the X-ray data. A polypeptide chain consisting of 94 amino acids would suffice to form two separate rings (Fig. 9a), a closed figure-eight structure (Fig. 9b) or an open figure-eight structure (Fig. 9c).

The first two structures possess no amino acid end groups. The lowest identifiable molecular weight would be 5000 in the case of Figure 9a, and 10000 if the configuration of Figure 9b applies. The configuration of Figure 9c has two end groups and a molecular weight of 10000.

A combined end-group and molecular-weight determination could ascertain which of these three structures is the correct one. According to *Menke*[21] the number of C-terminal amino acids amounts to 13; however, other authors[22–24] have found no amino acid end groups, so that at present this problem remains unsolved. However, for the purpose of a discussion of the membrane structure as envisaged in this paper such details concerning the tertiary structure are of little importance.

2.2.2. The Aggregation Behavior of the "2d-Lattice Protein"

Of predominant significance is the aggregation behavior of the protein subunit shown in Fig. 8, *i.e.* the quaternary structure or the superstructure of the 2d-lattice protein. In principle the margin of variation in aggregation is restricted by the circumstance that only a limited number of symmetry operations is admissible in planar protein lattices. We would stress that here, as in other proteins, only L-amino acids occur.

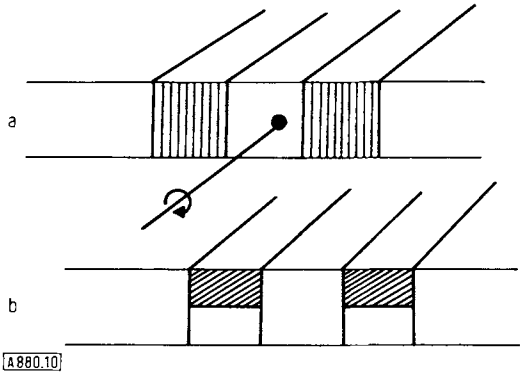


Fig. 10. a) Lamella with a twofold coplanar rotation axis, b) lamella without a coplanar rotation axis.

From the outset this very fact excludes symmetry centers and mirror planes. The only possible symmetry elements are limited to translations, transverse rotations (*i.e.* rotation axis vertical to the plane), and two-fold coplanar rotation- and screw axes (Fig. 10a). The combination of these symmetry elements permits the definition of 17 space groups[25].

In the case of biological membranes two essential restrictions in respect of possible symmetry operations are presupposed: it is alleged that biomembranes possess transverse and coplanar polarity. From our above discussion concerning the cross-sectional structure of the protein subunit it emerges that the 2d-lattice protein itself also possesses the property of transverse polarity. As regards the coplanar polarity of membranes it appears that this quality can only exist if it is provided by a two-dimensional lattice. On the other hand, two-dimensional lattices can only be imagined when formed by proteins. Therefore, we may also envisage tangential polarity in the protein layer. Transverse asymmetry (Fig. 10b) already reduces the potential number of planar space groups from 17 to 5, since all space groups with coplanar two-fold rotation- and screw axes are thereby excluded.

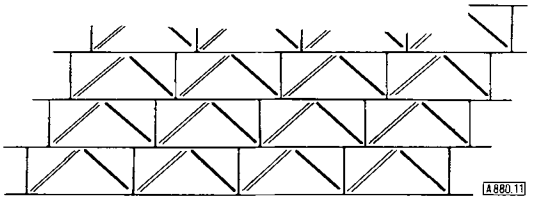


Fig. 11. Two-dimensional lattice of primitive polarity: One asymmetric protomer type forms an infinite 2d-lattice. The two thin lines and the bold one arranged at right angles within each protomer signify the position of the peptide rings.

Finally, allowing for tangential polarity, the transverse rotation axes are likewise eliminated so that out of the potential 17 space groups only one remains, namely that of the oblique planar lattice type as illustrated in Figure 11. This lattice type then would constitute the most complete but also the most primitive polarity possible: One single asymmetric protein subunit (protomer) would homogeneously cover the total membrane plane. However, this type of polarity does not seem to be desirable in biomembranes, since it would not allow any variability. The X-ray and electron-microscopic data of membranes so far available rather indicate that biomembranes are to be viewed as associations of linear superstructures which themselves may consist of a homogeneous distribution of subunits.

A second possibility is that two or more oligomeric superstructures may be arranged alternately in a linear pattern. Naturally, such a planar membrane design requires a higher number of different protomers (subunits). It is, however, quite admissible that such a variety is attributable to minute deviations in the primary structure of one and the same type of protomer. The photosynthetic membrane may serve to demonstrate this principle.

To permit a better understanding we must first of all explain that in the photosynthetic membrane of higher plants two types of light reactions or two photosynthetic systems (electron flow systems), known as system I and system II, cooperate. On the other hand, in the case of the photosynthetic bacteria (*e.g. rhodopseudomonas viridis*) only system I applies. A comparison of the structure of these two objects is most appropriate to demonstrate how on the molecular level a relatively simple structure, namely that of the bacteria, can develop into a complex structure designed to couple two systems. An electron-microscopic picture of the planar structure of a bacterial photosynthetic membrane recorded by *Giesbrecht*[26] reveals a homogeneous protein structure with two principal directions (Fig. 12). These two privileged directions enclose an angle of $\approx 56°$ and are accounted for by protein double strands 90 Å wide forming the membrane plane.

Further evidence is furnished by X-ray diagrams of the same object[27]. Two main interferences emerge which correspond to Bragg spacings of 77 and 51 Å. These interferences may be interpreted by means of the linear structure shown in Figure 13. The interferences corresponding to 77 and 51 Å and the angle of $\alpha = 56°$ (see Fig. 13a) indicate

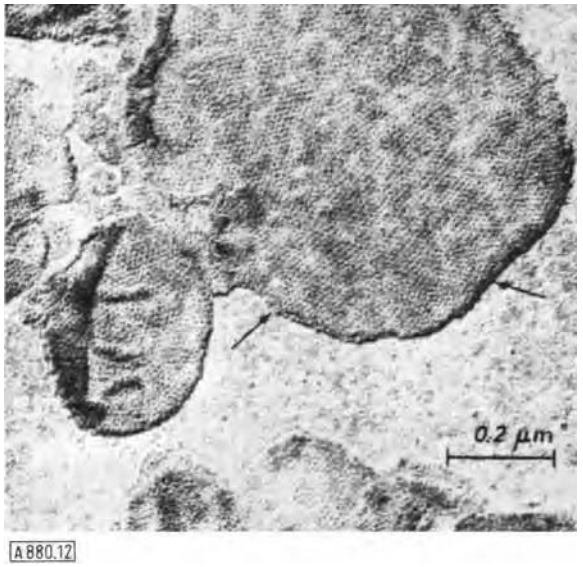


Fig. 12. Electron-microscopic plan view of thylakoids of *rhodopseudomonas viridis*. The surfaces are characterized by a regular planar arrangement of proteins in which two predominant directions exist (arrows). (After *P. Giesbrecht* [26].)

dimensions of the protein subunit of 41 and 93 Å. The existence of a planar structure, *i.e.* a structure possessing many net-planes in the x_1-direction as well as in the x_2-direction, can be ruled out because of the lack of a 41 Å-interference (Fig. 13a).

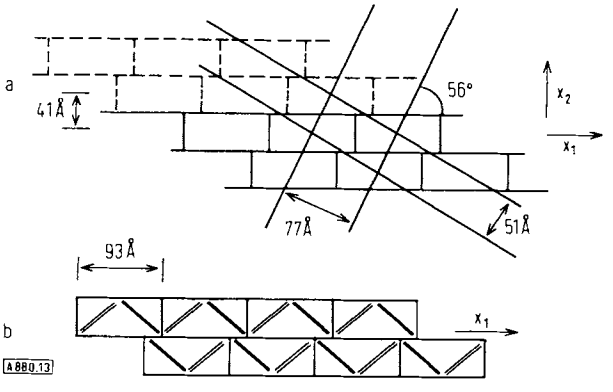


Fig. 13. Lattice arrangement which explains the occurrence of a 77 and a 51 Å reflection. Lattice b differs from a in the lack of the 41 Å periodicity. b corresponds to the real diffraction pattern.

A linear structure of the type shown in Figure 13b is, on the other hand, only plausible providing it is equipped with 2 twofold transverse rotation axes. In other words, this would presuppose preferential coupling between two rows of protein subunits. If we allow for the mass distribution of the structural protein subunit described earlier in the paper we come to a superstructure of the lattice protein of bacteria as depicted in Figure 13b.

We can now consider the construction principle of the lattice protein of the photosynthetic membrane of higher plants. Here also electron-microscopic pictures[28–30], *e.g.* that in Figure 14, reveal linear superstructures (chains), which, however, possess quite different dimensions from those in bacteria. The lateral distance between the chain axes amounts to about 190 Å, and the period along the chains to about 170 Å. The X-ray diagram of such objects consists of very strong interference corresponding to 41 Å, a strong interference corresponding to 31 Å, and a very weak interference corresponding to 62 Å which is, furthermore, considerably broader than the other two.

If for evaluation purposes one starts from the assumption that both in bacteria and in higher plants system I possesses a similar basic structure, then at least part of these reflections ought to be capable of interpretation by a modification of the lattice in Figure 13. The presence of a sharp 41 Å reflection and the absence of a 93 Å reflection indicates that in this case aggregation occurs in the x_2 direction but not in the x_1 direction. Moreover, the existence of a 62 Å reflection points to the fact that the aggregation in the x_2 direction forms an orthogonal lattice (Fig. 15). However, while the sharp 41 Å reflection provides evidence of a high



Fig. 14. Electron-microscopic picture providing the plane view of a thylakoid of higher plants showing linear superstructures. (After *R. B. Park* and *N. G. Pon* [28].)

aggregation state in the x_2 direction, the broad 62 Å reflection indicates that the aggregation breaks off after 4—5 periods. Although these findings may appear paradoxical we are able to furnish below a plausible explanation.

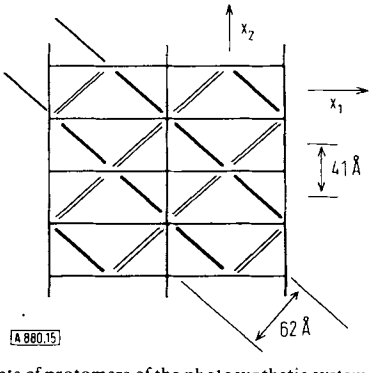


Fig. 15. Planar arrangements of protomers of the photosynthetic system I giving an explanation for the 62 Å reflection.

To this end we must first again touch upon the 31 Å reflection. Since it cannot be assumed that system I (Fig. 15) produces a 31 Å reflection, it seems justified to impute the said reflection to system II. There are two possible forms of aggregation of the protein subunit in the x_2 direction which could account for a 31 Å interference, the one being

polar and the other nonpolar (Figs. 16a and 16b). In the case of the polar structure in Fig. 16a there is no evidence as to why there should be a trend for a linear aggregation in the x_2 direction. One would far sooner expect there to be a two-dimensional association of any size, as shown in Figure 11. On the other hand, the association in Figure 16b satisfies the criteria for a linear structure and is therefore to be regarded as the most likely one. In addition to the 31 Å reflection, the lattice of Figure 16b should also produce a 41 Å reflection, the shape of which depends on the size of the linear aggregation in direction x_2.

We are now faced with the question of the coupling of systems I and II and the relative proportions of the two systems. As already pointed out, coupling can only take place under specific symmetry conditions, the ratios of the two systems being determined either by a definite number of different protomers, *i.e.* through the formation of finite associations (oligomers), or else through a definite ratio in the production rates of the subunits of system I and II. In the case under consideration it would appear that both possibilities apply. System I is turned into a finite structure

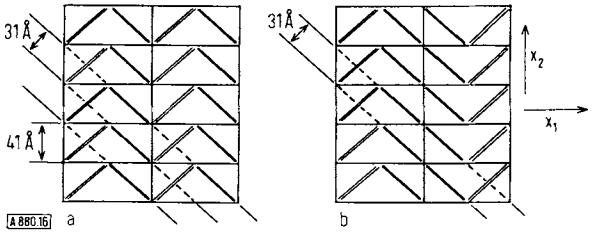


Fig. 16. Two possibilities for the planar distribution of system II protomers which can produce a 31 Å reflection. Configuration b is considered to be the true one.

by the input of several different protomers; however, the ratio between system II and I is determined by the production rate of each system.

Besides the X-ray criteria for the existence of a finite structure of system I (broad 62 Å reflection) and a fundamentally infinite structure of system II (sharp 31 Å reflection), there are also criteria provided by chemical experiments: It is possible to isolate system I oligomers from the membrane and to define their structural characteristics, whereas the remaining system II protomers join to give large superstructures, *i.e.* in the formal sense they constitute infinite structures[31-33]. X-ray investigations show that the dimensions of the system I oligomers in the x_1 and x_2 directions are 164 and 186 Å. Furthermore, we know from chemical experiments that the proportion of system I protein to system II protein is about 1:2[31]. Thus, in conjunction with the aforementioned symmetry conditions, the limits of the quaternary structure are traced.

From the dimension of the system I oligomers it can be deduced that they consist of eight protomers. For these oligomers to undergo coupling with the linear arrangements II, they would have to be equipped as a minimum with one twofold transverse rotation axis. On the other hand, the definite size of the system I oligomers can only be ensured if they consist of at least four different kinds of protomers, *i.e.* a definite set of binding sites. The symmetry and binding conditions are therefore in conformity.

The outcome of these considerations is the quaternary structure shown in Figure 17a, which as a whole will produce a broad reflection at 62 Å, a sharp one at 31 Å, and a very sharp one at 41 Å. The pseudo-contradiction concerning the sharpness of these reflections mentioned above is thus explained. This quaternary structure consists of five different protomers, four in system I and one in system II (Fig. 17b).

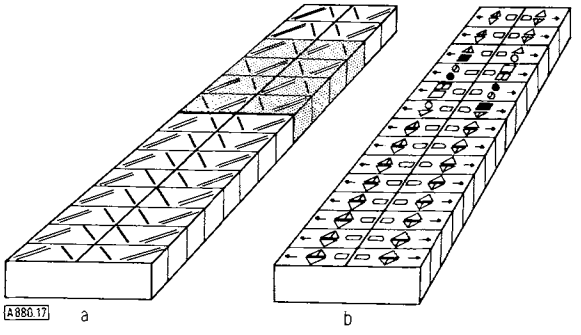


Fig. 17. a) Combined linear arrangement of system I and system II protomers which agrees with the X-ray diffraction data (41, 31, and a 62 Å reflection), b) the same arrangement demonstrating the necessary binding sites (number of different protomers) by different symbols.

In the case of an open tertiary structure as illustrated in Figure 9c one might expect a maximum of ten different terminal end groups in the 2d-lattice proteins. The ring structure and the closed figure-eight structure shown in Figure 9a and 9b would not allow for any end groups at all. A decision between these alternatives is not yet possible because of the aforementioned discrepancies in the amino acid end-group determinations.

Support for the general validity of these arguments is forthcoming from the X-ray investigations of the discs of rod outer segments (ROS) of the retina and the erythrocyte membranes. In ROS-discs the lattice protein provides the same interferences as were recorded in the case of photosynthetic bacteria, *i.e.* 77 and 51 Å reflections[34], and the erythrocyte planar lattice produce X-ray reflections corresponding to Bragg spacings of 41 and 33 Å.

The examples of the lattice protein configuration described above give an indication of the scope of variation of possible structural modifications. However, they also set limitations upon the principal realization possibilities: The given criteria allow for the existence of two-dimensional lattice types with primitive polarity (Fig. 11), linear lattice types with twofold rotation axes as shown in Figure 13b (ROS-discs, photosynthetic membranes of bacteria), in addition to more complex lattice types comprising several protomers and oligomer associations capable of performing most complicated functional tasks (Fig. 17) (photosynthetic membranes of higher plants). There is, however, one factor which appears to be of fundamental significance: For all these lattice types one single type of basic protomer, *i.e.* one type with identical or almost identical tertiary structure, suffices for every possible variation. In this context the chemical experiments on structural protein referred to earlier acquire particular significance since they have demonstrated that the structural protein of the membranes of various objects show only minute deviations in their

primary structure and that by the action of proteases or detergents they can be decomposed to basis peptides with a molecular weight of 5000, 10000, or 20000[20–24, 35–37].

This being so, what can be said about the required tangential polarity? The introduction of polarity into the anisotropic (linear) homogeneous structural elements obviously is brought about by the association of functional proteins. This creates periodically distributed linear bipolarity. That is to say, energy fluxes, impulses, or actions emanating from the polarity centers are propagated in a bipolar fashion. In this manner radial energy distribution, which would mean a waste of energy in this case, is prevented. A primitive polarity as shown in Figure 11 would permit an energy flux in only one direction, which would be less advantageous. In the more sophisticated linear structures consisting of several oligomers, strong polarity is also created in the phase boundaries between each pair of different oligomers.

A further feature of great importance for the construction of membranes is the distribution of hydrophobic and hydrophilic amino acids within the 2d-lattice protein subunit. We have learned from the Gauss synthesis of the cross-sectional structure of the protein unit that the ring centers represent hydrophobic areas[19]. In addition, that horizontal part of the ring with less mass would have to contain at least a predominance of hydrophobic amino acids. The latter statement derives from the sandwich behavior of the lattice protein in aqueous solution and the collapsing process in membranes dealt with in Section 3.2. This unusual distribution of amino acids will serve to clarify the fact that lipids are only associated with one side of the protein-layer (a feature considered in Section 2.3). And last, but not least, we must once again draw attention to the truly remarkable mass distribution inside the lattice protein subunit. The impression is gained that the aim is not to fill up the subunit with protein mass (and consequently also the protein layer), but rather as far as possible to keep the subunit free of protein mass. Such a structure opens up interesting possibilities with respect to the coupling of proteins with lipids and also of the lipid distribution and lipid superstructure.

2.3. Protein-Lipid Coupling

The answer to the question of protein-lipid coupling in biomembranes lies ultimately in their cross-sectional structure. It is only in the last decade that significant experimental progress has been made in this field. The first speculative concept advanced was that of a symmetrical membrane cross section[38]. However, it is evident that biophysically speaking such a membrane structure could give rise to no activity whatsoever, *i. e.* it would represent the biologically most unfavorable membrane. Indeed, our X-ray results on three different membranes point to an asymmetric membrane cross section. The most pronounced asymmetry seems to exist in the photosynthetic membrane of higher plants and the nerve myelin structure. On the other hand, the results so far obtained from rod outer segments of vertebrate retina indicate an alternate asymmetric membrane construction. It is to be expected that erythrocytes have the same type of membrane.

A fundamental asymmetry can be established in all membranes so far investigated by means of a fairly simple X-ray experiment, *i. e.* by a comparison of the X-ray data obtained in this experiment with electron-microscopic pictures of the same membrane system. The electron-microscopic pictures of membrane systems reveal that membranes always form closed vesicles. In flattened vesicles (*e. g.* ROS-discs, myelin membrane, photosynthetic membrane) two membranes are therefore arranged mirror-symmetrically and in this form give rise to the identity period observed in the membrane system (Fig. 18a).

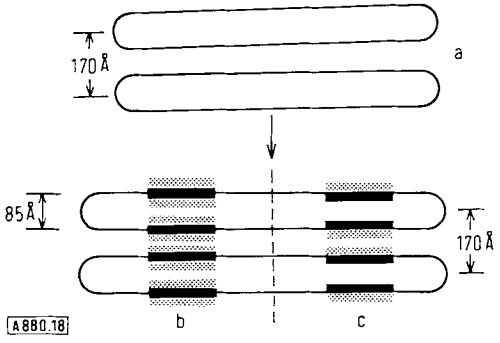


Fig. 18. Relationship between electron-microscopic and X-ray periods in lamellar systems. a) Electron-microscopic cross-section view of a flattened vesicle, b) X-ray period in the case of a symmetrical membrane, c) X-ray period in the case of an asymmetrical membrane.

The X-ray beam "senses" electron-density projections of these vesicles, such as for instance the electron-density projection onto the stacking axes which is under consideration here. This means that if the electron-microscopic periodicity is compared with that obtained by X-ray diffraction, the X-ray identity period would—in the case of a symmetric membrane (Fig. 18b)—amount to half of the periodicity visible on electron-microscopy. However, in the case of an asymmetric membrane cross section (Fig. 18a) the X-ray and electron-microscopic periods would be identical.

This comparison can best be made by using partly dehydrated membrane systems (up to 30% H_2O) of flattened vesicles, since the identity period then corresponds to the thickness of a single or of a double membrane. It is possible to make this comparison using chloroplasts of higher plants, nerve myelin, and ROS-discs. Each of these three membrane types yields an X-ray period which is comparable with that found by electron microscopy, that is to say, it is equal to or greater than twice a membrane thickness. (The situation is somewhat more complicated regarding membranes forming spherical vesicles. This aspect will be dealt with in Section 2.3.1.)

This result alone already justifies the statement that at least these three membranes have an asymmetric cross-sectional structure. Apart from this common characteristic, however, there are considerable deviations with regard to the magnitude of the period or the thickness of the vesicle. The period found in chloroplasts amounts in the dehydrated state to 150—170 Å, in ROS to 210—230 Å, and in myelin to

130—150 Å. The significance of these differences will be referred to in the detailed discussion on membrane cross sections. Let us first of all discuss the cross-sectional structure of the photosynthetic membrane, the most asymmetric one.

2.3.1. The Cross-Sectional Structure of the Photosynthetic Membrane

The structure of the photosynthetic membrane has been comprehensively dealt with in an earlier paper[14]. We may limit ourselves here to some essential aspects. The photosynthetic membrane of higher plants consists of three layers which are distinguished by three different sections in the electron-density diagram (Fig. 19a). The layer with the highest electron-density has proved to be a protein layer, that with the lowest density to be a porphyrin ring layer, and the layer with medium density to be a monomolecular

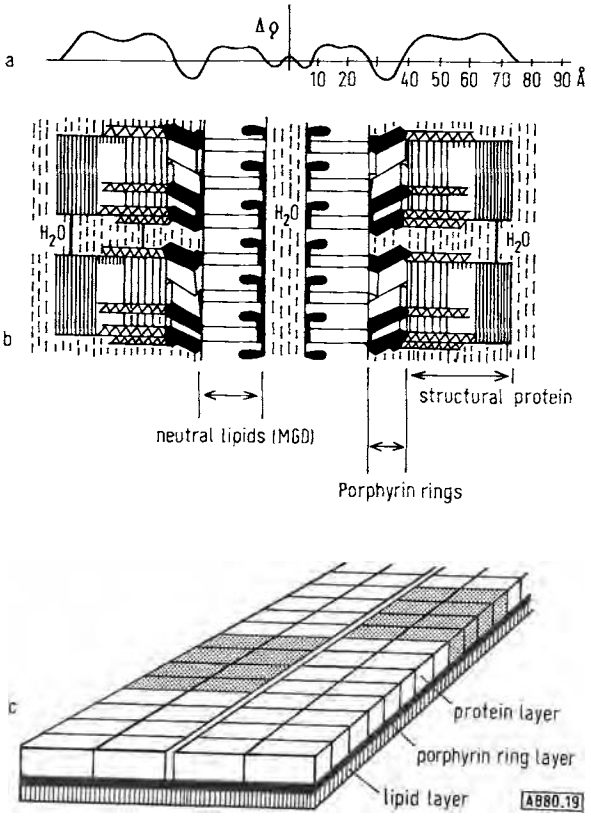


Fig. 19. Structure of the photosynthetic membrane of higher plants. a) Electron-density (ρ) distribution of the cross section of a vesicle (thylakoid) in the living state, b) its interpretation (see designations), c) plane view of one asymmetric membrane.

lipid layer (Fig. 19b). The mirror plane between the two membranes of the vesicle (thylakoid) is so arranged that the proteins form the outer layers.

The following points are essential for the discussion on the protein lipid coupling in Section 2.3.2:

1. Both chlorophyll a and b are not miscible with the principal lipid component MGD, with constitutes about two-thirds of the total lipids.

2. Phytol shows the same behavior.

3. Upon fragmentation of the membrane by detergents the major part of the chlorophyll adheres to the proteins[31].

4. In chlorophyll-protein complexes the lamellae are about 12 Å thicker than pure protein layers[31].

These results, which will not be further elucidated here, support the concept that chlorophylls are anchored in the 2d-lattice protein by means of the phytol chain and that the contact between protein and lipid is established by the porphyrin rings, which apparently partially penetrate into the unsaturated fatty acid zones of the lipid layer[14]. An overall view of the photosynthetic membrane of higher plants is given in Figure 19c.

2.3.2. General View of Protein-Lipid Coupling

Protein-lipid coupling by means of chlorophyll cannot apply to membranes containing no chlorophyll. However, the question arises as to whether we are confronted here with a special instance of a general coupling principle. Remarkably, most membranes studied hitherto have revealed a constant proportion of $30 \pm 5\%$ PC[6]. The only exception encountered is that of the photosynthetic membrane which has yielded only 1—2% of PC. The other phospholipids vary considerably from one membrane to another, depending upon their function. Once again the photosynthetic membrane provides an exception: The phospholipids are extensively replaced by galactolipids (MGD and DGD). Moreover, taking into account the fact that PC shows the least conformation and phase variability of all phospholipids, it emerges as the foremost candidate for a special structural role.

On the basis of these lipid qualities and experimental results obtained in respect of the photosynthetic membrane we postulated a general principle concerning protein-lipid coupling in biomembranes[14]: According to this postulation PC assumes the function of coupling between proteins and lipids in membranes containing no chlorophyll. The coupling is thought to be accomplished in such a manner that the fatty acids of PC interact hydrophobically with the peptide chains in the protein layer, while the choline groups penetrate the fatty-acid zone of the lipid layer (Fig. 20a). The stability of this type of coupling is assured on the one hand by the purely hydrophobic coupling between fatty acids and protein and on the other by the polar interaction of the choline group of PC with the polar groups of the coupled lipids (and the proteins). Maximum stability of the polar interaction is achieved by the fact that the interacting polar groups are embedded in hydrophobic fatty-acid phases (Fig. 20b). This coupling principle will be supplemented in this paper only to account for partial assumption of the role of PC by sterols in some membranes.

2.3.3. The Cross-Sectional Structure of the Nerve Myelin Membrane

In the past various phase combinations have been applied by different authors for calculation of the electron-density distribution of the myelin membrane cross section; consequently, different electron-density distributions were obtained (for summary, see [39]). In the last year we have

likewise made a calculation of the electron-density distribution of the myelin membrane cross section[40]. The evaluation method used by us (the Q_0-method), however, differs fundamentally from that employed by other authors. Our

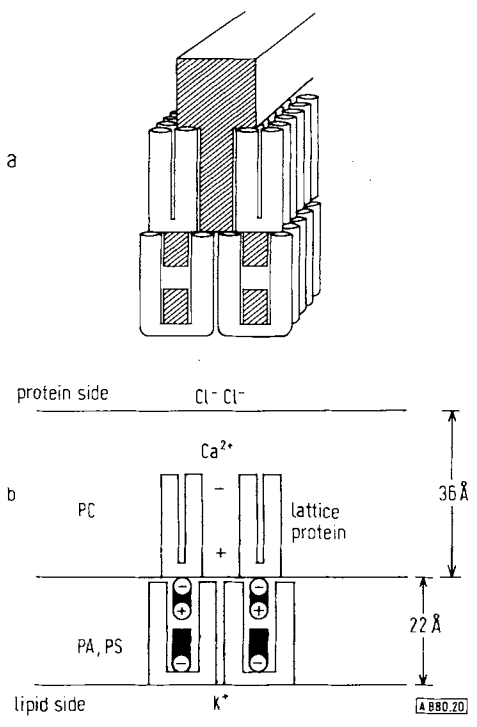


Fig. 20. General coupling concept of lattice proteins and lipids by PC. a) Spatial situation at one ring of the subunit (compare Fig. 8), b) charge distribution within such a coupling unit.

Q_0-method, which was developed for and applied in the structural investigation of the photosynthetic membrane[14], directly yields an unequivocal electron-density distribution from the intensity (and not as usual from the amplitude) distribution by straightforward calculation, leaving out the phase problem entirely. The electron-density distribution obtained for nerve myelin membrane *in vivo* is shown in Figure 21a.

We have interpreted these results as shown in Figure 21b. According to this concept the symmetry center of the electron-density projection is flanked by the cross-sectional profiles of mirror-symmetrically arranged lattice protein layers. These layers are first covered on the outside by a layer of the coupling choline groups and sterols, then by a pure fatty-acid layer, and lastly by a layer of polar groups of the lipids. In principle this structure corresponds to the cross-sectional structure of the chloroplast thylakoids if one replaces the chlorophylls by PC and sterols. There is, however, one important distinction: In the myelin structure the mirror plane is located between the two protein layers, whereas in the case of the photosynthetic membrane vesicles (thylakoids) it is positioned between the two lipid layers. We will refer to this again later in Section 3.1.

According to our membrane concept of nerve myelin each membrane possesses two C=C bond planes: one is formed by the C=C bonds of the unsaturated fatty acids of the PC located within the lattice protein, the other plane of the fatty acid C=C bonds being situated within the actual lipid layer. If it were possible to chemically label these double bond planes, for instance with OsO_4, our membrane concept could be tested experimentally. A difference-Fourier or difference-Q_0-evaluation would then directly yield the Os distribution in the membrane. Systematic incorporation experiments of this kind were first carried out by *Parsons* and *Akers*[39]. The Fourier-evaluation of these experiments by *Harker*[41] resulted in the same Os distribution as our evaluation *via* the Q_0-function (Fig. 21c)[40]. These evaluations reveal that each membrane possesses two planes with different Os concentrations and an Os enrichment between the membrane pairs. The best access for OsO_4 molecules is offered by the C=C bond layer within the protein layer,

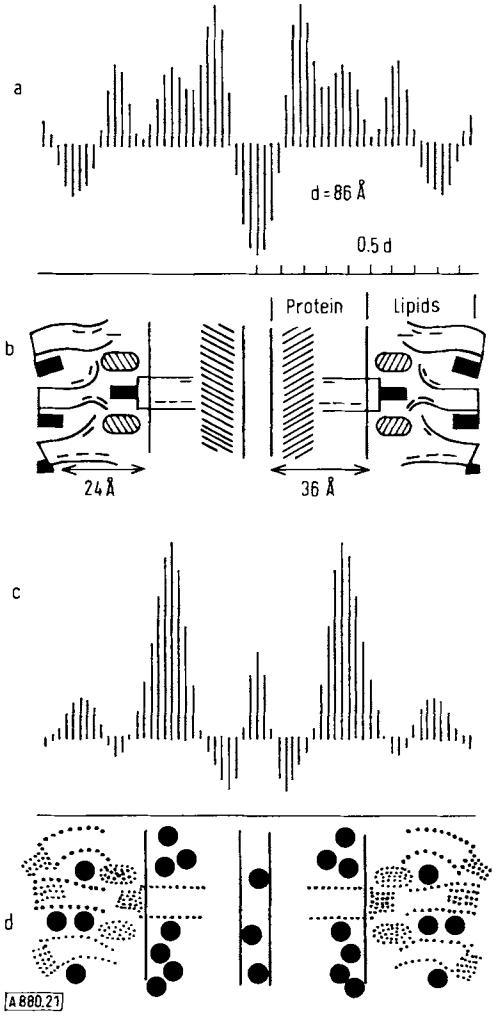


Fig. 21. Structure of the myelin membrane. a) Computer diagram of the electron-density (ρ) distribution of the cross section of a myelin membrane pair, b) its interpretation: Each membrane is composed of an inner protein layer and an outer lipid layer. The coupling is achieved by PC and sterols (hatched). A water interspace has to be envisaged between the two protein layers as well as between the two lipid layers, c) computer diagram of the pure Os distribution in the myelin membrane pair, d) Os distribution indicated by diagram c. Os atoms stain the two C=C bond planes within each membrane.

since the lattice protein is hydrated up to 70%. The action of the OsO_4 molecules on these double bonds can be carried out in an aqueous reaction medium. Therefore, the corresponding Os peak in Figure 21c is the most dominant one.

The situation is quite different with the second plane of C=C bonds. These double bonds are incorporated in a hydrophobic environment, which makes penetration and reaction of Os molecules more difficult. Accordingly, the corresponding Os peak in Figure 21c is considerably smaller. The Os distribution established within the membrane cross section agrees with our membrane concept of nerve myelin and consequently also with our concept of protein-lipid coupling in biomembranes.

A Fourier-transformation of the electron density distribution shown in Figure 21a and 21c provides the corresponding amplitude functions. They yield a phase set of $+ - - - -$ for the five reflection amplitudes of the nerve myelin *in vivo* and a phase set of $+ - - + +$ for the five reflection amplitudes of the pure Os distribution. The mirror-symmetrical phase set to the above phase set for nerve myelin *in vivo*, namely $- + + + +$, was already reported by *Moody* in 1963[42] as one of two possible phase sets ($- + + + +$ and $- + + - -$). In the case of the Os distribution *Harker*[41] found the same phase set as we did. *Harker* proposes the same phase set for the *in vivo* structure as for the Os distribution. Interestingly, these phase sets, which come nearest to, or are identical with, those determined unambiguously by us, were gained by systematic experimental phase determinations.

2.3.4. The Definition of the Basis Membrane

The calculation of the electron-density distribution of the cross section of the photosynthetic and myelin membranes has revealed totally asymmetric cross-sectional structures. Based on the particular cross-sectional structure of the photosynthetic membrane we were able to postulate a general coupling principle for lipids and proteins in biomembranes. And finally X-ray investigations on the myelin membrane have furnished support for this postulation. This structural knowledge combined with the intrinsic qualities of lipids and proteins and with the results of comparative chemical investigations of membranes permits the definition of a basis structure for biomembranes.

We may define the basis membrane as that part of the biomembrane which is exclusively constituted by 2d-lattice protein and the membrane lipids. Its cross-sectional structure is totally asymmetric and its planar structure is governed by the two-dimensional lattice formed by the proteins, while the coupling between the proteins and lipids is accomplished by PC. An area measuring 42×93 Å^2, covered by a single protein unit, accommodates 70—80 lipid molecules depending upon the conformational state. For the coupling of these molecules, 30 PC molecules are available, 15 per protein ring or 7—8 on each side of the rings. When arranged side by side these 7 or 8 lipid molecules can extend over a distance of *ca.* 35 Å or 70 Å, depending on whether the fatty acids are assembled in single or double file. In view of the fact that each structural protein ring has a diameter of *ca.* 30 Å, the double file assembly appears the more probable. This suggests a structural configuration as illustrated in Figure 20a. Each PC molecule couples one other lipid molecule. Over an area of 42×93 Å^2 there are thus left 40—50 uncoupled lipid molecules. These might be expected to form one of the micelle structures shown in Figure 2. Consequently the following possibilities for the cross-sectional structure of the basis membrane may be envisaged according to the type of uncoupled lipids present in the protein interspaces (Fig. 22):

a) Basis membrane with lipid regions of monomolecular symmetric construction and of homogeneous p_{ex}-conformation. This can apply to PG, PA, and PE (Fig. 22a).

b) Basis membrane with lipid regions of bimolecular symmetric construction and of homogeneous p_{ex}-conformation. This micelle structure can be formed by PA, PS, or PI (Fig. 22b).

c) Basis membrane with lipid regions of bimolecular symmetric construction and of homogeneous p_{in}-conformation. This micelle type could consist of PE or of PA (Fig. 22c).

d) Basis membrane with lipid regions of tubular construction. This configuration could be composed of PE alone or of mixtures of PE with PA and PS (Fig. 22d).

The specific type of micelles involved will depend upon the pH of the surrounding aqueous phase, whether CO_2 is present, and lastly upon the concentration of different cations (*e.g.* Na^+ or Ca^{2+}). This brings us to the question

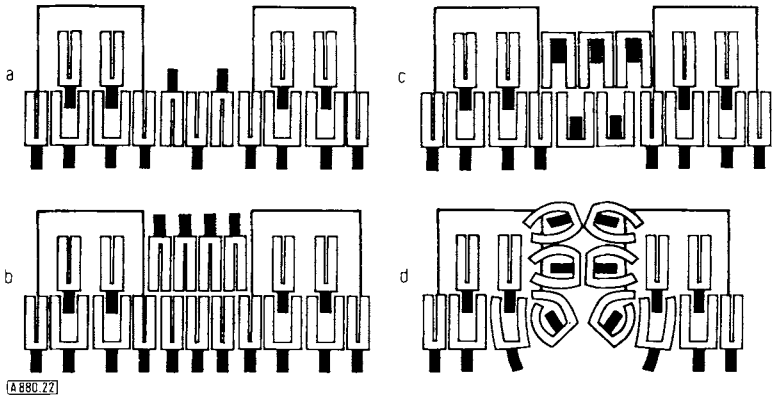


Fig. 22. Possible cross-sectional views of the basis membrane differing in their lipid interspaces (see text).

of the influence of the aqueous phases with their different constituents on the membrane structure. Section 3 deals with these functional aspects of biomembranes.

3. The Function Membrane

Before discussing actual functions of the membrane it is necessary to complete the structure of the basis membrane to give a function membrane. This completion may be achieved in three ways: By a loose association of functional proteins; by the incorporation of non-proteinaceous substances; and by the direct binding of prosthetic groups (*e.g.* heme groups) to the lattice protein, thus yielding modified or "converted lattice protein".

3.1. The Structure of the Function Membrane

The category of proteins which are loosely associated with the basis membrane comprises special functional proteins such as the ATPases which are indispensable for active transport of Na^+ and Ca^{2+} or the rhodopsin of the ROS membrane, *etc.* Some examples of non-proteinaceous substances of this category are NADP, ADP, acetylcholine, *etc.* We assume that the other category of membrane-bound functional proteins includes mainly converted lattice proteins (Fig. 23a). It is thought probable that they embrace a large proportion of the redox enzymes, *e.g.* the cytochromes f and b of the photosynthetic membrane.

At this point it may be noted that the mixture of pure lattice protein, converted lattice protein, and certain other coupled proteins has up to now been referred to as "structural protein". The converted lattice proteins should not differ essentially from the normal lattice protein; they should only vary slightly in their primary structure. Hence it is not surprising to find that the "structural proteins" of various membranes reveal only minute differences in their amino acid composition, that they can all be chemically fragmented in the same manner, and that they can be decomposed to the same peptide size. So far the structural proteins of the photosynthetic membrane[20–23], mitochondria[22,24], nerve myelin[36,37], the retina, and erythrocytes[24,35] have been analyzed by these procedures.

The coupling of the first category of proteins to the basis membrane may be achieved in two ways: on the protein side (Fig. 23b) or on the lipid side (Fig. 23c). The coupling to the protein side may occur specifically to the proteins or to the lipids, whereas on the lipid side the coupling can only occur specifically to the lipids. The lipid specificity is determined by the lipid composition of the membrane, and by the circumstance that coupling is only conceivable in those lipid regions which are not blocked by coupling PC molecules, *i.e.* in lipid regions of symmetrical micelle structure. These lipid regions are thereby converted from a symmetrical to an asymmetrical structure. Thus, the coupling of further addenda (*e.g.* proteins) to the basis membrane results either in a totally asymmetric function membrane (Figs. 23a and 23b), in an alternating asymmetric membrane (Fig. 23c), or in a mixture of both types.

It is to be expected that a coupling molecule is involved in the coupling of protein to the lipid side which is comparable in its action to PC in the case of the lattice-protein coupling. Presumably, however, these coupling molecules are bifunctional, *i.e.* apart from the coupling function they also have a role in the actual membrane process as characterized by the coupled protein. A typical example would appear to be the ATPase system. It is conceivable that ATP acts as the coupling molecule between the lipids and the ATPase, simultaneously serving as energy donor. An indication of this is certainly provided by experiments in which ADP and ATP were mixed with lipids[15].

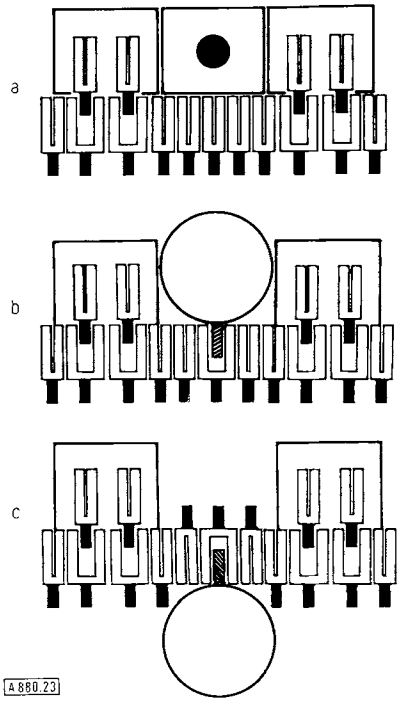


Fig. 23. Three possibilities for the association of functional proteins to the basis membrane. a) Conversion of a lattice protein subunit by the binding of a prosthetic group (●), b) coupling of an "other" protein molecule to the protein side by a coupling molecule (hatched) or by pure protein interaction, c) coupling of an "other" protein to the lipid side by a coupling molecule.

An example of the coupling of redox enzymes to the protein side is to be found in the electron transport chain in photosynthesis and respiration. The photosynthetic membrane therefore represents a typical asymmetric function membrane (Figs. 19, 23a, 23b). The same applies to the myelin membrane. Both these membranes have been dealt with earlier in this paper and only require completion in conformity with Figures 24a and 24b. Finally, it is necessary to discuss the second type of function membrane. Our experiments on ROS-discs have revealed that this membrane is representative of this category.

The straightforward calculation of the electron-density distribution of the ROS-disc membrane cross section *via* the Q_0-function[24] results in the distribution function shown in Figure 24a. [Recently, an electron-density distribution of the cross section of the ROS-discs was also calculated by *Blaurock* and *Wilkins*[43] by choosing a phase combination that most closely approached a symmetrical membrane cross section ("unit membrane"). For a further discussion, see [34].] The symmetry center of the electron-density diagram of Figure 24a is flanked by two peaks of high electron density followed by electron-density troughs

and then by two electron-density peaks of medium height. This electron-density distribution is, in our opinion, to be construed as illustrated in Figure 24b. Unlike the chloroplast thylakoids but in accordance with the myelin structure the lattice protein forms the two inner layers (the layers adjoining the symmetry center) of the discs, each layer being flanked on the outside by a monomolecular lipid layer. Furthermore, we assume that to the outside of the lipid layers the rhodopsin molecules are attached, which, together with the aqueous phase, account for the electron density in this region.

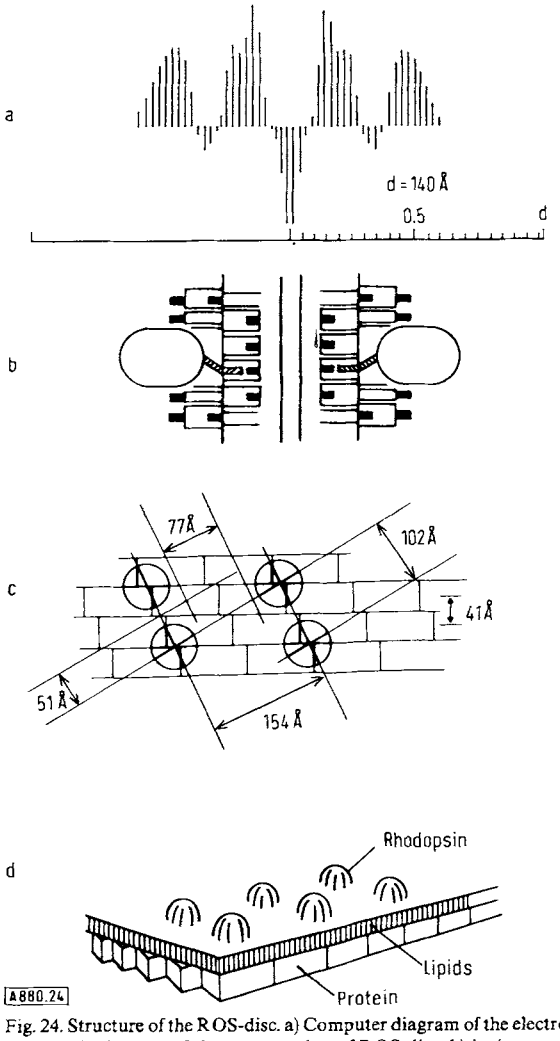


Fig. 24. Structure of the ROS-disc. a) Computer diagram of the electron-density distribution of the cross section of ROS-disc, b) its interpretation: two inner lattice protein layers flanked by lipid layers on the outer sides. Rhodopsin molecules are coupled to PE in the p_{in}-conformation by retinene, c) planar distribution of the lattice protein combined with a rhodopsin superlattice, d) overall view of the ROS-disc membrane.

Support for the concept of the rhodopsin molecules being attached to the outside of the lipid layer is provided by the following observations: Two different lattice types have been identified within the plane of the retina discs[34]. One lattice characterized by Bragg spacings of 51 and 77 Å, and the other by Bragg spacings of 154, 102, and 77 Å. The second lattice represents a superlattice of the first one (Fig. 24c). The first type of lattice has already been described in connection with photosynthetic bacteria in Section 2.2 and was attributed to the 2d-lattice protein. It is always found in those retina preparations in which the superlattice is disintegrated. The disintegration can be caused by operations resulting in the decomposition of the lipid layer or by light-induced uncoupling of the rhodopsin molecules[34]. Apparently the rhodopsin molecules are arranged in an oblique planar lattice with plane distances of 154 Å and 102 Å which is indirectly determined by the lattice protein on the opposite lipid side (Fig. 24d). These findings are in agreement with the results of *Blasie et al.* who could immunologically demonstrate that the rhodopsin molecules are arranged on the outside surface of the ROS-discs[44]. The ROS-disc membrane may, therefore, be classified as an alternating asymmetric type of membrane (Fig. 23c). For the sake of completeness it may be added that the electron-density distribution of Fig. 24a corresponds to a phase set of $+ - - - - - - -$ for the first seven reflection amplitudes.

Concluding these considerations on the structure of biomembranes it should be mentioned that the protein lattice structures and thus also the defined planar structure of the entire membranes discussed above are to be regarded as exceptional crystalline states which can exist only under special experimental conditions. *In vivo* these structures should exist in para-crystalline or still more fluidal crystalline states.

3.2. The Collapse of the Function Membrane

A feature providing significant information concerning the thermodynamic stability of function membranes and therefore also concerning the structure itself, is the phenomenon of function membrane collapse. In actual fact experiments carried out over the last ten years indicated the existence of this phenomenon, but it had not been recognized as such. The interrelationships became apparent when we recorded X-ray diffraction patterns of the ROS membranes. What happens is that in particular membranes of spherical vesicles, *e.g.* erythrocytes[45], photosynthetic bacteria[46], but also those of mitochondria[47] and the flattened vesicles of the ROS[34], in the partially dehydrated state (20—30% H_2O), produce a 58 ± 2 Å reflection in the X-ray experiment which is mostly accompanied by a 116 ± 4 Å reflection. Evidently these reflections must relate to a structural quality which is common to a wide variety of membranes.

The said reflections occur at the meridian when the three first mentioned membranes are orientated by drying on an object slide, *i.e.* they represent diffraction patterns analogous to those produced by membrane stackings. The quantitative analysis of the diffraction patterns of the photosynthetic membranes of *rhodopseudomonas spheroides* conducted by *Pape*[48] has revealed that the basic lamellar unit is a 115 Å thick double layer whose two asymmetric sublayers are arranged in mirror symmetry.

In our X-ray experiments on dehydrated orientated ROS-discs[34] we also encountered the 57 Å reflection but the amazing fact was that this reflection definitely came from the plane structure of the ROS-discs, *i.e.* the diffraction effects as compared with the corresponding effects in other membranes were swivelled through 90°.

For an interpretation of these findings it is necessary to divert briefly from the point. The original concept of the molecular membrane structure was that of a symmetrical membrane, *i.e.* a membrane construction of the highest thermodynamic stability was intuitively postulated[38]. This holds true, for instance, in the case of the photosynthetic membrane and the myelin membrane, *however not within one single membrane but in a mirror symmetrical arrangement of a membrane pair.* It should therefore not be surprising that these two membranes do not alter appreciably upon dehydration.

The situation is different with regard to membrane systems which form spherical vesicles or, in more general terms, in the case of those membranes, whose two lipid layers cannot adopt a mirror symmetrical arrangement, *i.e.* cannot stabilize upon dehydration. This formulation also applies to the ROS. In spherical vesicles contact between the lipid layers is inhibited by the "filling" of the vesicles, whereas in the case of the retina it is prevented by the rhodopsin molecules attached to the lipid side. The result is that when the water phase is eliminated upon drying, *i.e.* when the thermodynamic basis of the "hydrophobic bond"[49] is eliminated, and when the monomolecular lipid layers of the membranes are not stabilized by adjoining lipid layers, a protein-lipid dissociation takes place followed by a structural rearrangement of the proteins and the lipids (Fig. 25). However, it is to be expected that at this hydration stage of 20—30% water the PC molecules will still remain attached to the lattice protein and that only those lipids which form the proper monomolecular lipid layer of the membrane are disintegrated. The original thickness of the membrane is thereby reduced by about 25 Å, *i.e.* from 70 Å to 45 Å (45 Å = 36—38 Å lattice protein + 8 Å towering choline groups). A suspension of densely packed, flattened collapsed membrane vesicles which are 20—30% hydrated must contain 90 Å thick membrane pairs in mirror-symmetrical arrangement spaced by 20—30 Å water layers. When drying is complete the stacking period will shrink to about 90 Å (Fig. 25). Such a behavior was found by *Finean et al.* in X-ray experiments on mitochondria and erythrocytes[45,47].

Lipid extraction will result in a further state of collapse, or, more adequately expressed, state of denaturation: The elimination of the PC molecules from the lattice protein will be followed by a stabilization process of the pure lattice proteins. This stabilization is achieved by a tilting away of the protein subunits from the original lattice plane. In spite of the loss of the PC molecules this process leads to a thickening of the protein layer from 45 or 37 to about 55 Å. This membrane behavior is well established by electron-microscopic observations by *Fleischer* and *Stockenius*[50] as well as by X-ray investigations[51] (Fig. 25c_1 and 25c_2).

In electron-microscopic procedures, employing staining and alcohol dehydration, only collapsed membranes will be pictured, *i.e.* the pictures represent protein layers stained at their outer surfaces (Fig. 25d). There is no "*unit membrane*" but *a common appearance of denatured membranes. Sjoestrand* also comes to the same result in a comprehensive electron-microscopic study[52].

The ROS-discs represent an exception in so far as the orientating pressure is swivelled through 90° with respect to other membrane systems in such dehydration experiments. Whereas a transversal pressure is applied in the membrane systems discussed above, lateral forces have to be considered in the ROS-discs (Fig. 25b). In all X-ray experiments a strong 56 Å reflection appears when the 77 and 51 Å reflections of the initial 2d-lattice protein disappear on dehydration, indicating a breakdown of the 2d-lattice and the formation of a new linear lattice. We suppose that this 56 Å lattice is formed by the tilting away of the protein subunits from the lattice plane to arrange in a "pickaback" structure (Fig. 25b). (*Blasie* and *Worthington* attributed the 56 Å reflection to a liquid planar distribution of rhodopsin molecules[53].)

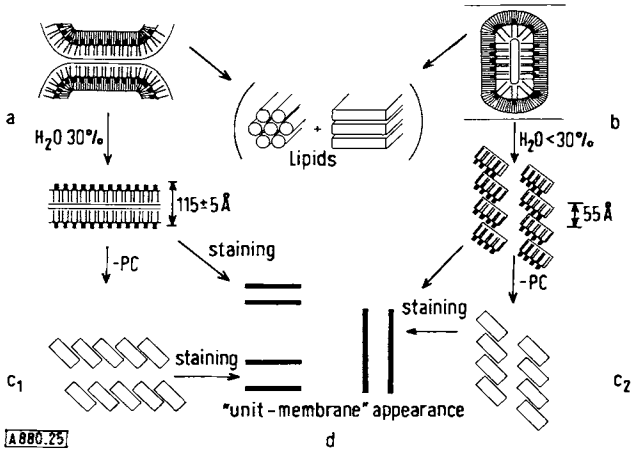


Fig. 25. Representation of the collapse process and the origin of the "unit-membrane" appearance in biomembranes. a) Collapse of membrane vesicles which are orientated by dehydration, b) collapse in ROS-discs on dehydration, c) thickening of the protein layers by rearrangement of the subunits after total lipid extraction, d) stained collapsed membranes: "unit-membranes".

3.3. Perspectives of Molecular Membrane Functions

On the basis of the membrane structure as projected in the preceding sections new possibilities are opened up concerning membrane functions on the molecular level. As an introduction to a consideration of this subject the following three directive postulations should be premissed:

1. The capability of the lipids to exist in two different conformational states and the control of conformational transitions by ligand binding may be regarded as the carrier basis of facilitated and active transport processes.

2. The maintenance of a definite permeability and its adjustability is founded on controllable phase transitions of phospholipids through binding or attachment of ligands as well as on the different binding capacities of individual lipids with respect to univalent and bivalent ions.

3. Proteins have the task of solving stereospecific structural problems, they are responsible for the enzymatic regulation of membrane processes, and in particular for governing the energy transmission between the outside aqueous phases and the membrane.

3.3.1. General Remarks on Carrier-Transport Mechanisms

The newly found intrinsic lipid characteristics point to the possibility of carrier-transport mechanisms based on conformational changes of phospholipids. (A "carrier" is considered to be a molecule which is able to effect a mechanical movement of substrate across the permeation barrier.) It is thought that the diversity in the mechanisms is due to the availability of different carrier molecules, and to the adaptability of various induction and energy-input systems to these individual carriers. In each instance, however, the initiation of the conformational change occurs by means of basically the same physico-chemical process, namely ligand binding or ligand exchange.

Despite the basic similarity of the carrier mechanisms, two categories are distinguishable from the energetic point of view. In the one case the ligands are only weakly associated, in the other they form a true chemical bond with the carrier. In conformity with the divergent energy requirements there are also two different types of energy supplies available. The energy is provided either by an efflux (source flux), *i.e.* by the maintenance of a concentration gradient, or in the form of chemically stored energy (*e.g.* in the form of energy-rich phosphate bonds).

The supply of chemically stored energy to the transport process, *i.e.* the conversion into a vectorial mechanical movement, is considered to be performed *via* the dissociation equilibria of the acid groups of the carriers. Thus, for instance, the energy supplied by the phosphoester bond of ATP enables exchange of protons from the carrier phospho acid groups for Na^+ or Ca^{2+}. The resulting alteration of intra- and intermolecular interaction energy results in a steric displacement of the polar carrier group which represents the actual mechanical transport process.

This type of mechanism naturally demands a considerably greater effort, as regards the substrate coupling and energy input directly at the membrane, than in the case of the efflux-driven transport mechanism. These two molecular mechanisms are probably identical with the so-called facilitated and active transport processes which are already well documented in the literature from the phenomenological point of view.

3.3.2. The Regulation of Permeability

The actual permeation barriers of biomembranes are formed by lipids. Consequently, the permeability parameters must ultimately depend on the lipid characteristics. Three fundamental aspects having an important bearing on permeability may be deduced from these lipid characteristics:

The first aspect concerns the thickness of the permeation barrier in biomembranes. It is certainly of decisive importance whether the permeation barrier is formed by a monomolecular lipid layer about 22 Å thick or by a bimolecular lipid layer at least 44 Å thick. The fact that the "outer" and "inner" aqueous phases surrounding biomembranes *in vivo* possess different pH-values as well as different ion concentrations makes it appear very improbable that bimolecular lipid layers exist in biomembranes. Structures as illustrated in Figure 22 will only be stable provided the two outer phases are identical, *i.e.* in membranes without a gradient. Such membranes are in a state of thermodynamic equilibrium, *i.e.* they are "dead". The "basis membrane" might therefore also be considered as the inactive basis form of biomembranes in thermodynamic equilibrium, the fictive ideal forms of which are shown in Figure 22. A membrane adapted to different "outer" and "inner" phases, *i.e.* a membrane in the biological steady state can, however, only exist if it forms monomolecular lipid layer domains which constitute, together with a one-sided protein association, a completely asymmetric structure. The asymmetric structures shown in Figures 23a, 23b, and 23c must therefore be regarded as the most stable membrane structures in the biologically steady state. In analogy to the definition of the basis membrane the "functional membrane" can be defined as the fully active biomembrane in the biological steady state.

These statements can be understood from the lipid characteristics. Let us assume that the pH of the cell interior is 6.5 and that of the cell exterior 7.5. In a bimolecular lipid micelle of PA for instance, the inner lipid layer would have to exist in the p_{in}-conformation, while the outer lipid layer would have to adopt the p_{ex}-conformation. According to our experience this is an unstable steric situation which results in a decomposition of the micelle. The reconstituted micelle of uniform conformation would, however, undergo the same process. This decomposition process would be repeated until a protein could become associated with one side of a monomolecular lipid layer. In other words, this process of reconstitution would again lead to a stable totally asymmetric structure of the kind shown in Figure 23. Conversely, it can also be envisaged that membranes which are removed from their *in vivo* milieu (*e.g.* by isolation *in vitro*) assume a tendency to undergo symmetrization and start symmetrization operations, *i.e.* they aim towards the basis membrane state.

We consider the jumplike permeability alterations, induced and regulated by pH-changes of the cell interior, to be a second essential aspect of permeability behavior. For the accomplishment of such unsteady permeability changes the CO_2- and pH-dependent phase transition of PE seems to be an appropriate system. It is considered that with this system the regulation of permeability is performed in the physiologically relevant pH-range of pH = 5.5 to 7.5, the steepest range of control lying at pH = 6.3 corresponding to the p*K*-value of the carbonic acid system. A further system which reacts even more sensitively to pH-changes than the PE/bicarbonate/carbonic acid system does is the complex formed by PS, Ca^{2+}, and inorganic phosphate. The normal binding capacity of PS for Ca^{2+} is enhanced many times in the small pH-range of pH = 6.3 to 6.4 if inorganic phosphate is available[54].

In conclusion a third aspect deserves brief consideration: just as important as the unsteady permeation—which most likely plays an essential role in the sensory signal conversion processes—is the establishment and control of a steady permeation flux (leak-flux). A constant permeation flux should be upheld by largely pH-independent Ca^{2+} binding to the phospholipids PA, PC, PE, and PS. The decisive parameter on which such a

leak-flux will largely depend is provided by the Ca^{2+}-concentration in the cell interior which for its part is determined by the active Ca^{2+} transport.

4. Conclusion

The general outline of membrane structure and functions given above is intended as an account of experimental results and of postulates based thereon. Taken as a whole it forms a comprehensive membrane hypothesis. This paper does not set out to furnish a complete membrane concept but rather to expound our standpoint regarding membrane problems and to advance new aspects which may lead to a widening of our understanding of molecular biology and molecular medicine.

I am especially indebted to Dr. H. Emrich for his valuable assistance in the preparation of this paper and for many discussions which have made a most helpful contribution to this study. Thanks are also due to Dipl.-Phys. S. Stange and to Dipl.-Ing. D. Walter who have provided many experimental data in connection with this work and to Dipl.-Phys. H. Pape for carrying out the computer calculations. I am also grateful to Miss G. Zippan for her technical assistance and for preparing the illustrations.

Received: June 2, 1971;
supplemented: April 27, 1972 [A 880 IE]
German version: Angew. Chem. *84*, 597 (1972)

[1] *V. Luzzati* and *F. Husson*, J. Cell Biol. *12*, 207 (1962).

[2] *H. Träuble*, Naturwissenschaften *58*, 277 (1971).

[3] *D. Chapman*, *R. M. Williams*, and *B. D. Ladbrooke*, Chem. Phys. Lipids *1*, 445 (1967); *B. D. Ladbrooke* and *D. Chapman*, *ibid. 3*, 304 (1969).

[4] *E. Rojas* and *J. M. Tobias*, Biochim. Biophys. Acta *94*, 398 (1965).

[5] *D. Papahadjopoulos*, Biochim. Biophys. Acta *163*, 240 (1968).

[6] *A. D. Bangham*, Progr. Biophys. Mol. Biol. *18*, 29 (1968).

[7] *T. Hainai*, *D. A. Haydon*, and *J. Taylor*, J. Theor. Biol. *9*, 278 (1965).

[8] *S. Ohki*, Biophys. J. *9*, 1195 (1969); J. Colloid Interface Sci. *30*, 413 (1969).

[9] *P. Läuger*, Proc. Coral Gables Conf. on Physical Principles of Biol. Membranes, 1970, p. 227.

[10] *K. S. Cole*, Proc. Coral Gables Conf. on Physical Principles of Biol. Membranes, 1970, p. 1.

[11] *J. C. P. Smith*, Chimia *25*, 349 (1971); *O. H. Griffith*, *L. J. Libertin*, and *G. B. Birnell*, J. Phys. Chem. *75*, 3417 (1971).

[12] *D. Chapman* and *A. Morrison*, J. Biol. Chem. *241*, 5044 (1966); *E. G. Finer*, *A. G. Flook*, and *H. Hauser*, FEBS Lett. *18*, 331 (1971).

[13] *J. B. Finean*, Experientia *9*, 17 (1953).

[14] *W. Kreutz*, Adv. Bot. Res. *3*, 54 (1970).

[15] *W. Kreutz* and *D. F. Walter*, to be published.

[16] *M. Blank* and *J. S. Britten*, Proc. Coral Gables Conf. on Physical Principles of Biol. Membranes, 1970, p. 143.

[17] *K. W. Butler*, *H. Dugas*, *I. C. P. Smith*, and *H. Schneider*, Biochem. Biophys. Res. Commun. *40*, 770 (1970).

[18] *U. Keller*, Diplomarbeit, Technische Universität Berlin (1971).

[19] *R. Hosemann* and *W. Kreutz*, Naturwissenschaften *53*, 298 (1966).

[20] *P. Weber*, Z. Naturforsch. *17b*, 683 (1962); Z. Naturforsch. *18b*, 1105 (1963).

[21] *W. Menke* and *E. Jordan*, Z. Naturforsch. *14b*, 234, 393 (1959).

[22] *R. S. Criddle* and *L. Park*, Biochem. Biophys. Res. Commun. *1*, 74 (1964); *R. S. Criddle*, *R. M. Bock*, *D. E. Green*, and *H. Tisdale*, Biochemistry *1*, 827 (1962).

[23] *J. L. Bailey*, personal communication.

[24] *M. T. Laico*, *E. I. Ruoslahti*, *D. S. Papermaster*, and *W. J. Dreyer*, Proc. Nat. Acad. Sci. USA *67*, 120 (1970).

[25] International Tables for X-Ray Crystallography. Kynock Press, Birmingham 1952.

[26] *P. Giesbrecht* and *G. Drews*, Arch. Mikrobiol. *54*, 297 (1966).

[27] *W. Kreutz*, *P. Giesbrecht*, and *A. Paulick*, in preparation.

[28] *R. B. Park* and *N. G. Pon*, J. Mol. Biol. *6*, 105 (1963).

[29] *K. Mühlethaler*, *H. Moor*, and *J. W. Szarkowski*, Planta *67*, 305 (1965).

[30] *St. H. Howell* and *E. N. Moudrianakis*, Proc. Nat. Academy Sci. USA *58*, 1267 (1967).

[31] *J. L. Bailey* and *W. Kreutz*, Int. Congr. Photosynthesis, Freudenstadt 1968.

[32] *J. S. C. Wessels*, Int. Congr. Photosynthesis, Freudenstadt 1968.

[33] *L. P. Vernon*, *B. Ke*, *H. H. Mollenhauer*, and *E. R. Shaw*, Int. Congr. Photosynthesis, Freudenstadt 1968.

[34] *S. G. Stange*, *H. M. Emrich*, and *W. Kreutz*, to be published.

[35] *L. J. Schneiderman* and *I. G. Janga*, Biochemistry *7*, 2281 (1968).

[36] *E. H. Eylar*, Proc. Nat. Acad. Sci. USA *67*, 1425 (1970); *E. H. Eylar*, *J. Salk*, *G. Beverdige*, and *L. Brown*, Arch. Biochem. Biophys. *132*, 34 (1969).

[37] *J. London*, Biochem. Biophys. Acta *249*, 188 (1971).

[38] *J. F. Danielli* and *A. Davson*, J. Cell. Comp. Physiol. *5*, 495 (1935).

[39] *C. K. Akers* and *D. F. Pearsons*, Biophys. J. *10*, 101, 116 (1970).

[40] *W. Kreutz* and *S. G. Stange*, to be published.

[41] *D. Harker*, Science, in press.

[42] *M. F. Moody*, Science *142*, 1173 (1963).

[43] *A. E. Blaurock* and *M. H. F. Wilkins*, Nature *223*, 906 (1969).

[44] *J. K. Blasie* and *C. R. Worthington*, J. Mol. Biol. *39*, 407 (1969).

[45] *J. B. Finean*, *R. Coleman*, *W. A. Green*, and *A. R. Linbrick*, J. Cell. Sci. *1*, 287 (1969).

[46] *W. Menke*, Brookhaven Symps. in Biol. *19*, 328 (1966).

[47] *J. E. Thompson*, *R. Coleman*, and *J. B. Finean*, Biochim. Biophys. Acta *150*, 405 (1968).

[48] *H. Pape*, Thesis, Technische Universität Berlin 1971.

[49] *G. Némethy* and *H. A. Scheraga*, J. Chem. Phys. *36*, 3382, 3401 (1962).

[50] *S. Fleischer*, *B. Fleischer*, and *W. Stoeckenius*, J. Cell Biol. *32*, 193 (1967).

[51] *W. Kreutz* and *W. Menke*, Z. Naturforsch. *15b*, 402 (1960).

[52] *F. S. Sjöstrand* and *L. Barajas*, J. Ultrastruct. Res. *25*, 121 (1968).

[53] *J. K. Blasie* and *L. R. Worthington*, J. Mol. Biol. *39*, 417 (1969).

[54] *J. M. Cotmore*, *G. Nichols*, and *R. E. Wuthier*, Science *172*, 1339 (1971).

Kinetics of Cooperative Conformational Transitions of Linear Biopolymers

By Gerhard Schwarz and Jürgen Engel[*]

Cooperative conformational transitions of proteins and nucleic acids are of decisive importance to many processes of molecular biology, and particularly to their regulation. They proceed *via* numerous interdependent elementary processes, and their kinetics are therefore often complicated. They are frequently also very fast. However, kinetic analyses can be carried out by chemical relaxation methods. The theoretical interpretation is comparatively simple in the case of linear biopolymers. When the linear Ising model extended for kinetics was applied to model peptides and polynucleotides, it provided an insight into the fundamental principles of cooperative transformations.

1. Introduction

The biological function of nucleic acids and proteins is largely determined by their specific conformation. This function can be modified by a change in external conditions. Conformational transitions are in fact important steps in many reactions of molecular biology (examples: allosteric regulation of enzyme activity[1, 2], replication of nucleic acids[3]). An important requirement here is that small effects should induce large changes. This can be achieved only by a positively cooperative interaction between the elementary steps of the transformation, as a result of which an elementary change that has already occurred at one part of the molecule strongly promotes other elementary changes that have not yet taken place.

We have already[4] discussed the general characteristics of cooperative conformational transitions of biopolymers for the case of linear systems, since these present comparatively simple conditions both theoretically and experimentally, and so form a good basis for the interpretation of more complicated systems. Equilibrium data on the helix-coil transitions of some synthetic polypeptides or oligonucleotides built up from identical subunits and on the structural transition between two conformations of poly-L-proline were analyzed by means of the linear Ising model. The experimental and theoretical foundations discussed in this connection form the basis of the present progress report.

To obtain a complete understanding of cooperative conformational transitions, one must consider the kinetics of such processes. Even in the case of linear model systems consisting of chemically identical residues, however, one may expect from the outset a very complicated reaction course. As an example, let us consider the α-helix-coil transition of a polyamino acid with N possible hydrogen bonds between the CO and NH groups of complementary peptide linkages. The transition to the random coil in this case obviously requires N elementary steps, *i. e.* N breakages of hydrogen bonds. Owing to the cooperativity of the transition, these individual steps must proceed at different rates according to whether or not adjacent hydrogen bonds have already been broken.

Meaningful interpretations and evaluations of kinetic experiments on systems involving very many reaction steps cannot be based directly on the classical methods of kinetics. The first or second order plots that are often found in the literature are therefore of doubtful value unless backed by theory.

Advantages are offered by the relaxation method, which involves the kinetic study of the approach to a new equilibrium after a generally small disturbance of the old equilibrium (*e. g.* by a temperature change). Relaxation curves obtained in this way reflect in principle not only the kinetics of the slowest unit process but also those of the other intermediate reactions. Their theoretical calculation for a postulated mechanism is facilitated by the fact that the kinetic differential equations can be linearized for small disturbances. However, the evaluation methods that have been found suitable for simple reactions with one or two steps[5] frequently cannot be used. It is nevertheless possible, even in complicated cases, to establish the desired quantitative relation between a reasonable reaction mechanism and the experimental curves by measurement and calculation of mean relaxation times[6, 7].

Conformational changes may be so fast as to necessitate the use of relaxation methods with very high time resolution. Thus in the case of the α-helix-coil transition, the temperature jump method revealed only that the transition time is evidently shorter than the heating time of the measuring cell (approximately 1 microsecond)[8, 9]. Only by still "faster" methods was it possible to determine transition times in the region of 10^{-8} to 10^{-6} seconds (see Section 3.1).

Other transitions can be followed by more conventional methods. Thus the denaturing time of very long-chain deoxyribonucleic acids are in the region of seconds to minutes, and the helix-I⇌helix-II transition of poly-L-proline is even slower.

[*] Prof. Dr. G. Schwarz and Prof. Dr. J. Engel
Abt. Biophysikalische Chemie, Biozentrum der Universität
CH-4056 Basel, Klingelbergstrasse 70 (Switzerland)

2. Theoretical Principles

2.1. Execution and Evaluation of Chemical Relaxation Experiments

A kinetic analysis by chemical relaxation experiments involves essentially three steps, *i.e.* the disturbance of a stationary state of the reaction system (usually of the chemical equilibrium), measurement of the time dependence of the subsequent change in a quantity P that depends on the concentration of the reactants (*e.g.* optical density, optical rotation), and finally the interpretation of the data in the context of an overall reaction. Whereas the first two steps present at most technical and experimental problems, complicated questions of mathematical theory may arise in the third for a reaction consisting of many unit steps.

As a concrete example, let us consider an experimentally fairly clear and versatile method, *i.e.* the temperature jump method. On the basis of the well-known van't Hoff equation for the temperature dependence of chemical equilibrium constants, a chemical equilibrium is displaced in a definite manner by a temperature change. This can be brought about experimentally in approximately a microsecond, *e.g.* by electric heating[5]. If the new equilibrium is established more slowly, the change in the quantity P as a function of time can be followed as a relaxation curve on the screen of an oscilloscope.

Similar curves are obtained with sudden changes in other parameters that influence the position of the equilibrium, such as pressure, electric field, solvent composition, and pH. As shown in Figure 1, a relaxation function $\Phi(t)$ that can be found directly by experiment is thus defined. This must now be correlated quantitatively and unambiguously with the underlying reaction mechanism.

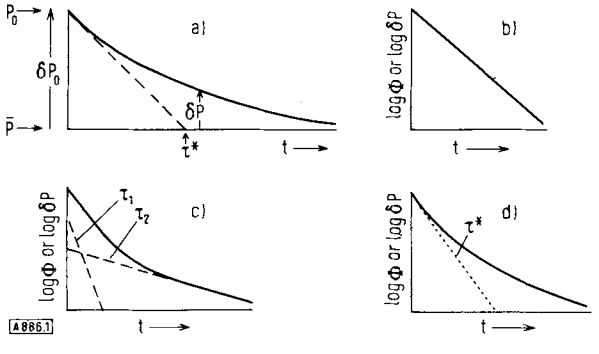


Fig. 1. Schematic representation of relaxation curves in jump experiments.
a) After a change in temperature, pressure, or other external parameter that is fast in relation to the reaction time, the initial equilibrium (measured quantity P_0) is replaced by a new equilibrium (measured quantity P). $\Phi(t) \equiv \delta P/\delta P_0$ defines a (normalized) relaxation function, which is directly obtainable by experiment. The tangent to $\Phi(t)$ at $t=0$ cuts the asymptote at $t=\tau^*$ [see eq. (4)]. b) When $\log \Phi(t)$ (or $\log \delta P$) is plotted against time, the resulting graph in the simplest case is a straight line with slope $= 0.434 \cdot 1/\tau$, when $\Phi(t)$ consists of a single exponential function. c) If there are two exponential functions with sufficiently different values of τ_1 and τ_2 (broken line), a curve with a linear tail is observed. This curve can still be satisfactorily broken down into its components. d) For several overlapping relaxation terms, an unambiguous breakdown is no longer possible, but the average relaxation time τ^* can be determined from the initial slope (dotted).

The situation is simple in a one-step process, *e.g.*

$$\mathrm{A} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \mathrm{B} \quad \text{where} \quad \frac{dc_B}{dt} = k_{12}c_A - k_{21}c_B \qquad (1a,b)$$

Because of the conservation of mass, $c_A + c_B$ is always constant, so that only one independent concentration variable is involved. This may be taken as *e.g.* c_B. The variation of any concentration-dependent parameter with time can then be calculated by solution of eq. (1b). We find here

$$\Phi(t) = e^{-t/\tau} \quad \text{where} \quad \frac{1}{\tau} = k_{12} + k_{21} \qquad (2a,b)$$

The relaxation time τ, as shown in Figure 1, can be easily determined graphically from the measured relaxation function $\Phi(t)$. If the equilibrium constant $K = k_{12}/k_{21}$ is known, the individual rate constants can be obtained directly from eq. (2b).

In more complicated reactions with more than one step, the variation of the concentration of each reactant can still be described by a differential equation. This includes the rate contributions of all elementary processes that lead to a change in the chemical state in question.

If the difference between the number of reactants and the number of mass conservation conditions is n (which corresponds to the number of "independent" reaction steps obtained when all the steps that lead to reaction cycles are struck out), the overall reaction is completely described by n kinetic differential equations. Naturally, these may be extremely complicated. However, they can be linearized (elimination of square and higher concentration terms) for small deviations from a time-independent reference state (small perturbations). A closed mathematical solution of the problem is now always possible in principle[6]. This is characterized by n time constants, the relaxation times $\tau_1, \tau_2, \tau_3 \ldots \tau_n$. These constants depend in a definite manner on the reaction mechanism, the kinetic constants, and the concentrations of the various reactants. It should be noted, however, that the individual relaxation times are not directly correlated with individual reaction steps. In particular, for the relaxation function $\Phi(t)$ of a sudden disturbance of the equilibrium, the theory gives

$$\Phi(t) = \sum_{i=1}^{n} \beta_i e^{-t/\tau_i} \quad \text{where} \quad \sum_i \beta_i = 1 \qquad (3a,b)$$

i.e. a sum of n exponential functions with the τ_i as time constants. The corresponding amplitude factors β_i do not contain any direct kinetic quantities. They are, however, dependent on the quantities measured and on the disturbing parameter. The β_i therefore generally change if *e.g.* the variation of the optical density with time is followed at a different wavelength or if a sudden change in pressure is used instead of a temperature change. However, such manipulations have no influence on the τ_i.

The complete set of relaxation times τ_i together with the corresponding amplitude factors β_i is known as the relaxation spectrum. A definite assignment of a relaxation spectrum to an experimental curve is practically impossible unless there are only a few τ_i with very different orders of

magnitude and comparable β_i (see Fig. 1b—1d). If this is not so, a kinetic analysis can be carried out with other parameters that are directly obtainable by experiment. A parameter that is particularly suitable for this purpose is the mean (reciprocal) relaxation time τ^*[6], which is defined by the following relation:

$$\frac{1}{\tau^*} \equiv \sum_i \frac{\beta_i}{\tau_i} = -\left(\frac{d\Phi}{dt}\right)_{t=0} = -\frac{1}{\delta P_0}\left(\frac{dP}{dt}\right)_{t=0} \tag{4}$$

(The relation with Φ is easily verified from eq. (3a).) As indicated in Figures 1a and 1d, τ^* is given by the tangent to the relaxation curve at time $t=0$ (instant of the disturbance). Because of this relation, τ^* is theoretically also relatively easy to obtain[6], provided that an equilibrium state of the system exists at $t=0$ (as is usually the case). Apart from a knowledge of the elementary processes and their kinetic constants, one then requires only equilibrium properties for the calculation of τ^*. There is thus no need to solve differential equations.

Very fast relaxation processes ($\tau \lesssim 1$ μsec) have so far been investigated only by methods that make use of a periodic disturbance in the form of a sine function, *e.g.* a sound wave or an alternating electric field. In this way, small fluctuations of the equilibrium state of the reaction system are produced. If the vibrations are fast enough in comparison with the reaction time, the actual change in concentration of the reactants with time will lag behind its equilibrium value. The theory then leads to an absorption of energy in the region around the relaxation frequency $\nu_R = 1/(2\pi\tau)$ (*e.g.* sound absorption when ultrasonic radiation is used, and ohmic or dielectric losses in an alternating electric field). The chemical relaxation times can be obtained by evaluation of corresponding measurements[6].

2.2. The Kinetics of the Linear Ising Model

As described earlier in some detail[4], the thermodynamic behavior of cooperative conformational transitions of linear biopolymers can be quantitatively understood with the aid of the linear Ising model. In this connection, the elementary states of the individual segments corresponding to the two extreme conformations are designated A and B. As kinetic elementary processes of the transition, therefore, we find reactions of the type

$$..XAY.. \rightleftharpoons ..XBY.. \tag{5}$$

at any point on the chain molecule; according to the basic assumption of the Ising model, the rate constants also depend on the two nearest neighboring states X and Y each of which may also be equal to A or B. We must therefore distinguish between two types of elementary reactions. The growth steps

$$\begin{matrix} ..AAB.. \\ ..BAA.. \end{matrix} \overset{k_F}{\underset{k_D}{\rightleftharpoons}} \begin{matrix} ..ABB.. \\ ..BBA.. \end{matrix} \quad \text{where } \frac{k_F}{k_D} = s \tag{6a,b,c}$$

describe the growth of existing A and B sequences, the equilibrium constant s being identical with the corresponding parameter of the Zimm-Bragg theory[4]. In the nucleation and decomposition steps

$$..AAA.. \overset{k_{FA}}{\underset{k_{DA}}{\rightleftharpoons}} ..ABA.. \quad \text{where } \frac{k_{FA}}{k_{DA}} = \sigma \cdot s \tag{7a,b}$$

and

$$..BAB.. \overset{k_{FB}}{\underset{k_{DB}}{\rightleftharpoons}} ..BBB.. \quad \text{where } \frac{k_{FB}}{k_{DB}} = \frac{s}{\sigma} \tag{8a,b}$$

the equilibrium constants σs and s/σ are fixed by the equilibrium theory, the cooperative parameter $\sigma \ll 1$ showing how much more difficult nucleation is than growth (a small σ indicates great difficulty of nucleation, *i.e.* high cooperativity). Since only the ratio of the equilibrium constants is fixed by thermodynamics, one kinetic parameter remains open for each of the processes. In the general case, special nucleation and decomposition steps for the ends of the molecule must also be taken into account, since only one nearest neighboring state exists in these positions[10].

In a chain with N segments, the sum of the molecules in the up to 2^N different conformational states must naturally remain constant. Since this at first sight is the only mass conservation condition, one should expect a practically continuous spectrum of 2^N-1 relaxation times. Fortunately, the problem can be further simplified to a greater or lesser extent according to the particular conditions. For example, the mean relaxation time can be calculated without special difficulties with the aid of the equilibrium theory and compared with experimental data.

In the common limiting case of very long chains with high cooperativity, *i.e.* for

$$N \gg \text{cooperative length } N_0 = \frac{1}{\sqrt{\sigma}} \gg 1$$

the effects at the ends of the molecule can be neglected[4]. Moreover, in the transition range (where A and B are present in roughly comparable quantities), the contributions of the processes (7) and (8) to the overall reaction become vanishingly small, since the "nuclei" ABA and BAB exist in very low concentrations in comparison with AAB, ABB, *etc.* The fraction of B segments, Θ, will therefore change almost exclusively by growth steps in accordance with eq. (6), *i.e.*

$$\frac{d\Theta}{dt} = 2k_F\gamma_{AAB} - 2k_D\gamma_{ABB} = 2k_D\{s\gamma_{AAB} - \gamma_{ABB}\} \tag{9}$$

where γ_{AAB} and γ_{ABB} are the fractions of A and B segments respectively with the neighbors A (left) and B (right) (the factor 2 arises because $\gamma_{AAB}=\gamma_{BAA}$ and $\gamma_{ABB}=\gamma_{BBA}$). If the equilibrium is suddenly disturbed at $t=0$, with the result that $s \rightarrow s+\delta s$ and the equilibrium value $\Theta_0 \rightarrow \bar{\Theta} = \Theta_0 + \delta\bar{\Theta}$, then according to eq. (4) (with $P=\Theta$, $\delta P_0 = -\delta\Theta$)[11,12]

$$\frac{1}{\tau^*} = \frac{1}{\delta\Theta}\left(\frac{d\Theta}{dt}\right)_{t=0} = 2k_D\frac{\bar{\gamma}_{AAB}}{(\delta\Theta/\delta s)} \tag{10}$$

(values with bars are equilibrium values). The thermodynamic theory enables us to express $\bar{\gamma}_{AAB}$ and $\delta\bar{\Theta}/\delta s$ by Θ and σ. Thus[10]

$$\tau^* = 4\Theta(1-\Theta)\tau^*_{max} \quad \text{where} \quad \tau^*_{max} = \frac{1}{4\sigma k_F} \tag{11a, b}$$

The maximum relaxation time τ^*_{max} thus occurs at the midpoint of the transition ($\Theta = 0.5$).

For $N \lesssim N_0$, end effects and nucleation can no longer be disregarded in the kinetics of the transition. With plausible assumptions for the nucleation rates, τ^* is obtained as a complicated function of the general form[10]

$$\tau^* = f(\Theta, \sigma, \beta', \beta'', N) \cdot \tau^*_{max} \tag{12}$$

(β', β'' describe the end effects[4, 10]). The function f always lies below the limiting function $4\Theta(1-\Theta)$ that is valid for $N \gg N_0$ according to eq. (11a), *i.e.* the transition becomes faster with decreasing chain length.

A calculation of the chemical relaxation behavior of cooperative transitions that goes beyond the average value τ^* can be carried out relatively easily in some cases if use is made of special properties of the system and special experimental conditions. Examples are the "all-or-nothing" behavior of short-chain poly-L-prolines (see Section 3.2) and oligonucleotides (see Section 3.3) and the "suppressed nucleation" in poly-L-proline (see Section 3.2). More complete calculations of kinetic curves have also been attempted for the case of long chains, with simplifying assumptions for the kinetics of the elementary processes[13-15] or by computer calculations[16, 17].

It has recently become possible to place the theory on a generally valid basis. It has been shown for any chain length that the complete kinetics of the linear Ising model are described by $4N-5$ independent, non-linear differential equations[18]. For $N \to \infty$ (*i.e.* $N \gg N_0$), the number of equations decreases to four. Three of the relaxation times defined in this way occur with vanishing amplitudes in the transition range with sufficiently high cooperativity ($N_0 \gg 1$), so that the fourth must be identical with τ^*. In this limiting case, which is of practical importance, the transition is therefore described by a single relaxation time [as eq. (2a)], despite the complicated reaction course[19].

3. Experiments on Simple Linear Model Systems

3.1. The α-Helix⇌Coil Transition

The experiments were carried out with sufficiently long polypeptide chains ($N \gg N_0$) to enable one to expect a relaxation time in accordance with eq. (11) in the transition range. The essential elementary process of the transition consists in the growth and degradation of helix fragments within a polypeptide chain by formation and rupture of hydrogen bonds at the junctions between coil and helix regions. The rate constant k_F describes the formation of such a hydrogen bond. This formation does not require any appreciable activation energy[20], but a favorable steric position of the correct CO and NH groups must be reached by suitable rotation about two intervening C—C or C—N bonds (see Fig. 2). With an activation energy of a few kcal/mole for the rotation, therefore, one may expect a k_F value of about 10^{10}—10^{11} s^{-1}. Since the σ values for polypeptides are in the region of 10^{-4}—10^{-2}, depending on the system, eq. (11b) gives maximum relaxation times of about 10^{-8} to 10^{-6} seconds for the helix-coil transition[11, 12].

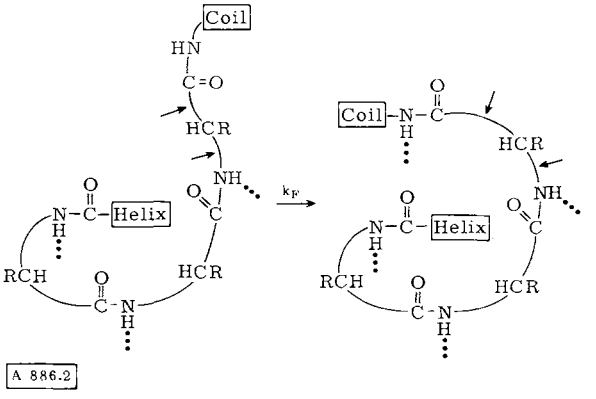


Fig. 2. Transition of a peptide linkage from the coil state to the helix state at a helix/coil junction with formation of a hydrogen bond characteristic of the α-helix between a NH and a CO group. The C—C and C—N single bonds of the amino acid residue (indicated by arrows), which allow free rotation in the coil state, are fixed by the formation of this bond.

This estimate agrees well with the experimental data obtained so far. Sound absorption measurements on polyglutamic acid (see Fig. 3) show the maximum effect at $\Theta = 0.5$ and 15 MHz[21]. According to the theory, the additional sound absorption coefficient α per wavelength λ (in aqueous solution) produced by the helix-coil transition should be

$$\alpha\lambda = \frac{\pi\rho v_\infty^2}{RT}(\Delta V)^2 \frac{2}{\sqrt{\sigma}} \{\Theta(1-\Theta)\}^{3/2} c_0 \frac{\omega\tau}{1+(\omega\tau)^2} \tag{13}$$

(ρ = density, v_∞ = velocity of sound in the solvent, ΔV = change in molar volume in the coil-helix transition, c_0 = concentration of the polypeptide in moles of monomer per unit volume[24]). From $\nu_R = 15$ MHz, τ_{max} is found to be 1×10^{-8} s. With $\sigma = 3 \times 10^{-3}$[4], therefore, eq. (11b) gives $k_F = 8 \times 10^9$ s^{-1}. Moreover, from the maximum value of $\alpha\lambda$, eq. (13) gives $\Delta V = 0.5$ cm³/mol, in agreement with direct measurements of ΔV[22].

Similar experiments with poly-L-ornithine[23] also gave $\tau^*_{max} \approx 10^{-8}$ s. The measured dependence on the degree of transition Θ confirms the formula (11a).

Measurements on poly-(γ-benzyl-L-glutamate) were carried out with the aid of a new chemical relaxation principle, which is based on the displacement of a chemical equilibrium in the direction of stronger dielectric polarization by an electric field[20]. If the associated chemical relaxation is much faster than the rotation of the dipoles involved in the reaction, in addition to the usual dielectric relaxation caused by rotation diffusion there is a further relaxation effect at higher frequencies which reflects the chemical

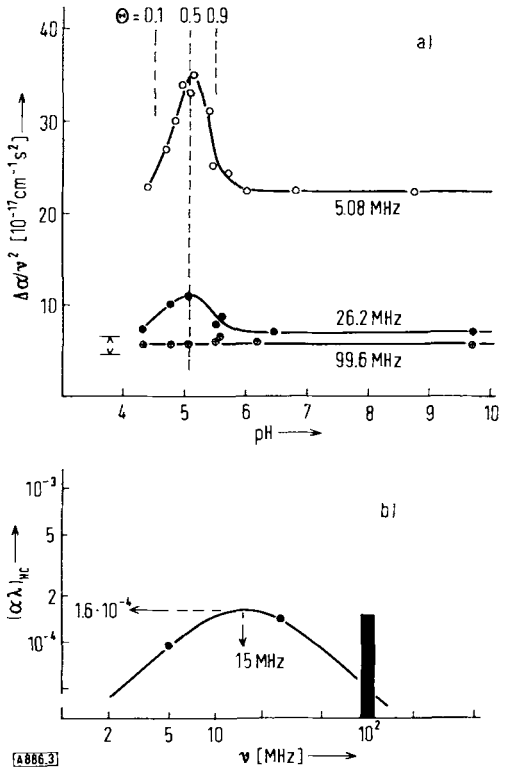


Fig. 3. Ultrasonic measurements of the helix-coil transition of polyglutamic acid in aqueous solution (after *Saksena et al.* [21]). The transition is brought about (reversibly) by pH changes in the region pH = 4 to 6. The midpoint ($\Theta = 0.5$) is situated at about pH = 5.1.
a) According to eq. (13), $\Delta\alpha/\nu^2$ ($\Delta\alpha$ = sound absorption coefficient of the solution minus that of the solvent, ν = sound frequency) should have a maximum at $\Theta = 0.5$. The experimental data plotted show this clearly for the frequencies 5.08 MHz and 26.2 MHz, whereas at 99.6 MHz, the accuracy of the measurements is evidently no longer sufficient to show the maximum. b) The sound absorption per wavelength $(\alpha\lambda)_{HC}$ resulting from the helix-coil transition (at $\Theta = 0.5$) is plotted on a double logarithmic diagram against the frequency. According to eq. (13) one should obtain a characteristic curve fixed by only two experimental points in accordance with the function $A\omega\tau/(1+\omega^2\tau^2)$ ($\omega = 2\pi\nu$, A = constant factor), which has a maximum at $\omega = 2\pi\nu_R = 1/\tau$. The values found here for ν_R and $A/2$ are indicated. They give τ and, with the aid of eq. (13), the reaction volume ΔV.

relaxation[24]. These conditions are satisfied for poly-(γ-benzyl-L-glutamate). In the transition range, the polypeptide chains consist of a sequence of coil regions and helix fragments, the latter having a considerable electric dipole moment. The applied electric field displaces the equilibrium between helix and coil regions in such a way that the helix dipoles increase in the field direction, while they decrease in the opposite direction. Since the rotation diffusion of the helices, because of their length, is much slower than the chemical relaxation of the helix growth, a relatively fast dielectric polarization occurs in addition to the rotational relaxation process. As expected, this effect is found to reach a maximum at the midpoint of the transition (see Fig. 4), as in the case of the sound absorption. The Θ-dependence, which was also measured, agrees well with eq. (11a)[25]. The effect was recently also found for the similar system poly-(β-benzyl-L-aspartate) in *m*-cresol[26].

From the τ^*_{max} of 5×10^{-7} s found for poly-(γ-benzyl-L-glutamate) and the value $\sigma = 0.4 \times 10^{-4}$ that is valid for this polypeptide at the high concentrations used[25], it is found that k_F is 1.3×10^{10} s^{-1}, which is still within the region of our earlier estimate. Another important result of these experiments is the observation that an electric field can directly influence a conformational transition. Calculation shows that a field strength of 200 kV/cm (such as occurs on biological membranes) can cause an almost complete structural transition in the system discussed here in times of about 1 μsec. It is therefore conceivable that *e.g.* nerve impulses may act directly on molecular processes by a cooperative conformational change.

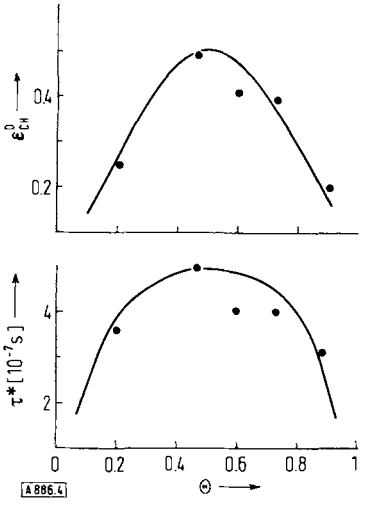


Fig. 4. Increment (maximum) of the dielectric constant (ε^0_{CH}) due to the helix-coil transition of a concentrated solution of poly-(γ-benzyl-L-glutamate) as a function of the degree of transition Θ (after [25]). The τ^* values are calculated from the dielectric data. The curves shown correspond to the calculated course.

An interpretation of double signals of the $C_\alpha H$ and NH protons in the nuclear magnetic resonance as resulting from a helix⇌coil exchange with a value of only 10^{-2} s for τ[27,28], which contradicts these results, has recently been refuted by a different interpretation of the signals[29,30].

3.2. The Helix I⇌Helix II Transition of Poly-L-proline

This transition between two ordered conformations is very cooperative[4]. A nucleus of the I form (*cis* state of the peptide linkage) inside a II helix (*trans* state of the peptide linkages) is about 10^5 times less probable at $\Theta = 0.5$ than an uninterrupted helix, and *vice versa* ($\sigma \approx 10^{-5}$, $N_0 \approx 300$). This is due to energetically unfavorable conditions at the I/II and II/I junctions. These therefore occur only relatively infrequently. For short chains, even the content of molecules containing only one junction is small in relation to the concentration of molecules in the pure forms (without such junctions).

Table 1 shows that this "all-or-nothing" case is still largely satisfied for $N = 20$. The probability that a junction occurs somewhere in the chain naturally increases with increasing chain length. It is found quantitatively (Table 1) that with $N = 100$ (*i.e.* about 1/3 of the cooperative length N_0), the content of molecules having one junction can no longer be disregarded, whereas the content of nuclei (two junctions)

is still very small ("suppressed nucleation"[17]). This simplification finally disappears above about $N=200$.

A relaxation process of the transition can be initiated by a sudden change in the solvent composition. Because of the fairly slow elementary steps of the *cis*⇌*trans* isomerization of the peptide linkage (with an activation energy of 20 kcal/mole), the course of the transition with time can be measured easily and very accurately (by polarimetry). The system thus becomes an ideal model for checking detailed predictions regarding the kinetics of cooperative transitions. Some interesting special cases will be discussed first.

Table 1. Fraction of polyproline molecules that contain I/II or II/I junctions in relation to the fraction of the pure forms I ... I and II ... II in benzyl alcohol/*n*-butanol at 70 °C and $\Theta \approx 0.5$ (calculated from the equilibrium data [4]).

Chain contains	Chain length N		
	20	100	200
only I	1	1	1
one junction	0.113	0.6	1.22
two junctions	0.003	0.09	0.37
only II	1	1	1

The kinetics of the "all-or-nothing" case are particularly simple. Since the system consists almost exclusively of chains with practically identical elementary states, we formally obtain a one-step process with first order reactions, *e.g.* for $N=4$:

$$\text{II II II II} \underset{\vec{k}}{\overset{\vec{k}}{\rightleftharpoons}} \text{I I I I} \qquad (14)$$

This process must naturally proceed *via* intermediate states. Only those with at most one junction need be considered (since all others are even less probable). If we also assume, for simplicity, that all growth steps (including those at the ends) are described by the same rate constant, the complete kinetic mechanism for (14) is found to be

$$\begin{array}{ccccc} \text{II II II II} & \underset{k_D}{\overset{k_F}{\rightleftharpoons}} & \text{I II II II} & \underset{k_D}{\overset{k_F}{\rightleftharpoons}} & \text{I I I I} \\ \sigma_I' k_F \downarrow\uparrow k_D & & & & \sigma_{II}'' k_D \downarrow\uparrow k_F \\ \text{II II II II} & & & & \text{I I I I} \\ k_D \downarrow\uparrow \sigma_I'' k_F & & & & k_F \downarrow\uparrow \sigma_{II}' k_D \\ \text{II II II I} & \underset{k_D}{\overset{k_F}{\rightleftharpoons}} & \text{II II II I} & \underset{k_D}{\overset{k_F}{\rightleftharpoons}} & \text{II I I I} \end{array} \qquad (15)$$

(σ_I', σ_I'', σ_{II}', σ_{II}'' = nucleation parameters at the chain ends[4]). Since all the intermediate states Z are present in very low concentrations, the well-known steady-state condition $dc_Z/dt=0$ may be assumed. We thus find from eq. (15) for the rate constants that occur in eq. (14)[31]:

$$\vec{k} = (\sigma_I' + \sigma_I'')\, s^{N-1} \frac{1-s}{1-s^N} k_F, \quad \bar{k} = (\sigma_{II}' + \sigma_{II}'') \frac{1-s}{1-s^N} k_D \qquad (16a,b)$$

($s = k_F/k_D$). According to eq. (2), the chemical relaxation of eq. (14) should be described by a single relaxation time $\tau = 1/(\vec{k}+\bar{k})$. Corresponding behavior was in fact found experimentally for $N<20$ (see Fig. 5a).

Relaxation curves for chains of medium length (*e.g.* $N \approx 100 \approx N_0/3$), for which the "suppressed nucleation" approximation is valid (see Table 1), proceed formally according to a zero-order rate law for a certain time if the initial equilibrium lies in the transition range (see Fig. 5b).

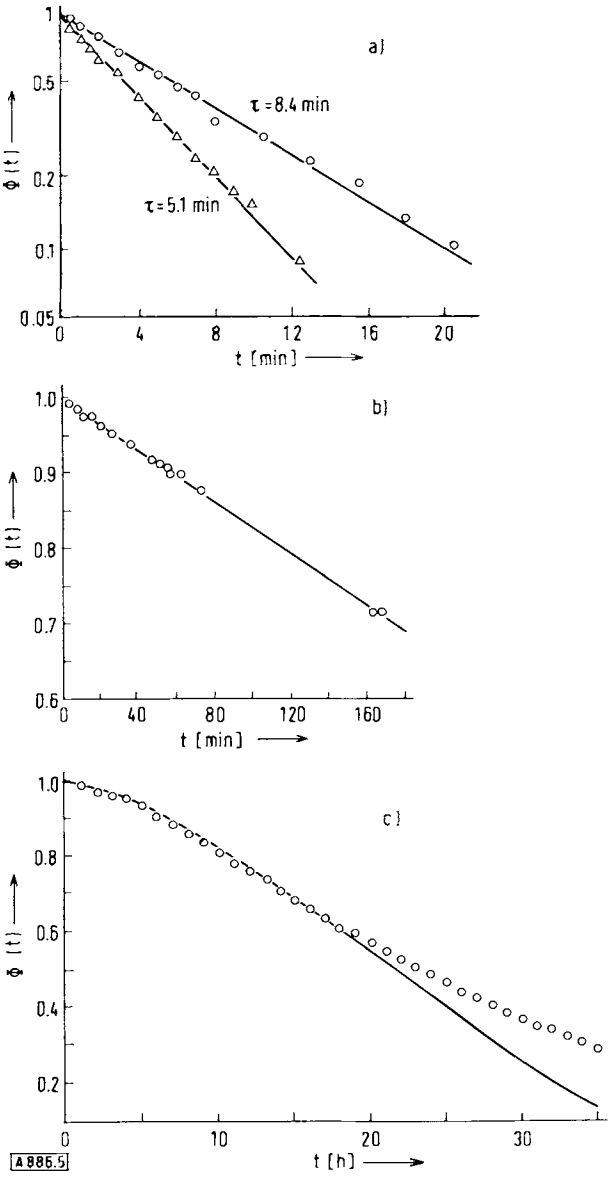


Fig. 5. Three limiting cases of the kinetics of the I⇌II transition of poly-L-proline (from [31]).
a) Semilogarithmic plot of two relaxation curves in the "all-or-nothing" range $N=18$. Change from 90 to 60 vol.-% of *n*-butanol in benzyl alcohol, whereupon $\Theta_I = 0.5 \rightarrow 0.1$ (—○—) and $0.1 \rightarrow 0.5$ —△—). The τ values differ because of the different starting conditions [corresponding to different *s* values in eq. (16)]. b) Course of the transition with time (linear plot) in the case of suppressed nucleation ($N=217$, change from $\Theta_I = 0.34$ to 0.71). The reaction rate remains constant for some time. c) Sigmoid build-up curve of the transition for $\Theta_I = 1 \rightarrow 0$ at $N=113$. Experimental values ○○○, calculated values ———.

The lack of dependence on the concentration of the I or II states still present is explained by the fact that under the above conditions, the number of actual reaction sites, *i.e.* of I/II and II/I junctions, remains constant for some time. The transition occurs essentially by a displacement of these sites in growth steps. New junctions are formed and disappear only very slowly and in comparatively small

numbers. This effect therefore becomes important only toward the end of the reaction. The initial rate in Figure 5b is thus proportional to the product of $k_F - k_D = (1 - {}^1/_s)k_F$ and the number of junctions. If the latter is known for the initial equilibrium (*e.g.* from Table 1) as well as s for the final state, k_F can be determined[31].

Another instructive special case is where the initial state chosen for long chains is outside the transition range, so that only one practically pure form exists at first ($\Theta = 0$ or 1). The fast growth steps can now occur only after the first junctions have been formed by nucleation, which is a very much slower process. The result is sigmoid build-up kinetics (see Fig. 5c). Experimental verification proves the validity of the special assumption in this case, namely that the rate constant of the nucleation is considerably smaller that that of the growth step. Note that the small equilibrium constant of the nucleation, $\sigma.s$, would also be explained by a correspondingly fast reverse reaction (destruction of a nucleus).

Whereas calculation of the total relaxation curve was at least approximately possible in the special cases described, the kinetic analysis was based in the general case on mean

equilibrium investigations[4,41], the "zipper model" (see Fig. 6, also Fig. 10 in[4]) proved useful for the interpretation of the kinetic data. For the short chains chosen by *Pörschke* and *Eigen* ($N \leq 18$), the all-or-nothing approximation is valid:

$$2A_N \underset{\vec{k}}{\overset{\vec{k}}{\rightleftharpoons}} (A_2)_N$$

$$A_N + U_N \underset{\vec{k}}{\overset{\vec{k}}{\rightleftharpoons}} (AU)_N \qquad (17a, b)$$

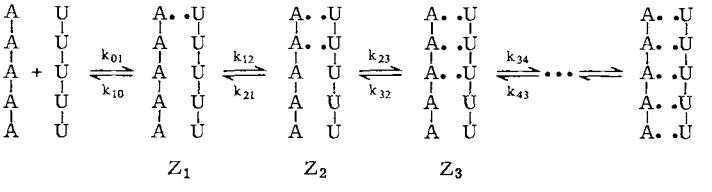
(Coil) (Double helix)

Only one relaxation time is in fact found, and this varies with the concentration of chains in the coil form as follows

$$1/\tau = 4\,\vec{k}c_{A_N} + \vec{k}$$

$$1/\tau = \vec{k}(c_{A_N} + c_{U_N}) + \vec{k} \qquad (18a, b)$$

according to the relations[5] for bimolecular single-step reactions. As in the "all-or-nothing" case of polyproline (see Section 3.2), $\vec{k}$ and $\overleftarrow{k}$ can be expressed by the elementary



$$A_5\text{-Coil} + U_5\text{-Coil} \underset{2.10^9 s^{-1}}{\overset{10^8 l\ mol^{-1} s^{-1}}{\rightleftharpoons}} Z_1 \underset{2.10^7 s^{-1}}{\overset{10^7 s^{-1}}{\rightleftharpoons}} Z_2 \underset{2.10^6 s^{-1}}{\overset{10^7 s^{-1}}{\rightleftharpoons}} Z_3 \underset{2.10^6 s^{-1}}{\overset{10^7 s^{-1}}{\rightleftharpoons}} Z_4 \underset{2.10^6 s^{-1}}{\overset{10^7 s^{-1}}{\rightleftharpoons}} (AU)_5\text{-Double helix}$$

Fig. 6. Top: Zipper model of the formation of a double helix from a poly-A and a poly-U strand for $N = 5$. Helices in which the base pairs (..) have not yet all been formed occur in small concentrations as intermediates (Z_1 to Z_4) ("all-or-nothing" case).
Bottom: Numerical values of the rate constants.

relaxation times[31-33]. As in the α-helix⇌coil transition, the theoretically[10] required maximum of τ^* in the region of $\Theta = 0.5$ was found. It was possible to determine τ^*_{max} from the dependence of τ^* on the chain length. From this and eq. (11b), the rate constant for the growth of *cis* (helix I) sequences was found to be $k_F = 1.5\ s^{-1}$ (at 70 °C in 60 vol.% *n*-butanol in benzyl alcohol), a value that agrees satisfactorily with that obtained by evaluation of the special cases described above. Similar values have in fact also been obtained completely independently for the *cis*⇌*trans* isomerization of the amide linkage in *N*,*N*-dimethylacetamide by measurement of the nuclear magnetic resonance[34-36] and from IR data[37,38].

3.3. The Double Helix⇌Coil Transition of Oligonucleotides

The formation and decomposition of short double helices of polyriboadenylic acid (poly-A) and of polyribouridylic acid (poly-U), respectively, with poly-A was investigated by *Pörschke* and *Eigen*[39,40] by the temperature jump method and by rapid mixing in a flow apparatus. As in the kinetic constants of the scheme in Figure 6 assuming steady-state conditions for all intermediate states. These are thus obtainable experimentally by measurement of the dependence of $\vec{k}$ and $\overleftarrow{k}$ on the chain length.

However, the discussion here is rather different from that in the case of polyproline. A satisfactory interpretation of the "all-or-nothing" kinetics of poly-L-proline was achieved by the assumption that in the interior of the chain, all elementary steps have equal rate constants [k_F and k_D in eq. (15)], and that only one elementary step, the nucleation step, has a different constant. On application of this simplest assumption to the formation of the double helix, $\vec{k}$ would be equal to the elementary rate constant of the nucleation step k_{01}, since by analogy with eq. (16a),

$$\vec{k} = k_{01}\frac{s^{N-1}(1-s)}{1-s^N} \approx k_{01} \qquad (19)$$

as $s \gg 1$ under the experimental conditions chosen by *Pörschke* and *Eigen*. It was found, however, that eq. (19), and hence the simplest reaction scheme on which it is

based, cannot be valid in this case, since measurement of the temperature dependence of the reaction gave a strong negative activation energy E_a for $\vec{k}$, whereas only positive activation energies are possible for rate constants of elementary reactions, *i.e.* for k_{01}. An increase in the rate with falling temperature points to one or more fast equilibria that precede the slower subsequent steps. The ΔH values of these equilibria (which are evidently negative here) contribute to the measured activation energy. It was concluded from the quantitative data (for ΔH and E_a) that Z_1, the first intermediate complex of two chains (with one base pair) though rapidly formed, also decomposes rapidly. The next intermediate state with two base pairs was also found to be labile. A stable nucleus results only for the next step (k_{23}).

The rate constants for the poly-A/poly-U system[42] at the midpoint of the transition, which agree best with the experimental data, are entered in the lower line of Figure 6. It can be seen that the formation and dissociation of a base pair takes place very rapidly (within 10^{-7} to 10^{-6} s). Nevertheless, the dissociation of a long section of helix can take considerable times (about 1 s for $N = 15$), since each opened pair in the interior of the chain closes again on average two to five times before the next pair is opened. This follows from the ratio of the rate constants of the propagation steps $s = 2$—5.

Eigen[43] has pointed out that the mutual recognition of the nucleic acid codon and anticodon of more that three nucleotides would be much too slow for biosynthesis, though increased specificity could be achieved in this way. The actual codon length of three units agrees with the length found for a stable pair; the time for the formation and redissociation is approximately 10^{-6} s.

4. Outlook for More Complicated Systems

The rate of coil formation of natural nucleic acids, because of their very great chain lengths, is determined by an effect that is negligible for short chain lengths. Since the chains in the helix are strongly twisted together, a considerable hydrodynamic resistance must be overcome in the coiling of long chains. *Crothers*[44] was the most successful in the theoretical treatment of this case, but because of various complications, no final conclusion has yet been reached[45].

The situation is even less clear for proteins, because of their more complicated three-dimensional structure. With very high cooperativity, one can expect an "all-or-nothing" mechanism with only two states that are appreciably occupied, and a correspondingly slow transition[46]. The reader is referred here to the progress report by *Pohl*[47].

To conclude, the following observation is valid for all cooperative systems. The greater the cooperativity of a system, the greater is the stability *e.g.* of a protein structure due to interactions that are very weak in some cases, and the more specific *e.g.* an enzyme can be. However, the rates of cooperative processes, *e.g.* of a conformational transition that is important to allosteric regulation, decreases. It must be assumed that in the evolution of biological macromolecules, a compromise has been reached in many cases between stability and dynamics.

Received: May 21, 1971 [A 886 IE]
German version: Angew. Chem. *84*, 615 (1972)
Translated by Express Translation Service, London

[1] *J. Monod, J. Wyman*, and *J. P. Changeux*, J. Mol. Biol. *12*, 88 (1965).
[2] *M. Kirtley* and *D. E. Koshland*, J. Biol. Chem. *242*, 4192 (1967).
[3] *J. D. Watson*: Molecular Biology of the Gene. Benjamin, New York 1965.
[4] *J. Engel* and *G. Schwarz*, Angew. Chem. *82*, 468 (1970); Angew. Chem. internat. Edit. *9*, 389 (1970).
[5] *M. Eigen* and *L. DeMaeyer* in *S. L. Friess, E. S. Lewis*, and *A. Weissberger*: Techniques of Organic Chemistry. Wiley, New York 1963, Vol. VIII/2, p. 895.
[6] *G. Schwarz*, Rev. Mod. Phys. *40*, 206 (1968).
[7] *G. Schwarz*, Habilitationsschrift, Technische Universität Braunschweig 1966.
[8] *R. Lumry, R. Legare*, and *W. G. Miller*, Biopolymers *2*, 489 (1964).
[9] *E. Hamori* and *H. A. Scheraga*, J. Phys. Chem. *71*, 4147 (1967).
[10] *G. Schwarz*, Biopolymers *6*, 873 (1968).
[11] *G. Schwarz*, Ber. Bunsenges. Phys. Chem. *68*, 843 (1964).
[12] *G. Schwarz*, J. Mol. Biol. *11*, 64 (1965).
[13] *D. A. McQuarry, J. P. McTague*, and *H. Reiss*, Biopolymers *3*, 657 (1965).
[14] *J. B. Keller*, J. Chem. Phys. *37*, 2584 (1962); *38*, 325 (1963).
[15] *A. C. Pipkin* and *J. H. Gibbs*, Biopolymers *4*, 3 (1966).
[16] *M. E. Craig* and *D. M. Crothers*, Biopolymers *6*, 385 (1968).
[17] *A. Silberberg* and *R. Simha*, Biopolymers *6*, 479 (1968).
[18] *G. Schwarz*, Ber. Bunsenges. Phys. Chem. *75*, 40 (1971).
[19] *G. Schwarz*, J. Theor. Biol., in press.
[20] *K. Bergmann, M. Eigen*, and *L. DeMaeyer*, Ber. Bunsenges. Phys. Chem. *67*, 819 (1963).
[21] *T. K. Saksena, B. Michels*, and *R. Zana*, J. Chim. Phys. *65*, 597 (1968).
[22] *H. Noguchi* and *J. T. Yang*, Biopolymers *1*, 359 (1963).
[23] *G. G. Hammes* and *P. B. Roberts*, J. Amer. Chem. Soc. *91*, 1862 (1969).
[24] *G. Schwarz*, J. Phys. Chem. *71*, 4021 (1967).
[25] *G. Schwarz* and *J. Seelig*, Biopolymers *6*, 1263 (1968).
[26] *A. Wada*, Chem. Phys. Lett. *8*, 211 (1971).
[27] *E. M. Bradbury, C. Crane-Robinson, H. Goldman*, and *H. W. E. Rattle*, Nature *217*, 812 (1968).
[28] *J. A. Ferretti* and *L. Paolillo*, Biopolymers *7*, 155 (1969).
[29] *R. Ullmann*, Biopolymers *9*, 471 (1970).
[30] *J. A. Ferretti, B. W. Ninham*, and *V. A. Parsegian*, Macromolecule *3*, 34 (1970).
[31] *D. Winklmair, J. Engel*, and *V. Ganser*, Biopolymers *10*, 721 (1971).
[32] *J. Engel*, Biopolymers *4*, 945 (1966).
[33] *J. Engel*, Proceedings of the Symposium on Peptide Chemistry 1969, North-Holland Co., in press.
[34] *R. C. Neumann, Jr.* and *V. Jonas*, J. Amer. Chem. Soc. *90*, 1970 (1968).
[35] *K.-I. Dahlquist, S. Forsén*, and *T. Alm*, Acta Chem. Scand., in press.
[36] *P. A. Temussi, T. Tancredi*, and *F. Quadrifoglio*, J. Phys. Chem. *73*, 4227 (1969).
[37] *T. Miyazawa*, Bull. Chem. Soc. Japan *34*, 691 (1961).
[38] *T. Miyazawa* in *M. A. Stahlmann*: Polyamino Acids, Polypeptides and Proteins. Wisconsin Press, Madison 1962, p. 201.
[39] *D. Pörschke*, Diplomarbeit, Universität Göttingen 1966, and Dissertation, Technische Universität Braunschweig 1968.
[40] *D. Pörschke* and *M. Eigen*, J. Mol. Biol. *62*, 316 (1971).
[41] *M. Eigen* and *D. Pörschke*, J. Mol. Biol. *53*, 123 (1970).
[42] *M. Eigen*, Lecture delivered at the conference "Biochemische Analytik", München 1970.
[43] *M. Eigen*, Nobel Symposium 1967.
[44] *D. M. Crothers*, J. Mol. Biol. *9*, 712 (1964).
[45] *H. C. Spatz* and *D. M. Crothers*, J. Mol. Biol. *42*, 196 (1969).
[46] *R. Lumry, R. Bilton*, and *J. F. Brandts*, Biopolymers *4*, 917 (1966).
[47] *F. Pohl*, Angew. Chem., in press; Angew. Chem. internat. Edit., in press.

Genetic Aspects of Hemoglobin Synthesis

By Berthold Schmidt[*]

Dedicated to Professor Fritz Strassmann on the occasion of his 70th birthday

The blood pigment hemoglobin (Hb) occurs in red blood cells in a higher concentration than the other proteins which are present. It is therefore particularly suitable for the investigation of genetically induced changes in protein molecules. Unlike the monomeric myoglobin (Mb) of muscle, the blood pigment is tetrameric. Several types of subunits are known that can tetramerize to hemoglobins having different properties. The information for all hemoproteins probably originated from the same primary gene. Doublets of this primary gene have developed differently, and now code different protein species. It is possible to establish from the Hb molecule the possible consequences of a mutation to the conformation and function of a protein molecule.

1. Introduction

Hemoglobin (molecular weight 64500) is a chromoprotein (containing heme as the prosthetic group), which, with a total content of barely 1 kg in the human organism, is responsible for the transport of O_2 from the lungs to O_2-consuming tissue, and also to a large extent for the transport of CO_2 in the reverse direction. The oxygen molecule reacts reversibly with the heme iron (Fe^{2+}-protoporphyrin) without oxidizing the iron, which is protected by the coordinate bond of Fe—N(histidine) (Fig. 1).

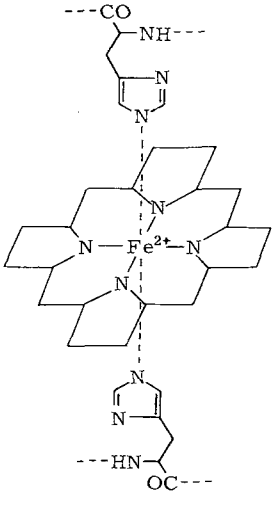


Fig. 1. Bonding of heme iron in hemoglobin. The coordination number 6 is reached by four pyrrole N and two imidazole N of histidine residues of the globin chain as ligands.

Hemoglobin (Hb) constitutes about 95% of the dry protein mass in red blood cells (erythrocytes), each of which contains 2.8×10^8 molecules of hemoglobin. Hemoglobin can therefore be investigated for genetically induced microheterogeneities or abnormalities, which cause distinct clinical symptoms, without previous purification steps, which are always accompanied by partial denaturation. Hemoglobins can be differentiated electrophoretically by differences in their migration rates. Sequence differences in individual peptide chains can be established by means of fingerprint mapping, which is based on two-dimensional chromatographic and electrophoretic development of the hydrolysis products obtained by standardized degradation with trypsin. The most accurate differentiation can be achieved by comparative overall analysis or sequence analysis of the amino acid composition of the peptide chains.

Evolutionary relationships can also be demonstrated by comparative biochemical paleogenetic studies. Thus it is practically never possible to isolate traces of proteins from fossil material, but proteins can be investigated in "living fossils", and by comparison of the amino acid sequences, they can be correlated with recent homologous proteins, *i.e.* proteins having the same function.

The genetic "experiments" set up by nature, which lead by inheritance to pathological symptoms (hemoglobinopathies) of various degrees of severity in man, produce changes[1] in the rate of synthesis and[2] in the amino acid sequence of the hemoglobin molecule. Therefore, it is possible to deduce the importance of individual amino acids to the conformation, quaternary structure, and functional modification of erythrocyte-bound Hb.

In addition to the major component hemoglobin A_1, the erythrocytes of adults also contain 1.5 to 4% of hemoglobin A_2 (A = adult). Each hemoglobin type has a pronounced quaternary structure, and is a tetramer. The three-dimensional structure was established by *Perutz*[3-8] for horse hemoglobin. The spherical molecule ($64 \times 55 \times 50$ Å^3) consists of two pairs of identical peptide chains. These globin subunits each contain a heme, and form the tetramer by noncovalent bonds (weak interactions)[3, 5, 7]. Hb A_1 consists of two α and two β chains: $\alpha_2\beta_2$. The minor component Hb A_2 can be written as $\alpha_2\delta_2$. During embryonal development, an Hb F: $\alpha_2\gamma_2$ (F = fetal) dominates, and this is preceded by an $\alpha_2\varepsilon_2$ hemoglobin type (during the first third). Starting with the last third of the embryogenesis up to the end of the first year of life, Hb F is gradually replaced by Hb A_1 (Fig. 2).

[*] Prof. Dr. Dr. B. Schmidt
Physiologisch-Chemisches Institut der Universität
65 Mainz, Postfach 3980 (Germany)

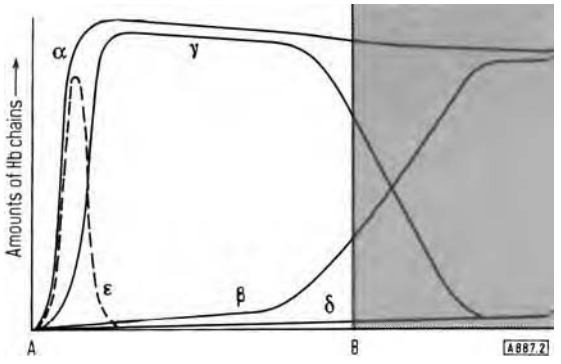


Fig. 2. Synthesis of the Hb subunits during the embryonal development (A-B) and after birth (B) [4].

Faults in the structure of the hemoglobin usually manifest themselves in functional losses and clinical symptoms, which may appear singly or together and in various degrees of severity (Table 1):

Instability of Hb to oxidation. Hemoglobin (Fe^{2+}) is converted into hemiglobin or methemoglobin (Fe^{3+}), which is no longer able to transport oxygen.

Increased or decreased O_2 binding capacity. An essential property of Hb is that O_2 transport is possible, *i.e.* O_2 uptake at the oxygen partial pressure in the lung and release of O_2 to other heme proteins (O_2 storage) in the tissue. A change in the Hb molecule may increase the strength with which O_2 is bound (Table 1, Nos. 11 and 12), so that the O_2 cannot be released where it is needed. Conversely, if O_2 binding is too weak (Table 1, No. 13), an insufficient O_2 number of oxygen molecules is bound and transported.

Instability of the Hb can considerably shorten the average life (120 days) of the erythrocyte as an Hb carrier: hemolytic anemia. Increased release of immature erythrocytes (reticulocytes) occurs from the red bone marrow, the site of formation of the Hb-carrying blood cells. The skin also assumes a yellow color (icterus), which is due to the increased quantities of bile pigments that result from the increased breakdown of Hb.

Table 1. Abnormalities in the Hb structure [2].

No.	Name [a]	Amino acid change [b]	Disturbance occurring	
1	Hb Sabine	β^{91} (F 7) Leu → Pro	fracture of F-helix	disturbance of conformation of globin subunit
2	Hb Santa Ana	β^{88} (F 4) Leu → Pro	fracture of F-helix	
3	Hb Genova	β^{28} (B 10) Leu → Pro	fracture of B-helix	
4	Hb Leiden	$\beta^{6\,or\,7}$ (A 3) Glu-deficiency	fracture of A-helix	
5	Hb Freiburg	β^{23} (B 5) Val-deficiency	fracture of B-helix	
6	Hb Borås	β^{88} (F 4) Leu → Arg	superficial loss of charge	
7	Hb Sydney	β^{67} (E 11) Val → Ala	"gap"	
8	Hb Köln	β^{98} (FG 5) Val → Met	"overfilling"	
9	Hb Toulouse	β^{66} (E 10) Lys → Glu	charge reversal, disturbance of the $\alpha^1\beta^1$ contact	
10	Hb Philly	β^{35} (C 1) Tyr → Phe	loss of H donor (hydrogen bridge)	disturbance of the $\alpha^1\beta^2$ contact
11	Hb Rainier	β^{145} (HC 2) Tyr → His	donor/acceptor reversal of a hydrogen bridge, stronger O_2 binding	
12	Hb Yakima	β^{99} (G 1) Asp → His	change of charge, stronger O_2 binding	
13	Hb Kansas	β^{102} (G 4) Asn → Thr	loss of charge, weaker O_2 binding	
14	HbS	β^{6} (A 3) Glu → Val	discharge on surface	polyagglomeration sickle cell anemia
15	HbC	β^{6} (A 3) Glu → Lys	discharge on surface	
16	Hb Bristol	β^{67} (E 11) Val → Asp	β^{63} His ..... HO_2C (Asp)	
17	HbM Milwaukee	β^{67} (E 11) Val → Glu	negative charge in heme pocket stabilizes Fe^{3+}	occurrence of methemoglobin (HbM) or hemiglobin
18	HbM Iwate	α^{87} (F 8) His (prox.) → Tyr	Fe^{3+} can readily be formed due to absence of the lone pair (imidazole-N)	
19	HbM Boston	α^{58} (E 7) His (dist.) → Tyr		
20	HbM Hyde Park	β^{92} (F 8) His (prox.) → Tyr		
21	HbM Saskatoon	β^{63} (E 7) His (dist.) → Tyr		
22	Hb Zürich	β^{63} (E 7) His → Arg	imidazole replaced by guanidyl-N: danger of methemoglobinemia occurring	
23	Hb Hiroshima	β^{143} (H 21) His → Asp	absence of basic point of attack for acid effectors: stronger O_2 binding	

[a] Abnormal hemoglobins are usually named after a place or person connected with their first detection.
[b] A symbol of the type β^{91} refers to the amino acid position 91 of the β chain, while F 7 denotes the seventh position of helix segment F.

2. Genetic Information

It is assumed[9, 10] that the information for the present-day variants of the heme proteins, *i.e.* of substances that can bind (myoglobin) or transport (α,β,γ,δ subunits of hemoglobin) O_2, is derived from a phylogenetically old gene. It is concluded from comparisons of amino acid sequences between heme proteins that are available at present that this primary gene could have coded a protein containing 154 (or more) amino acids.

Most genes are present in the chromosomes of a cell in several "redundant copies". In the case of protein synthesis the cell can thus rapidly synthesize a given type of protein with the aid of its ribosomal apparatus. This multiplicity is due to gene duplications that have occurred in the course of time.

From these identical gene doublets, mutations that affect individual gene loci separately can lead to modified genes, which contain modified information for the protein synthesis. Growing independence (migration of gene sections that have been split off, loss of base triplets) may lead to the formation of genes that contain the information for homologous proteins instead of for identical species.

The oldest heme protein from the homologous Mb/Hb group is myoglobin (Mb). This "muscle pigment" is a monomeric heme protein. Its peptide chain consists of 153 amino acids (molecular weight 17000). The sequence of sperm whale Mb has been elucidated[11]. The three-dimensional structure was determined by *Kendrew*[12, 13] for horse Mb.

Comparison of the amino acid sequence of the globin subunits of Hb with that of Mb reveals differences in 120 ± 5 positions[14]. The amino acids agree only in about 30 positions. The variation ± 5 arises when sperm whale Mb is compared with the subunits of all the vertebrate Hb types investigated so far. It means that differences between species may be regarded in the same way as an error range in connection with the statement that *the* Mb chain differs from *the* Hb subunit in 120 amino acid positions.

From these amino acid differences, *Pauling*[15] has tried to calculate the times required for such changes in the course of evolution. The basis of his arguments is as follows. Comparison of the amino acid sequence of the globin subunits of mammalian Hb (horse, pig, ox, rabbit) shows differences in 22 positions between the α and β chains. If each chain developed independently, this corresponds to 11 changes per chain. If one assumes that the development of the higher mammals began about 80 million years ago, one finds a period of 7 million years for each mutation (*i.e.* for each change). For events that happened very far back in time, it is advisable to reckon on the next higher order of magnitude, *i.e.* 10 million years per amino acid difference.

On application of the 10^7 year value to the myoglobin/globin difference, it is found that the Mb/Hb dichotomy occurred $(120/2) \times 10^7 = 600 \pm 50$ million years ago. "Snapshots" of this development are provided by species of animals that have developed only slightly since their first appearance. The earliest Hb forms can be studied in such "living fossils". Monomeric Hb types with 146 amino acids have been isolated from Cyclostomi[*] (hagfishes, lampreys)[16, 17].

From the pool of primary gene, the information for myoglobin (Mb) developed first, characterized by the loss of a base triplet that was retained in later gene doublets. The genetic information for the synthesis of early heme proteins of the Hb type shows the same deletion as for Mb, with the addition of a further loss, which may have resulted from a gene displacement. Thus the early monomeric Hb types show a deficit of 7 amino acids at the C-terminal end of the chain in relation to Mb. The primitive vertebrate Hb in the oxygenated state exhibits monomeric character, like Mb.

The gene pool for the primary form of monomeric Hb, which aggregated only weakly, was probably the basis of the development of the information for the α chain, which also exhibits no tendency to aggregate with its own kind. On comparison of the amino acid sequences, it is found that in the α-subunit of Hb, as in Mb and primary Hb, a deletion has occurred within the chain, as well as shortening by 6 amino acids at the C-terminus. The α subunit is characterized by two further "gaps" totaling 6 amino acids, and giving a typical number of 141 amino acids for the α chain.

The information for the synthesis of non-α chains developed from the gene pool much later than the information for the α subunit. The assumption of the later development is based on the fact that the non-α chains differ from the α chain only in 85 ± 10 positions[14]. *Pauling* believes that the α gene and the non-α gene separated 380 million years ago.

All the non-α chains exhibit the C-terminal shortening by 6 amino acids in relation to Mb that is characteristic of the globin subunits. They lack the "old" triplet deletion that occurs in Mb and primary Hb. It is replaced by a deletion of two triplets that is characteristic of the non-α chains. The characteristic length of the non-α chains is thus found to be 154 (primary gene) $-6-2=146$ amino acids.

The oldest non-α gene is the β gene, which contains the information for the synthesis of the β chain. Other non-α globins have probably developed from doublets of the β gene, since they exhibit a greater similarity to the β chain.

The information for the synthesis of the γ subunits evolved first from doublets of the β gene. According to *Pauling*'s ideas, 42 ± 6 amino acid differences between the β and γ chains indicates that the development of the γ gene from the β gene pool occurred about 150 million years ago. The γ gene remained immediately adjacent to the β gene. 35 million years ago, the δ gene separated from the β-γ gene assembly[9]. Here again, the time is deduced by the application of *Pauling*'s ideas to the difference of 10 amino acids between the δ and β chains.

The close neighborhood of the β-gene family in the genome[19] is deduced from experimental findings. A relation must exist between the transcription of β and γ genes, such that γ-globin suppresses the synthesis of β-globin. If the synthesis of the γ chains slowly dies out, the inhibition of the β-globin synthesis also vanishes, and this synthesis increases in proportion to the decrease in the γ-globin

[*] Cyclostomi are the oldest vertebrates (still without mandible). They developed 450 million years ago.

synthesis (cf. Fig. 2)[20]. The β and δ genes are even closer together. Investigation of the effect of hormone (erythropoietin[21]) on the Hb synthesis shows that the rates of synthesis of the β and δ chains increase in a constant ratio of 40:1[22]. There are various possible reasons for the greater rate of synthesis of the β chain: 1. The transport of the same amino acid may be effected by different tRNA's[23,24]. A deficit of one type of tRNA can lead to a deficit in the synthesis of a protein. 2. It is conceivable that complications arise in the folding for the younger δ chain. 3. The mRNA's or their ribosomal adducts may differ in their stability for the various globin subunits[1]. It is not yet known which of these is the true cause.

Closeness of the β and δ genes is also indicated by the occurrence of hybrid globin subunits, which have an N-terminal δ structure and a C-terminal β structure in the non-α chain. Three such hybrids are known at present[25,26].

Little is known about an ε subunit, which occurs in the first third of the embryonal Hb synthesis (Fig. 2). It disappears when the synthesis of the γ chains begins, just as the synthesis of the γ chains disappears later as soon as β chains are synthesized.

Though up to 120 positions in the sequence of the homologous hemoproteins may be differently occupied, depending on phylogenetic age, 11 positions are always identically occupied in all the peptide chains investigated so far[10]; these include the two histidine residues, which guarantee heme binding, and close to these a proline, which prevents any interfering helix formation in the vicinity of the heme binding site.

The globin subunits of the non-α type exhibit the property of aggregation even in the oxygenated state. Homotetramers and heterotetramers may be formed. Homotetramers of the type β_4 appear under pathological conditions, and are much less suitable for the transport of O_2 than the heterotetramer $\alpha_2\beta_2$, which first appears in the phylogeny of the vertebrates with the formation of the mandible. An early Hb of this type has been investigated in the carp, a teleost[18].

3. Changes in the Rate of Synthesis

After the embryonal development, the synthesis of Hb occurs under physiological conditions only in one type of cell of the red bone marrow, *i.e.* the (pro)erythroblasts. In these nucleated precursors of the (in mammals) later non-nucleated erythrocyte, the information required for the Hb synthesis can be totally recalled from the genome, *i.e.* only here can the requirements be satisfied for all the partial steps of the Hb synthesis. It is not clear how the cellular Hb synthesis is terminated. Hb probably represses certain genome sections after its synthesis, so that further transcription is suppressed. The globin synthesis continues until intact messenger-RNA is present for all peptide types[27] and a functioning *ribosomal* apparatus is available (cf. Fig. 3).

During the transcription, the copies of some genome sections required for the synthesis of the globin subunits are produced in the form of messenger-RNA. From each gene section there will be different mRNA's produced, *i.e.* the cistron codes an individual peptide chain. The unicistronal mRNA's for the synthesis of globin subunits have a remarkably long life of the order of days. They can be isolated from reticulocytes that have long been without nuclei, and Hb can be synthesized (starting at the N-terminal end) with the aid of the mRNA's from these reticulocytes in protein-synthesizing *in-vitro* systems[28].

In the translation of the mRNA information into α subunits, the polysomes (functional aggregates of the ribosomes for the translation of an mRNA) are found to be mostly pentamers, whereas hexamers can be detected in the synthesis of β subunits. It is possible that the β-mRNA, which is about 15 nucleotides longer, provides room for an additional ribosome.

The stoichiometric aggregation of α and β chains to form the complete tetramer takes place at the ribosomal level[29-31]. As in the myoglobin synthesis, the complete α chains separate from the ribosomes and are released into the cytosol. They do not form tetramers, but they may clump together in cases of pathological overfilling (β-thalassemia). Under physiological conditions, the free α chains enter into interaction with the longer, still growing globin subunits of the β family, whereupon αβ dimers detach themselves from the polysomes[29-33]. It is no longer believed that the β subunits detach themselves independently and influence the termination of the α subunits[34-36]. The αβ dimers then undergo interaction with the heme pool[37-39] of the cytosol[40]. Though monomeric α-globin does not bind heme[32], the affinity of heme for α-globin is greater than that for the β subunit[41,42], so that the α subunits of the dimers first become charged with the heme, and then the β subunits.

A deficit in preparation of special globin subunits is usually found if the rate of synthesis of one subunit is decreased. In α-thalassemia, the α chains are synthesized in insufficient quantity[1]. Since the α-gene occurs in isolation in the genome[43], the preparation of the non-α chains is not inhibited. The rate of synthesis of the β chains is then higher by a factor of 1.5 to 3. Under these conditions, the non-α chains form homotetramers[44], and an Hb H (β_4) can be detected in the erythrocytes[45,46]. This functionally inferior Hb form is unstable, and tends to form clumps, which can be detected as Heinz inclusion bodies (in the erythrocytes). Since the disturbance of the synthesis occurs during the embryonal development, self-aggregation of the γ chains occurs here, and Hb Bart (γ_4) appears[47].

In β-thalassemia, the rate of synthesis of the β chains is reduced. α chains are synthesized in sufficient quantity and released into the cytosol. Instead of the formation of α_4 tetramers, however, clumping occurs[48]. Because of the close neighborhood of the β family in the genome, it is possible that partial filling of the β pool can occur if *e.g.* the γ gene is not inactivated. The result is a persistence of Hb F, since the γ chains are available to the α chains for tetramer formation even after birth. The synthesis of δ chains is also increased under these conditions, so that where there is a deficit of Hb A_1 increased quantities of Hb F and Hb A_2 are found.

4. Replacement of Individual Amino Acids

Whereas changes in the rate of synthesis of the globin subunits probably occur at the ribosomal level, point mutations, which may lead to the replacement of individual amino acids, take place in the genome. Each amino acid is coded in the genome (Fig. 3) by a base triplet. By transcription the triplet information from DNA appears as the codon in the mRNA. Most amino acids are fixed only by the first two bases of their codons in the mRNA. For some, the third base position of the codon may be occupied by any base, but in most cases one of two bases may appear without making the coding uncertain.

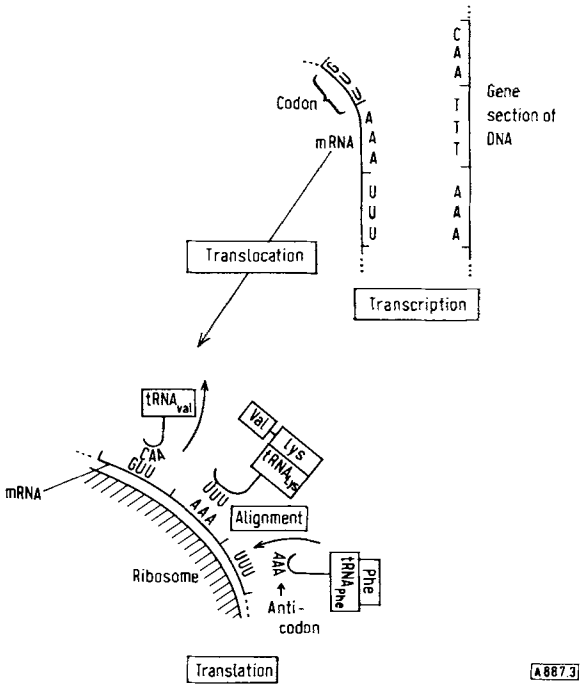


Fig. 3. Scheme of protein synthesis. At the top right, the mobile mRNA is synthesized enzymatically on an exposed gene segment of the DNA (transcription). The mRNA migrates to the ribosome, *i.e.* to the protein-synthesizing apparatus (translocation). In a checking process (according to the rule of base pairing), the anticodon of the transfer RNA (tRNA) charged with amino acid moves to the codon of the mRNA (translation). The newly supplied amino acid (in this case phenylalanine by $tRNA_{Phe}$) is attached to the already synthesized peptide residue (in this case valine-lysine).

For example, the amino acid glycine (Gly) is represented by the mRNA codon GGX, where X may be A, G, C, or U. Only one amino acid, *i.e.* methionine (Met), has an invariable code (the codon AUA).

Consequently, every point mutation, *i.e.* every base exchange, in the gene need not lead to a change in an amino acid in the protein chain. If a tolerated base exchange occurs in the third position of the codon (wobbling), there is no change in the amino acid. On the other hand, base faults in the first two positions of the codon nearly always lead to an amino acid change: $GA^A_G \rightarrow GU^A_G$ causes the replacement of glutamic acid by valine (Glu→Val), which leads to the formation of HbS (sickle cell anemia) if it occurs in position 6 of the β chain.

More than 100 amino acid changes have so far been found in globin subunits, more of these being in the β chains[15, 50] than in the α chains, probably because the oxygenation of Hb is promoted by a change in the conformation of the β subunit, and changes in the β chains are therefore more likely to be clinically noticeable. This means that the mutations that are *found* most often are not necessarily identical with those that *occur* most often, since one looks for molecular changes only if pathological symptoms appear. In tolerated mutations, other types of base exchange may occur more frequently[49].

The most common base exchange is the replacement of A by G in the codon. An example is AA^A_G (Lys)→GA^A_G (Glu). As far as the interactions between the side chains of the amino acids in the protein are concerned, this exchange means a charge reversal (Lys = $-NH_3^+$, Glu = $-CO_2^-$). The reverse exchange (A in place of G) is also common: GG^U_C (Gly)→GA^U_C (Asp). That means a neutral amino acid with a very low bulk (glycine) is thus replaced by a polar amino acid (aspartic acid), which can enter into ionic interactions or form hydrogen bonds, and which can cause disturbances by these properties.

If this exchange of two purine bases (A and G) of the codon is projected into the genome, it corresponds there to "confusion" between the pyrimidine bases cytosine and thymine, which may also result from a disturbance of the transfer of amino and methyl groups in the cell nucleus (Fig. 4).

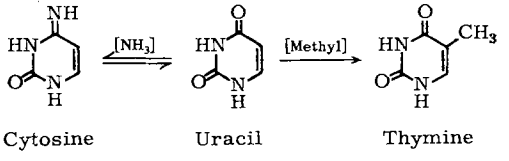


Fig. 4. The two most important pyrimidine bases of the nucleic acids. They are linked by enzymatic amination and methylation.

The replacement of a polar side chain, which enters into ionic interactions, will always lead to a change in conformation, particularly if a charge reversal occurs (Table 1, No. 9).

Hydrogen bonds between peptide structures or between the side chains of individual amino acids, *e.g.* between phenolic hydroxyl (Tyr) and a hetero atom (carboxyl O, heterocyclic N), will also collapse if one partner is absent.

5. The Globin Subunit

The globin subunits of Hb have a characteristic conformation, which is very similar to that of Mb[12]. 75% of the secondary structure consists of helix structures, which are grouped into eight sections A to H (see Fig. 5)[66]. Hydrophobic contacts predominate in the interior of the structure, particularly between the amino acids leucine, isoleucine, valine, and phenylalanine[5, 51, 52]. The replacement of such amino acids by others with polar side chains can lead to the breakdown of the conformation. If the same exchange takes place on the surface of the molecule, the conformation

is only slightly affected (Table 1, No. 6). On replacement of one amino acid by another, even the difference in bulk may be sufficient to labilize the conformation (Table 1, Nos. 7

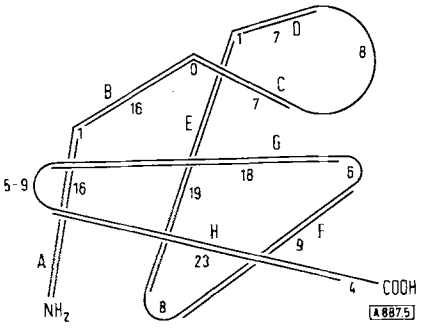


Fig. 5. Schematic representation of helical (double lines) and nonhelical (single lines) sections in myoglobin [67]. The numbers indicate how many amino acids are present in the various sections.

and 8), or the α-helix typical of a section of the conformation may be interrupted (also by the omission of an amino acid), and this again leads to unstable hemoglobins (Table 1, Nos. 1—3, 4 and 5).

5.1. Globin-Globin Contacts

In addition to the polar and nonpolar interactions within a globin subunit, side chains of amino acids in its external zone must allow the establishment of contacts between the subunits so that the quaternary structure can be formed from four subunits. The interactions between the four monomers differ in their nature. There is a stronger type of bond $\alpha^1\beta^1$ and $\alpha^2\beta^2$ and a weaker globin-globin contact $\alpha^1\beta^2$ and $\alpha^2\beta^1$. In the case $\alpha^1\beta^1$, 110 atoms from side chains of 34 amino acids approach to a distance of <4 Å. In the case $\alpha^1\beta^2$, contacts (with a distance of <4 Å) are formed between 80 atoms of the side chains of 19 amino acids[7]. The dissociation of the tetramer into dimeric subunits leads to the "stronger" $\alpha^1\beta^1$ dimer[53]: $\alpha_2\beta_2 \rightleftharpoons 2\,\alpha^1\beta^1$. The difference in the strength of the bonds between the subunits is a necessary condition for conformational changes in the Hb molecule, as it allows the two $\alpha^1\beta^1$ dimers to slip in relation to each other. This conformational change allows an allosteric activation of the oxygenation (charging with O_2) and indirectly of the deoxygenation (release of O_2) of the Hb in the erythrocyte. In the deoxygenated state, the conformation of the β chain has a loose structure, while in the oxygenated state it has a more compact structure. The conformation compression[8] occurs by widening of the heme pocket and reversible replacement of a coordinate Fe—N bond by an Fe—O_2 bond.

The optimum reversible charging with O_2 is possible only on the heterotetramer $\alpha_2\beta_2$. The homotetramers β_4 and γ_4 bind O_2 more strongly and exhibit no allosteric promotion of the binding of O_2[54]. Hb F ($\alpha_2\gamma_2$) binds O_2 more strongly than Hb A_1, since a lower O_2 partial pressure is available for supplying the fetal circulation. If the binding of O_2 is too strong, as in the homotetramers, the release of O_2 in the tissue, *e.g.* to Mb, is impossible, and O_2 transport is thus prevented.

If amino acids that are essential to the formation of the quaternary structure are replaced, the $\alpha^1\beta^1$ contacts (Table 1, No. 9) or the $\alpha^1\beta^2$ contacts (Table 1, Nos. 10—13) may be labilized.

Instead of leading to breakdown of the quaternary structure, the replacement of an amino acid may result in an increased tendency to aggregate. Since hydrophobic interactions predominate by far[7] among the secondary valence forces forming the tetramer, an excess of nonpolar side chains can lead to higher aggregates. The formation of Hb polymers results macroscopically in clumping of the Hb with a corresponding functional loss in the transport of O_2. The increased tendency to aggregate is particularly noticeable in deoxygenated Hb, since a looser conformation here facilitates interactions between the subunits. The best-known example of a pathological Hb type with an amino acid exchange on the surface of the molecule is sickle cell Hb (Table 1, Nos. 14 and 15). The replacement of the negatively charged side chain of Glu by the nonpolar Val leads to the formation of a hydrophobic contact in excess, which can induce polyaggregation. The clumping of Hb results in a decrease in the cell volume, and the characteristic sickle cell shape of the erythrocytes is produced.

5.2. Heme-Globin Contact

The function of Hb is extremely sensitive to disturbances in the amino acid sequence in the immediate neighborhood of the heme bonding site. The following are essential: 1. One proline, which suppresses the formation of a helical structure in this region. 2. Two histidines in this region, whose imidazole N serves for coordination of the Fe^{2+}. 3. The side chains of other amino acids, *e.g.* $\beta^{41\,Phe}$, $\beta^{42\,Phe}$, in the vicinity of the histidine residues. These side chains help to maintain a hydrophobic medium, in which the planar heme is embedded (Fig. 6). If this hydrophobic medium is disturb-

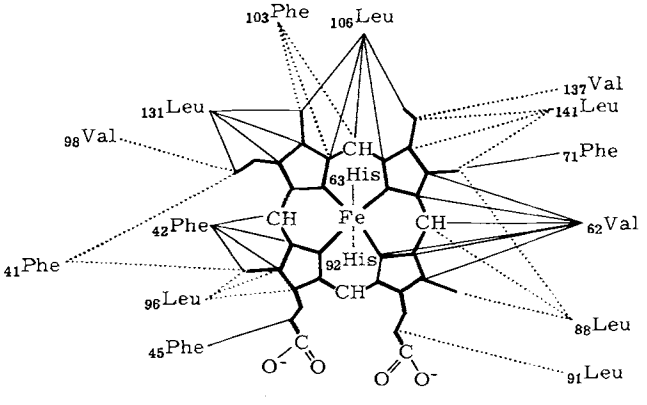


Fig. 6. Heme-globin contacts [7]. The diagram shows which amino acid side chains of the β chain interact with the porphin system of the heme in the β subunit. Continuous lines lead to amino acids lying above the plane of the heme, and dotted lines to those lying below this plane. The numbers indicate the positions of the amino acids in the β chain.

ed (even disturbances without charge effects are sufficient), the degradation of the Hb may be induced (Table 1, Nos. 7 and 8). A more striking effect is the labilization on incorporation of amino acids with polar groups. If a negative charge (Table 1, No. 17) appears in the heme pocket, the conditions for stabilization of a trivalent Fe are satisfied. Under physiological conditions, autocatalytic oxidation of Fe^{2+} (hemoglobin) to Fe^{3+} (hemiglobin, HbM) of the order of a few % occurs on oxygenation. The Fe^{3+} is reduced again by the hemiglobin reductase, which is NADP-dependent. The reduction equivalents are provided by the carbohydrate metabolism of the erythrocytes. If a negative charge is available to stabilize the Fe^{3+}, no enzymatic reduction can take place, and the hemiglobin is lost for the transport of O_2.

If the proton of a carboxyl group or the H donor of a hydrogen bond enters into competition with the electron gap of the heme Fe for the imidazole N (His), the Fe—N (His) bond is not formed, and Fe oxidation is possible (Table 1, No. 16). Loss of the Fe—N (His) bond by replacement of the histidine always leads to oxidation of the Fe and to the appearance of Hb M. All four conceivable possibilities of His replacement are found in nature; either the proximal or the distal His in α and β chains may be replaced (Table 1, Nos. 18—21). If the imidazole N is replaced by another ligand containing N, *e.g.* guanidyl N (Arg) (Table 1, No. 22), the Fe is more susceptible to oxidation than when bonded to His—N. Under the action of nitro derivatives (drugs), methemoglobinemia may occur.

6. Effectors

Allosteric changes in the conformation of enzyme proteins can greatly alter the activity of the enzyme. Substances that bring about such changes in the conformation of a protein are known as effectors.

The function of the Hb molecule can also be influenced by effectors. Oxygenation promotes further O_2 uptake after the manner of allosteric activation (Fig. 7). Deoxygenation can similarly be promoted. A cavity that remains free in the molecule of the $\alpha_2\beta_2$ heterotetramer contains basic side groups ($\beta^{143\,His}$), which allow the attack of CO_2 (Bohr effect) by formation of carbimino groupings[55-57]. If such a point of attack is lacking (Table 1, No. 23), deoxygenation is hindered[58-60].

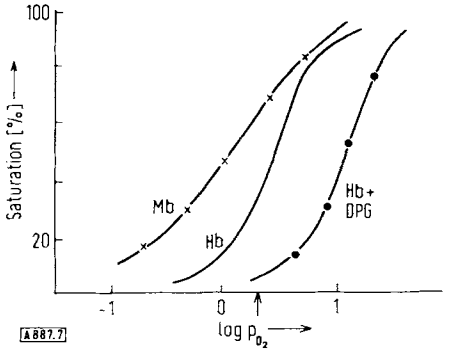


Fig. 7. O_2 binding curves. At the O_2 partial pressure prevailing in the tissue (↑), the tetrameric Hb is only slightly charged with O_2, while large quantities are bound to Mb, corresponding to the functions of Hb (O_2 transport) and Mb (O_2 storage). The dissociation of O_2 from Hb is particularly favored when it is bound in erythrocytes (–·–), *i.e.* in the presence of 2,3-diphosphoglycerate (DPG) [62].

Investigations on erythrocyte-bound and free Hb showed differences in the strength with which O_2 is bound (see Fig. 7). The mammalian erythrocyte contains a high concentration of a glycolysis metabolite that occurs only in catalytic quantities in other glycolyzing tissues; this substance is 2,3-diphosphoglycerate (DPG). When bonded molarly 1:1 to basic functions (His) of the heterotetramer $\alpha_2\beta_2$[62], DPG induces a change in conformation within the erythrocyte such that the bonding of O_2 is weakened and deoxygenation is promoted[63-65]. In bird erythrocytes, the function of DPG is taken over by an inositol hexaphosphate[62]. This allosteric control by acidic effectors is possible only in the phylogenetically youngest $\alpha_2\beta_2$ ($\alpha_2\delta_2$) heterotetramers[61] (Hb F contains an $\alpha^{138\,Ser}$ or $\gamma^{143\,Ser}$ instead of $\beta^{143\,His}$). The homotetramers β_4 and γ_4 exhibit no Bohr effect and no loosening of O_2 by DPG[54].

Received: March 10, 1971 [A 887 IE]
German version: Angew. Chem. *84*, 649 (1972)
Translated by Express Translation Service, London

[1] *D. J. Weatherall*, Annu. Rev. Med. *19*, 217 (1968).
[2] *E. R. Huehns*, Annu. Rev. Med. *21*, 157 (1970).
[3] *M. F. Perutz, M. B. Rossmann, A. F. Cullis, H. Muirhead, G. Will*, and *A. C. T. North*, Nature *185*, 416 (1960).
[4] *M. F. Perutz*, Sci. Amer. *211*, No. 5, p. 11 (1964).
[5] *M. F. Perutz, J. C. Kendrew*, and *H. C. Watson*, J. Mol. Biol. *13*, 669 (1965).
[6] *M. F. Perutz* and *H. Lehmann*, Nature *219*, 902 (1968).
[7] *M. F. Perutz, H. Muirhead, J. M. Cox*, and *L. C. G. Goaman*, Nature *219*, 131 (1968).
[8] *H. Muirhead, J. M. Cox, L. Mazzarella*, and *M. F. Perutz*, J. Mol. Biol. *28*, 117 (1967).
[9] *E. Zuckerkandl* and *L. Pauling* in *M. Kasha* and *B. Pullmann*: Horizons of Biochemistry. Academic Press, New York 1962, p. 189.
[10] *E. Zuckerkandl*, Sci. Amer. *212*, No. 5, p. 110 (1965).
[11] *A. B. Edmundson*, Nature *205*, 883 (1965).
[12] *J. C. Kendrew, R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Phillips*, and *V. C. Shore*, Nature *185*, 422 (1960).
[13] *C. L. Nobbs, H. C. Watson*, and *J. C. Kendrew*, Nature *209*, 339 (1966).
[14] *C. Nolan* and *E. Margoliash*, Annu. Rev. Biochem. *37*, 727 (1968).
[15] *H. Lehmann* and *R. G. Huntsman*: Man's Haemoglobins. North Holland Publishing Co, Amsterdam 1966.
[16] *V. Rudloff, M. Zelenik*, and *G. Braunitzer*, Hoppe-Seylers Z. Physiol. Chem. *344*, 284 (1966).
[17] *G. Braunitzer*, J. Cell. Comp. Physiol. Suppl. *1*, 1 (1966).
[18] *K. Hilse, U. Sorger*, and *G. Braunitzer*, Hoppe-Seylers Z. Physiol. Chem. *344*, 166 (1966).
[19] *C. Baglioni*, Proc. Nat. Acad. Sci. U. S. A. *48*, 1880 (1962).
[20] *C. L. Conley, D. J. Weatherall, S. N. Richardson, M. K. Shepard*, and *S. Charache*, Blood *21*, 261 (1963).
[21] *A. Carmena, D. Howard*, and *F. Stohlman, jr.*, J. Clin. Invest. *46*, 1043 (1967).
[22] *R. M. Winslow* and *V. M. Ingram*, J. Biol. Chem. *241*, 1144 (1966).
[23] *B. Weisblum, S. Benzer*, and *R. W. Holley*, Proc. Nat. Acad. Sci. U.S.A. *48*, 1449 (1962).
[24] *H. A. Itano*, J. Cell. Comp. Physiol. Suppl. *67*, 65 (1966).
[25] *D. Labie, W. A. Schroeder*, and *T. H. J. Huisman*, Biochim. Biophys. Acta *127*, 428 (1966).
[26] *W. Ostertag* and *E. W. Smith*, Eur. J. Biochem. *10*, 371 (1969).
[27] *S. Granick* and *R. D. Levere*, Fed. Proc. *23*, 222 (1964).
[28] *H. M. Dintzis*, Proc. Nat. Acad. Sci. U. S. A. *47*, 565 (1961).
[29] *J. R. Schaeffer, P. K. Trostle*, and *R. F. Evans*, Science *158*, 488 (1967).

[30] *J. R. Shaeffer*, Biochem. Biophys. Res. Commun. *28*, 647 (1967).

[31] *A. L. Cline* and *R. M. Boch*, Cold Spring Harbor Symp. Quant. Biol. *31*, 321 (1966).

[32] *C. L. Baglioni* and *T. Campana*, Eur. J. Biochem. *2*, 480 (1967).

[33] *A. S. Tavill, A. I. Grayzel, I. M. London, M. K. Williams*, and *G. A. Vanderhoff*, J. Biol. Chem. *243*, 4987 (1968).

[34] *B. Colombo* and *C. Baglioni*, J. Mol. Biol. *16*, 51 (1966).

[35] *E. R. Huehns* and *E. M. Shooter*, Nature *193*, 1083 (1962).

[36] *C. Baglioni* in *J. H. Taylor*: Molecular Genetics. Academic Press, New York 1963, Vol. 1, p. 405.

[37] *S. Granick* and *R. D. Levere* in *C. V. Moore* and *E. B. Brown*: Progress in Hematology. Grune & Stratton, New York 1964, p. 1.

[38] *I. M. London, G. P. Bruns*, and *O. Karibian*, Medicine (Baltimore) *43*, 789 (1964).

[39] *J. Lascelles*, J. Gen. Microbiol. *23*, 487 (1960).

[40] *L. Felicetti, B. Colombo*, and *C. Baglioni*, Biochim. Biophys. Acta *129*, 380 (1966).

[41] *K. H. Winterhalter*, Nature *211*, 932 (1966).

[42] *K. H. Winterhalter* and *D. A. Deranleau*, Biochemistry *6*, 3136 (1967).

[43] *S. Ohno*: Evolution by Gene Duplication. Springer, Berlin, Heidelberg, New York 1970.

[44] *J. G. Clegg* and *D. J. Weatherall*, Nature *215*, 1241 (1967).

[45] *R. E. Benesch, H. M. Ranney, R. Benesch*, and *G. M. Smith*, J. Biol. Chem. *236*, 2926 (1961).

[46] *D. A. Rigas, R. D. Koler*, and *E. E. Osgood*, Science *121*, 372 (1956).

[47] *S. Ohno* and *M. Morrison*, Science *154*, 1034 (1966).

[48] *E. R. Huehns, E. M. Shooter*, and *N. Dance*, Biochem. Biophys. Res. Commun. *5*, 362 (1961).

[49] *H. Lehmann* and *R. W. Carrell*, Brit. Med. Bull. *25*, 14 (1969).

[50] *V. M. Ingram*: The Haemoglobins in Genetics and Evolution. Columbia University Press, New York 1963.

[51] *W. Kauzmann*, Advan. Protein Chem. *14*, 1 (1959).

[52] *I. M. Klotz*, Brookhaven Symp. in Biol. *13*, 25 (1960).

[53] *M. A. Rosemeyer* and *E. R. Huehns*, J. Mol. Biol. *25*, 253 (1967).

[54] *E. Antonini*, Physiol. Rev. *45*, 123 (1965).

[55] *M. F. Perutz, H. Muirhead, L. Mazzarella, R. A. Crowther, J. Greer*, and *J. V. Kilmartin*, Nature *222*, 1240 (1969).

[56] *J. V. Kilmartin* and *L. Rossi-Bernardi*, Nature *222*, 1243 (1969).

[57] *J. V. Kilmartin* and *L. Rossi-Bernardi*: Conference on Carbon Dioxide, Haverford, Pennsylvania, 1968.

[58] *M. F. Perutz*, Nature *224*, 269 (1969).

[59] *H. B. Hamilton, I. Iuchi, T. Miyaji*, and *S. Shibata*, J. Clin. Invest. *48*, 525 (1969).

[60] *K. Imai*, Arch. Biochem. Biophys. *127*, 543 (1968).

[61] *C. H. De Verdier* and *L. Garby*, Scand. J. Clin. Lab. Invest. *23*, 149 (1968).

[62] *R. Benesch* and *R. E. Benesch*, Nature *221*, 618 (1969).

[63] *A. Chanutin* and *R. R. Curnish*, Arch. Biochem. Biophys. *121*, 96 (1967).

[64] *R. Benesch, R. E. Benesch*, and *C. I. Yu*, Proc. Nat. Acad. Sci. U.S.A. *59*, 526 (1968).

[65] *R. Benesch* and *R. E. Benesch*, Biochem. Biophys. Res. Commun. *26*, 162 (1967).

[66] *M. F. Perutz*, J. Mol. Biol. *13*, 646 (1965).

[67] *H. C. Watson* and *J. C. Kendrew*, Nature *190*, 670 (1961).

Fluorinated β-Sultones

By I. L. Knunyants and G. A. Sokolski[*]

Fluorinated β-sultones are formed on addition of sulfur trioxide to fluorinated olefins. Tetrafluoroethanesultone has been studied particularly thoroughly. The title compounds are characterized by the ease with which they undergo ring cleavage to give, *e.g.*, derivatives of α-sulfo carboxylic acids, of sulfonic acids, of carboxylic acids, and of sulfuric acid. Fluorinated compounds of this type containing an α-hydrogen atom are especially valuable in preparative work.

1. Introduction

The name sultones refers to the inner esters of hydroxyalkanesulfonic acids, which may also be regarded as sulfur analogs of lactones. As with lactones, there exist α-, β-, γ-, δ-sultones and numerous other cyclic sulfonates of this kind. Among the unsubstituted compounds, the γ- and δ-sultones having five- and six-membered rings, respectively, are the most stable. Unsubstituted β-sultones decompose

$$X_2C{=}CF_2 + SO_3 \longrightarrow X_2\langle\begin{smallmatrix}SO_2\\ \diamond\\ O\\ F_2\end{smallmatrix} \quad (1)$$

extremely readily and have not yet been isolated. In contrast, fluorinated β-sultones of type *(1)*, formed by addition of sulfur trioxide to polyfluoroolefins, are relatively stable. Their formation by this reaction has been well studied for numerous examples. Moreover, a synthesis *via* sulfene intermediates has also been described[1a].

2. Synthesis of β-Sultones

That sulfur trioxide reacts with olefins was demonstrated as long ago as the beginning of the 19th Century for the case of ethylene[1b,2]. The reaction was subsequently extended to a large variety of substituted ethylenes[3–6], to a number of chloroolefins[7–11], and fairly recently to fluoroolefins[12–18].

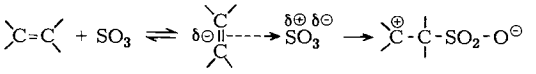
The reactions of sulfur trioxide with polar reagents of type A-B can be described by a series of equilibria.

$$\overset{\delta\oplus\ \delta\ominus}{A\text{-}B} + SO_3 \rightleftharpoons \overset{\delta\oplus\delta\ominus}{A\text{-}B\text{-}SO_2\text{-}O^{\ominus}} \rightleftharpoons \overset{\oplus}{A}\text{-}B\text{-}SO_2\text{-}O^{\ominus} \rightleftharpoons B\text{-}SO_2\text{-}O\text{-}A$$

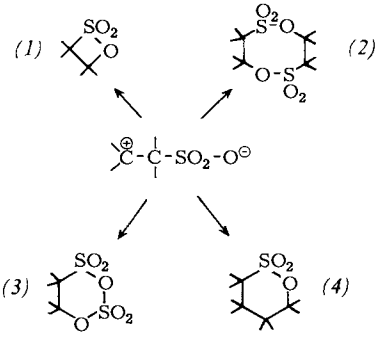
The initial step in the reaction of sulfur trioxide with olefins is an electrophilic attack by sulfur trioxide on the double

[*] Prof. Dr. I. L. Knunyants and Prof. Dr. G. A. Sokolski
Institute for Organoelement Compounds of the
Academy of Sciences of the USSR
Moscow V 312, Ul. Vavilova 28 (USSR)

bond[6, 19, 20]. The intermediate π-complex isomerizes to give a zwitterion in which the sulfur atom is bonded covalently to the carbon atom having an enhanced electron density.



Further reaction of the zwitterion is determined by the properties of the starting olefin and the reaction conditions. Apart from the β-sultones *(1)*, the eight- and six-membered heterocycles *(2)* and *(3)*, each containing two —SO_2—O— groups, and the δ-sultones *(4)* may be formed in individual cases.



Addition of sulfur trioxide to unsubstituted olefins proceeds extremely readily and is so exothermic that the primary adduct is very difficult to trap. It is therefore necessary to subdue the electron-accepting properties of sulfur trioxide, which is readily accomplished by using sulfur trioxide in the form of its quasi-complexes, *e.g.* with dioxane (Suter-Bordwell method) or with pyridine (Terent'ev method).

The presence of electron-withdrawing substituents in the olefin reduces its proclivity to add sulfur trioxide. Whereas ethylene[21] and vinyl chloride[10] even react with pyridine-sulfur trioxide, addition to dichloro-, trichloro-, and tetrachloroethylene occurs only with free sulfur trioxide. 1,2-Dichloroethylene reacts exothermally at room temperature[9] but trichloroethylene[8, 11] and especially tetrachloroethylene react only on heating[7, 22]. Reaction products of β-sultones are formed in all these cases.

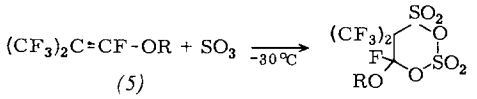
The opposite is observed on going from chloro- to fluoro-compounds within the series of perhalogenoolefins: fluoroolefins react more readily with sulfur trioxide than do their chlorine analogs. Thus tetrachloroethylene and fluorotrichloroethylene react with sulfur trioxide at 180—200 and 160—180 °C[22] respectively, symmetrical and unsymmetrical difluorodichloroethylene at 80 °C[12, 15, 18], and tetrafluoroethylene at 40—50 °C[17].

The optimum temperatures for the reaction of various fluoroethylenes with sulfur trioxide are given below:

$F_2C{=}CF_2$	$FHC{=}CF_2$	$H_2C{=}CF_2$	$H_2C{=}CHF$
40—50 °C	20—30 °C	0 °C	−30 °C

Finally, an alkoxy group in a fluoroolefin activates the molecule so strongly that some of these compounds of type *(5)* still even react with sulfur trioxide at −30 °C[23].

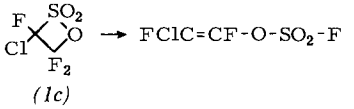
Reaction of polyfluoroolefins correspondingly gave β-sultones or compounds of type *(3)* (Table 1). Attempts to isolate the highly unstable primary adducts formed by vinyl fluoride[18] and fluorotrichloroethylene[22] were unsuccessful. Tetrafluoroethylene gives not only the β-sultone *(1f)* and the six-membered heterocycle *(3b)*, but also the eight-membered cyclic compound *(2a)*[24]; we were unable to



(5)

confirm whether tetrafluoroethanesultone *(1f)* is accompanied by tetrafluoro-1,3,2-dioxathiolane 2-oxide[15, 18]. This cyclic glycol sulfite was not isolated but merely postulated to explain the results of alkaline hydrolysis of *(1f)* and the ^{19}F-NMR spectra of its hydrolysis products.

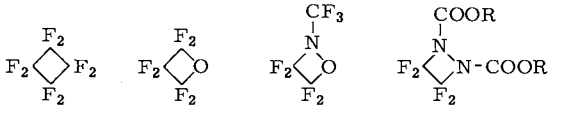
It was later established[29] that the observed deviations are due to isomerization of the β-sultone *(1f)* to the alkenyl fluorosulfate (see Section 3). A similar explanation probably applies to the unconfirmed report[15, 18] that a mixture of two β-sultones results on reaction of chlorotrifluoroethylene with sulfur trioxide. It is reasonable to assume that, in this case too, only the α-chloro β-sultone *(1c)* is formed which then isomerizes to the alkenyl fluorosulfate.



(1c)

The data listed in Table 1 show that strict orientation always prevails in the addition of sulfur trioxide to unsymmetrical polyfluoroolefins. This definite orientation confirms the ionic character of the reaction and the intermediacy of a zwitterion (see above). Further evidence is provided by the additional, and sometime predominating, formation of six-membered cyclic compounds of type *(3)*. This is also the only possible explanation of the formation of the eight-membered cyclic by-product *(2a)* on reaction of tetrafluoroethylene with sulfur trioxide. Styrene and sulfur trioxide are known to form a similar compound[30].

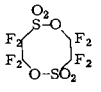
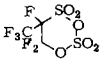
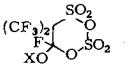
The stability of fluorinated β-sultones came as no surprise. Many different types of polyfluorinated four-membered ring compounds are already known, *e.g.* perfluorocyclobutane *(6)* and the extremely stable perfluorooxetane *(7)*, as well as the relatively stable polyfluorooxazetidines *(8)* and polyfluorodiazetidines *(9)*.



(6) *(7)* *(8)* *(9)*

The comparatively high stability of fluorinated β-sultones permits their large-scale production by heating a mixture of sulfur trioxide and polyfluoroolefin in a pressure reactor or passing the gaseous components through a heated tube. The accessibility of fluorinated β-sultones was the main reason for the detailed study of their chemical properties and for their suggested use as intermediates in the laboratory and in industry.

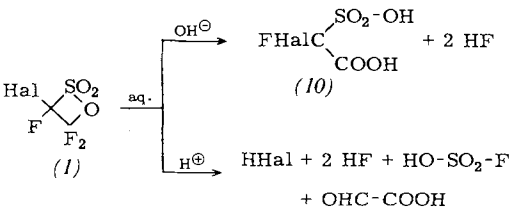
Table 1. Products of reactions between halogenoolefins and sulfur trioxide.

Olefin	Product		Ref.
$H_2C=CF_2$		*(3a)*	[15, 18]
$Cl_2C=CF_2$		*(1a)*	[15, 18]
$FClC=CFX$			
$X=Cl$	*(1b)*		[12, 15, 18]
$X=F$	*(1c)*		[12–16, 18]
$X=OCH_3$	*(1d)*		[23]
$X=OC_2H_5$	*(1e)*		[23]
$F_2C=CF_2$		*(1f)*	[13–16, 18, 25, 26]
		*(2a)*	[24]
		*(3b)*	[15, 18, 24, 27]
$F_3C-CF=CF_2$		*(1g)*	[12–16, 18]
		*(3c)*	[15, 18, 28]
$F_3C-CCl=CCl-CF_3$		*(1h)*	[12]
$(CF_3)_2C=CF-OX$			
$X=CH_3$	*(3d)*		[23]
$X=C_2H_5$	*(3e)*		[23]
$XFC=CF_2$			
$X=H$	*(1i)*		[13–16, 18]
$X=FCl_2C-CF_2$	*(1j)*		[12]
$X=F_2ClC-CFCl-CF_2$	*(1k)*		[12]
$X=n\text{-}C_4H_9$	*(1l)*		[15, 18]
$X=n\text{-}C_5F_{11}$	*(1m)*		[34]
$X=F_2ClC-(CFCl-CF_2)_2$	*(1n)*		[12]
$X=H-(CF_2)_6$	*(1o)*		[15, 18]
$X=F_2ClC-(CFCl-CF_2)_3$	*(1p)*		[12]
$X=F_2ClC-(CFCl-CF_2)_4$	*(1q)*		[12]

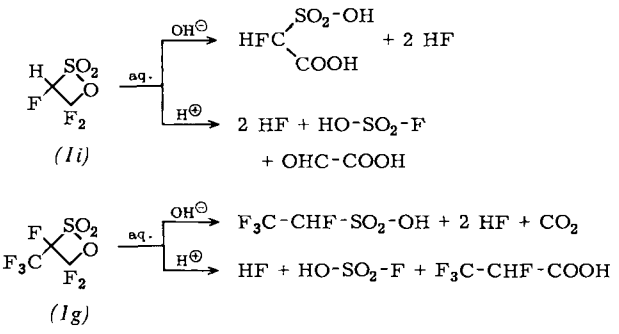
3. Possible Reactions of β-Sultones

Fluorinated β-sultones dissolve readily in saturated hydrocarbons, in their fluoro and chloro derivatives, and in polyhalogenoolefins. With water and most inorganic and organic compounds β-sultones undergo vigorous decomposition to give derivatives of sulfonic acids or sulfuric acid, depending upon the nature of the reagent.

The hydrolysis of fluorinated β-sultones is very informative. Thus alkaline hydrolysis of tetrafluoroethanesultone or of 1-chlorotrifluoroethanesultone gives dihalogenosulfoacetic acid *(10)*, whereas fluorosulfuric acid and glyoxylic acid are obtained on hydrolysis with sulfuric acid.



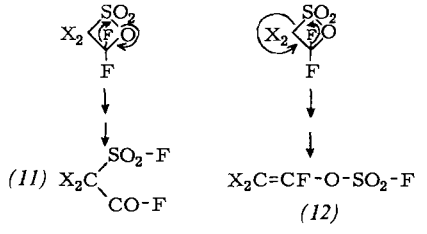
Various differences in dependence upon the pH value of the solution are also observed in the hydrolysis of other fluorinated β-sultones, *e.g.* 1,2,2-trifluoroethanesultone *(1i)* and perfluoro-1,2-propanesultone *(1g)*.



(1i)

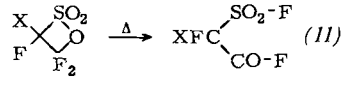
(1g)

The reactivity and in particular the chemical properties of fluorinated β-sultones on hydrolysis can be explained in terms of Scheme 1[31,32].

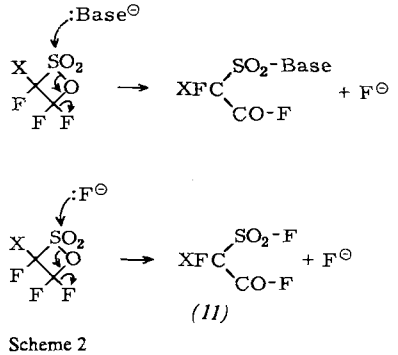


Scheme 1

On prolonged heating, β-fluorinated β-sultones isomerize to α-fluorosulfonyl polyfluoro carbonyl fluorides *(11)*[26,31,33]. Isomerization is initiated by nucleophilic reagents including triethylamine[15,18], ammonia[34], and dioxane[33,35]. Even on brief exposure to moist air some isomerization is observed. The best catalysts for this reaction are hydrogen fluoride and alkali metal fluorides.

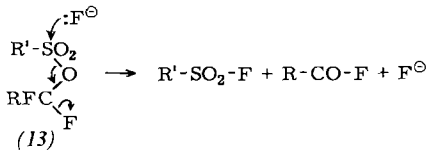


The course of this isomerization and its initiation by nucleophilic compounds can be represented as a chain process (Scheme 2) in which the fluoride ion—liberated from fluorinated β-sultone—plays the main role[35].



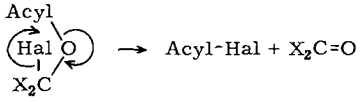
Scheme 2

Decomposition of α-fluoroalkyl sulfonates of type *(13)* is also initiated by nucleophilic compounds[36-38].

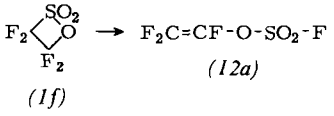


(13)

The well-known decomposition of α-halogeno alkyl esters and thio esters of phosphoric acid, nitrous acid, and even of carboxylic acids can be explained similarly. These reactions confirm the lability of esters bearing an α-halogen, which class includes the fluorinated β-sultones.

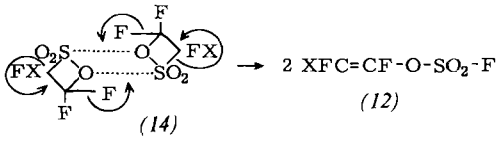


The second kind of isomerization of fluorinated β-sultones has so far been observed in one case only, *viz.* conversion of tetrafluoroethanesultone *(1f)* into trifluorovinyl fluorosulfate *(12a)* which occurs on prolonged storage at room temperature in the absence of water[29].



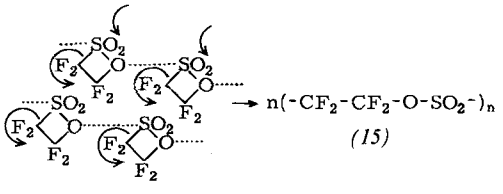
(1f)

The process is accelerated by phase transitions, *i.e.* by repeated crystallization and melting (between −40 and 0 °C). It was assumed[20] that isomerization is facilitated by the orientation of the β-sultone molecules [cf. *(14)*].



(14)

Such an orientation occurs randomly in the liquid phase but regularly on crystallization: isomerization is therefore incomparably slower in the former case than in the latter. If crystalline tetrafluoroethanesultone is kept for a long time at −78 °C it yields a polymer *(15)* whose formation is also attributable to the regular arrangement of molecules[39].

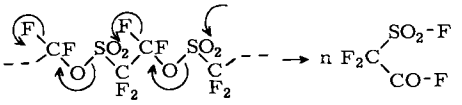


(15)

On heating or in the presence of nucleophiles depolymerization sets in to give fluorosulfonyldifluoroacetyl fluoride *(11a)*[39].

The combination of the sulfonyl group and a fluorine atom in a strained four-membered ring is a particular feature of

fluorinated β-sultones. These characteristics and the thermodynamic stability of the fluorosulfonyl group[40,41] would suggest ready ring cleavage to form that group.

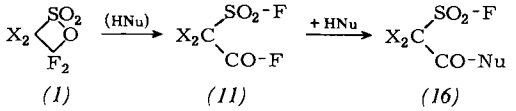


(15) *(11a)*

If the process is initiated by nucleophilic attack by an electron donor on the sulfonyl group, derivatives of α-sulfo polyfluoro carboxylic acids of type *(11)* are formed by heterolysis of the ester linkage. Under phase transition conditions, on the other hand, heterolysis of the S—C bond ensues giving sulfates of type *(12)* or polysulfates of type *(15)*. Transformations of this kind in stable compounds under phase transition conditions represent a truly remarkable phenomenon.

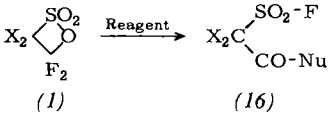
3.1. Conversion of β-Sultones into Derivatives of α-Sulfo Carboxylic Acids

Treatment of β-fluorinated β-sultones with nucleophilic compounds containing mobile hydrogen atoms furnishes derivatives of α-sulfo carboxylic acids. The β-sultone initially isomerizes to a linear α-fluorosulfonyl polyfluoroacyl fluoride of type *(11)* that subsequently acylates the nucleophile to give *(16)*[20,31,35]. The reactions summarized in Table 2 are in accord with this view.



(1) *(11)* *(16)*

Table 2. Formation of α-fluorosulfonyl polyfluoro carboxylic acid derivatives *(16)* from β-sultones *(1)*.

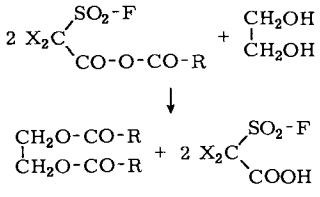


(1) *(16)*

Reagent	Nu	Ref.
H_2O	OH	[14–16, 18, 42, 43]
ROH	OR	[14–16, 18, 33, 44–46]
H_2S	SH	[15, 18]
RSH	SR	[14–16, 18, 47]
KSCN	SCN	[15]
R_2NH	NR_2	[14–16, 18, 46]
$(NH_2)_2CO$	NH—CO—NH_2	[15]
RCOOH	O—CO—R	[48, 49]

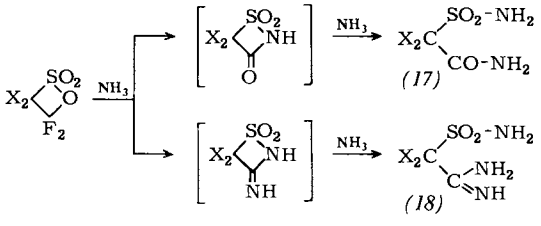
Fluorosulfonylfluoroacetic acid and fluorosulfonyldifluoroacetic acid are isolable; they are stable and behave as strong carboxylic acids. The fluorosulfonyl carboxylic acids can be converted into anhydrides, acyl halides, esters, thio esters, amides, hydrazides, *etc.* by the usual methods. Synthesis and investigation of numerous derivatives of α-fluorosulfonyl carboxylic acids have permitted derivation of the molar refraction of the fluorosulfonyl group bound to carbon: $R_{F-SO_2} = 10.54$ cm^3[50].

Mono- and polybasic aliphatic and aromatic acids have been used to form mixed anhydrides with β-sultones. The resulting mixed anhydrides of carboxylic and α-fluorosulfonyl polyfluoro carboxylic acids are effective acylating agents for alcohols, phenols, and thiols[51]. Reaction yields derivatives of the carboxylic acid[48,49].



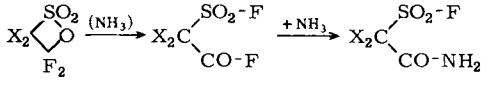
Only in those cases in which a strong carboxylic acid is made to react with the β-sultone does the acylation reaction lead to a derivative of the α-fluorosulfonyl carboxylic acid alongside the major product. The ratio of the strengths of the two acids apparently determines which product is formed in this process (S_N1 or S_N2)[49]. Thus the mixed anhydride of fluorosulfonyldifluoroacetic acid and trifluoroacetic acid reacts with alcohols to give both expected products in the approximate ratio 1:1.

Exhaustive ammonolysis of fluorinated β-sultones yields the diamides *(17)* and the amidoamidines *(18)* whose formation can be explained by repeated conversions involving β-sulfam derivatives[34].



(17) *(18)*

Ammonolysis undoubtedly starts with isomerization of the β-sultone followed by formation of the α-fluorosulfonyl carboxamide.

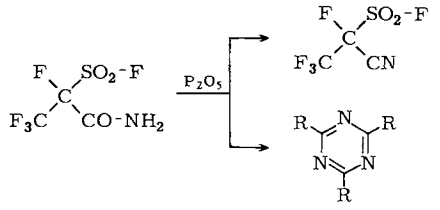


α-Fluorosulfonylperfluoropropionamide has been isolated and converted into the nitrile and the triazine derivative *(19)*[52,53]. The nitrile is stable; it can yield the triazine derivative only by way of the imidoyl chloride or the imidic ester[52]. It was concluded from this observation that the simultaneous formation of nitrile and triazine on dehydration of the amide must be due to presence of the isomeric imidic acid *(20)*.

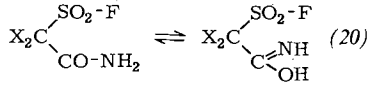
This peculiarity of the amide would also explain the result of exhaustive ammonolysis reported above.

Fluorinated β-sultones can be made to react with nucleophilic compounds under conditions unfavorable for isomerization by liberated fluoride ions. An appropriate method

is to work with a large excess of the nucleophile[35]; initial attack by an anion affords a derivative of the α-sulfo carboxylic acid whose sulfonyl group bears a substituent

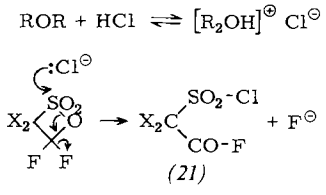


(19), R = $F_3C-CF-SO_2-F$



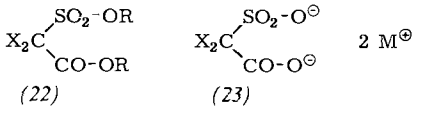
(20)

other than fluorine. The reaction of a β-sultone with an excess of hydrogen chloride in ethereal solution to give the α-chlorosulfonyl polyfluoro acyl fluoride *(21)* may be cited as an example[35].



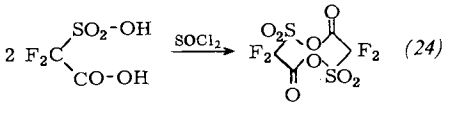
(21)

Analogously, diesters of α-sulfo polyfluoro carboxylic acids *(22)* are formed with an excess of alkali metal alkoxide in an alcohol[35]. On treatment with aqueous alkali, fluorinated β-sultones are converted into salts of α-sulfo carboxylic acids *(23)*[15, 18, 54].



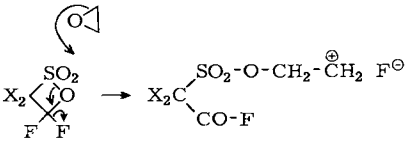
(22) *(23)*

It proved possible to isolate free sulfodifluoroacetic acid as a crystalline hydrate after hydrolysis of tetrafluoroethanesultone *(1f)*. The acid yields derivatives including a cyclic dianhydride *(24)*[54].



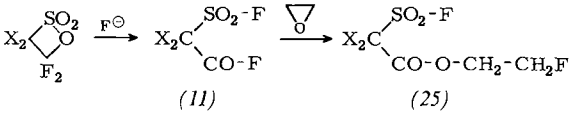
(24)

Competition between the nucleophilic reagents is illustrated particularly well by the reaction of fluorinated β-sultones with ethylene oxide[55]. Addition of ethylene oxide to the β-sultone furnishes the 2-fluoroalkyl ester of the α-fluoro-



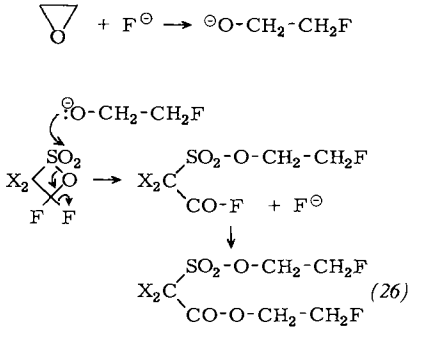
sulfonyl carboxylic *(25)* as major product. If addition is carried out in the reverse order the bis(2-fluoroethyl ester) of the α-sulfo carboxylic acid *(26)* is formed. In both cases reaction begins with a nucleophilic attack by ethylene oxide with elimination of a fluoride ion.

Excess β-sultone is isomerized by fluoride ion; the resulting α-fluorosulfonyl acyl fluoride *(11)* cleaves the ethylene oxide, as could also be confirmed in an independent experiment. The diester *(26)* is not formed[55].



(11) *(25)*

If an excess of ethylene oxide is present it is cleaved by fluoride ion[56, 57]; the α-fluoroethoxy anion then converts the β-sultone into α-(2-fluoroethoxysulfonyl) acyl fluoride which reacts with ethylene oxide to give the diester *(26)*. By-products are naturally also formed by telomerization of the ethylene oxide[57].

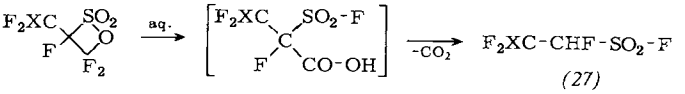


(26)

To summarize, it may be said that when reaction begins with nucleophilic attack by the reagent the β-sultone ring is always opened with elimination of fluoride ion and formation of an α-sulfo carboxylic acid derivative.

3.2. Conversion of β-Sultones into Derivatives of Polyfluoroalkanesulfonic Acids

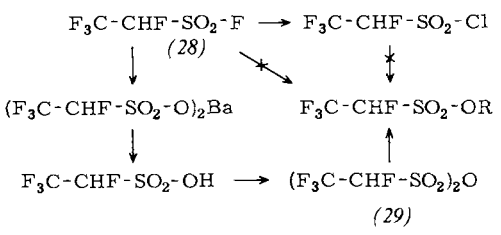
Hydrolysis of β-sultones based on hexafluoropropylene and other higher fluoroolefins yields unstable α-fluorosulfonyl polyfluoro carboxylic acids which readily undergo decarboxylation[58, 59]. Whereas fluorosulfonylfluoroacetic acid and fluorosulfonyldifluoroacetic give off carbon dioxide only on heating[59, 60], higher homologs decarboxylate at room temperature to give α-monosubstituted polyfluoroalkanesulfonyl fluorides *(27)*[33, 58, 59].



(27)

Classical methods cannot always be used with these acids for conversion of one derivative into another[61–64].

Thus attempts to synthesize esters from acyl halides were unsuccessful. In neutral and acidic solution the acyl halides are inactive towards alcohols; even in the presence of alkali metal hydroxides or alkoxides as well as tertiary amines they do not yield esters but salts of the sulfonic acid.



The methyl and ethyl esters can only be prepared by the action of the sulfonic anhydride *(29)* on the corresponding ether[63].

$$(F_3C{-}CHF{-}SO_2)_2O + R{-}O{-}R \rightarrow 2\,F_3C{-}CHF{-}SO_2{-}OR$$
(29)

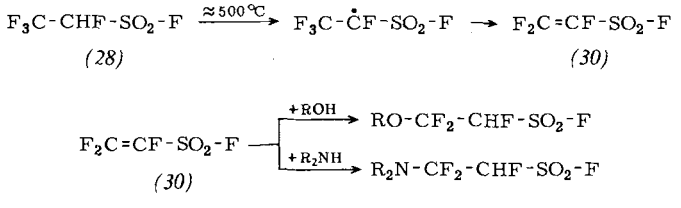
Aminolysis of the sulfonyl fluoride *(28)* also took a surprising course: The expected sulfonamides are accompanied by β-aminoalkanesulfonamides, in some cases as major product[61].

$$F_3C{-}CHF{-}SO_2{-}F \xrightarrow{R_2NH}$$
(28)

$$F_3C{-}CHF{-}SO_2{-}NR_2 + R_2N{-}CF_2{-}CHF{-}SO_2{-}NR_2$$

The peculiarities shown by some of the reactions of these 1,2,2,2-tetrafluoroethanesulfonic acid derivatives were interpreted as being due to the mobility of the hydrogen atom[61] resulting from the inductive effect of the sulfonyl and the trifluoromethyl group.

Pyrolysis of 1,2,2,2-tetrafluoroethanesulfonyl fluoride *(28)* yields trifluoroethylenesulfonyl fluoride *(30)*[58] which readily adds nucleophiles.



The lability of the C—H bond in the derivatives of 1,2,2,2-tetrafluoroethanesulfonic acid is particularly obvious on solvolysis with bases. The sulfonyl fluoride *(28)*, like alkali metal sulfonates, forms stable adducts with tertiary amines[65].

$$F_3C{-}\overset{\ominus}{C}F{-}SO_2{-}F \quad \overset{\oplus}{H}NR_3$$

A method for the synthesis of α-substituted polyfluoroalkanesulfonyl compounds has been worked out on the basis of similar compounds having carbanion character. The method consists in the electrophilic substitution of the hydrogen in α-monosubstituted polyfluoroalkanesulfonyl halides under base-solvolysis conditions. Thus α-chlorosulfonyl halides of type *(31)* could be prepared in the presence of tertiary amines and chlorine or sulfuryl chloride; the halides could be converted into the sulfonic acids, their anhydrides, esters, amides, and a few other derivatives[61,66,67]. Derivatives of tetrafluoroethanesulfonic acid containing bromine, nitroso, acyl groups, or cyano in the α position were prepared similarly[61,66].

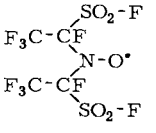
$$F_3C{-}CFCl{-}SO_2{-}F \quad (31)$$

Of the compounds listed, particular attention attaches to α-nitrosotetrafluoroethanesulfonyl fluoride *(32)* which is characterized by the instability of the sulfonyl fluoride and nitroso moieties. It was transformed into numerous novel compounds, *e.g. (33)—(35)*[61].

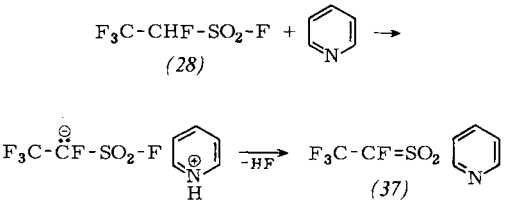
$F_3C{-}CF(NO){-}SO_2{-}F$ *(32)* $\qquad$ $F_3C{-}CF(NO_2){-}SO_2{-}X$ *(33)*

$F_3C{-}CF(N{=}NR){-}SO_2{-}X$ *(34)* $\qquad$ $F_3C{-}CF(NR_2){-}SO_2{-}X$ *(35)*

In addition, transition of the α-nitroso sulfonyl fluoride *(32)* into relatively stable radicals, *e.g.* bis(α-fluorosulfonyltetrafluoroethyl)aminyl oxide *(36)*, was shown by the ESR spectrum[61].


(36)

Finally, under conditions of base solvolysis 1,2,2,2-tetrafluoroethanesulfonyl fluoride *(28)* gives trimethylfluorosulfene[*] as a complex *(37)* with pyridine[65,68].



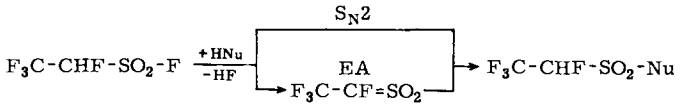
Sulfenes have so far defied all attempts at isolation; they have only been demonstrated as intermediates in the reactions of sulfonyl compounds[69,70]. A similar complex *(38)*, which likewise is extremely unstable, could be isolated on dehydrochlorination of methanesulfonyl chloride[71,72].

$$H_3C{-}SO_2{-}Cl \xrightarrow{(C_2H_5)_3N} H_3C{-}SO_2{-}CH{=}SO_2N(C_2H_5)_3$$
(38)

The detection of complexed trifluoromethylfluorosulfene permits a new interpretation to be given for the reaction

[*] We suggest the name "sulfonenes" instead of "sulfenes" for such compounds in order to emphasize the presence of both a sulfonyl group and a double bond.

of 1,2,2,2-tetrafluoroethanesulfonyl fluoride *(28)* with nucleophilic reagents. The mechanistic alternatives for this reaction are an S_N2 substitution or elimination with subsequent addition (EA).



The thermodynamic stability of the sulfonyl fluoride group[40,41] makes the S_N2 process appear highly unlikely. The results of potentiometric titration of some sulfonyl fluorides can be explained by invoking the EA reaction mode[67]. The rate constants of their alkaline hydrolysis in the presence of potassium chloride are listed in Table 3,

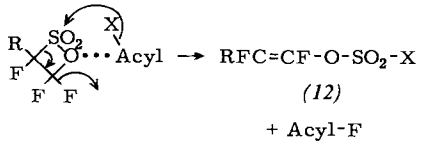
Table 3. Rate constants of alkaline hydrolysis K_c of sulfonyl fluorides in the presence of potassium chloride at 25 °C and pH 10.0.

R—SO_2—F R	K_c (l mol^{-1} s^{-1})
F_3C—CFCl	3.3
C_6H_5	8.2
H_2C=CH	18.3
H_3C	46.1
C_6H_5—CH_2	912
F_3C—CHF	923

from which it may be seen that sulfonyl fluorides having no α-hydrogen atom react least readily with nucleophilic reagents and which sulfonyl fluorides can only undergo S_N2 substitution. Methane and particularly ω-toluene- and 1,2,2,2-tetrafluoroethanesulfonyl fluorides are distinguished by their high rate constants. The reactivity of these compounds is apparently due to the intermediacy of a sulfene.

3.3. Conversion of β-Sultones into Derivatives of Alkenylsulfuric Acids

Treatment of fluorinated β-sultones with some acyl chlorides or esters furnishes derivatives of fluoroalkenylsulfuric acids *(12)* and acyl fluorides. The reaction must pass through a transition state having both the sultone and the reagent in favorable orientations. The transition state is stabilized by cleavage of the sultone S—C bond.

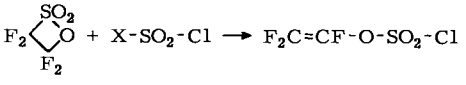


When carried out with an acyl chloride (acyl-X) the reaction yields fluoroalkenyl chlorosulfate. In this way trifluorovinyl chlorosulfate was obtained from tetrafluoroethanesultone and pentafluoropropenyl chlorosulfate from hexafluoro-1,2-propanesultone. Derivatives of sulfuric acid and sulfonic acids, nitrous acid, phosphoric and phosphonic acids, and silicon- and titanium tetrachloride were used as acid chlorides.

The success of the reaction is determined by two factors: Firstly by the coordinative accessibility of the central atom in the acid chloride and secondly by the acylating power of this reagent. Thus silicon tetrachloride and titanium tetrachloride do not react with fluorinated β-sultones (up to 100 °C). This observation was explained by the coordinative saturation of silicon and titanium which hinders formation of a transition state with the β-sultones[73]. In contrast, reaction with nitrosyl chloride occurs at −35 °C. Similarly vigorous reactions are observed between β-sultones and methylphosphonyl dichloride (at −10 °C) and phosphorus oxide trichloride (at −20 °C); the resulting fluorochlorophosphoric acids can also react with β-sultones[73].

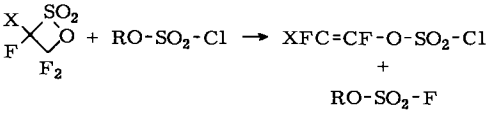
The reactions with chlorosulfuric acid derivatives[73–77] such as alkanesulfonyl chlorides[76,77], alkyl chlorosulfates[76,77], chlorosulfuric acid[75,77], and sulfuryl chloride[76] proceed analogously. The reaction temperatures required and the yields of alkenyl chlorosulfate are consonant with the acylating power of the chlorosulfonyl compounds (Table 4).

Table 4. Temperature and yield in the reaction



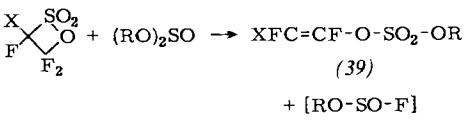
X	T(°C)	Yield (%)
R	20–60	90–95
RO	30–80	65–80
HO	80–100	70–80
Cl	100	20

The reaction of fluorinated β-sultones with alkyl chlorosulfates is the sole general method available for the preparation of aliphatic esters of fluorosulfuric acid (RO—SO_2—F)[76,78].

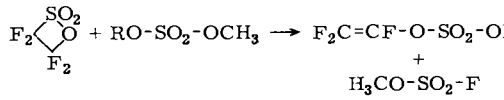


This route was used to prepare methyl and *n*-hexyl fluorosulfate[76] and thereby permitted estimation of the refraction of the fluorosulfate group: $R_{F-SO_2-O} = 11.50$ cm^3. Alkyl fluorosulfates are powerful alkylating agents.

Reaction of fluorinated β-sultones with sulfurous esters gives esters of fluoroalkenylsulfuric acids *(39)*[77,79,80]. Esters of trifluorovinylsulfuric acid were obtained from tetrafluoroethanesultone[77,79] and esters of pentafluoropropenylsulfuric acid from hexafluoro-1,2-propanesultone[79,80]; the refractions of the polyfluoroalkenyl groups are $R_{F_2C=CF} = 9.82$ cm^3 and $R_{F_3C-CF=CF} = 15.71$ cm^3.



Fluorinated β-sultones react with dialkyl sultates to give esters of fluorosulfuric acid and of fluoroalkenylsulfuric acid; however, this reaction is recommended only for the preparation of fluoroalkenylsulfates of higher alcohols because lower dialkyl sulfates are more typically alkylating rather than acylating agents[81]. This is particularly obvious from the reaction of fluorinated β-sultones with unsymmetrical alkyl sulfates[73]: The products are the fluoroalkenylsulfate of the higher and the fluorosulfate of the lower alcohol.



The derivatives of trifluorovinylsulfuric acid are characterized by their ability to react with nucleophiles; thus their alkaline hydrolysis leads in a vigorous fashion to complete decomposition of the reactants[29, 75, 80].

$$F_2C{=}CF{-}O{-}SO_2{-}F + 4KOH \rightarrow HOOC{-}CHO + 3KF + KOSO_2F + H_2O$$

$$F_2C{=}CF{-}O{-}SO_2{-}Cl + 6KOH \rightarrow HOOC{-}CHO + 3KF + KCl + K_2SO_4 + 2H_2O$$

$$F_2C{=}CF{-}O{-}SO_2{-}OR + 4KOH \rightarrow HOOC{-}CHO + 3KF + KOSO_2OR + H_2O$$

The initial step in their alcoholysis is substitution in the vinyl group[29, 82].

$$F_2C{=}CF{-}O{-}SO_2{-}X + ROH \rightarrow RO{-}CF{=}CF{-}O{-}SO_2{-}X + HF$$

Excess alcohol then adds to the product. Thus a bis(alkoxy) compound *(40)* could be isolated on reaction of trifluorovinyl chlorosulfate[82]. Only addition occurs to give compounds like *(41)* and *(42)* on reaction with acids[75, 82].

$(RO)_2FC{-}CHF{-}O{-}SO_2{-}Cl$ *(40)*

$H_3C{-}COO{-}CF_2{-}CHF{-}O{-}SO_2{-}Cl$ *(41)*

$Cl{-}SO_2{-}O{-}CF_2{-}CHF{-}O{-}SO_2{-}Cl$ *(42)*

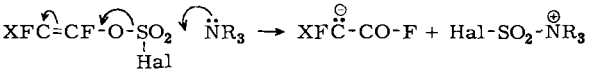
Derivatives of pentafluoropropenylsulfuric acid can also react with nucleophiles[77, 83]. The results of alkaline hydrolysis and alcoholysis show the double bond in these compounds to be polarized, unlike that in the trifluorovinyl compounds. The trifluoromethyl group therefore appears to exert a more pronounced effect than the sulfonyl group.

$$F_3C{-}CF{=}CF{-}O{-}SO_2{-}Cl + 5KOH \rightarrow F_3C{-}CFH{-}COOK + KF + K_2SO_4 + KCl + 2H_2O$$

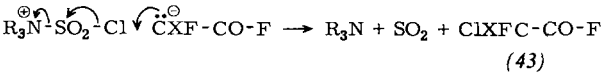
$$F_3C{-}CF{=}CF{-}O{-}SO_2{-}OR + 3KOH \rightarrow F_3C{-}CHF{-}COOK + KF + KOSO_2OR + H_2O$$

$$F_3C{-}CF{=}CF{-}O{-}SO_2{-}X \xrightarrow{ROH} F_3C{-}CHF{-}COOR$$

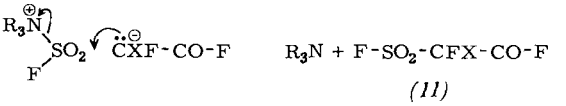
The behavior of fluoroalkenyl halogenosulfates towards tertiary amines, which initiate decomposition of the chlorosulfates and isomerization of the fluorosulfates of these acids, occupies a special place[84]. In both cases the reaction starts with a nucleophilic attack on the sulfonyl group with cleavage of the ester.



What then ensues is determined by the reaction of the carbanion with the sulfonylammonium ion. In the case of a chlorosulfonylammonium ion attack is centered on the chlorine atom and an α-chloro acyl fluoride *(43)* is formed; with a fluorosulfonylammonium ion the sulfonyl group is attacked and an α-fluorosulfonyl acyl fluoride *(11)* results.

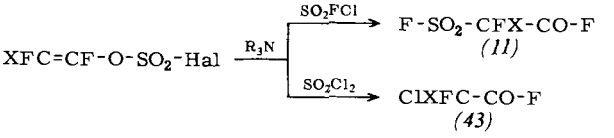


(43)



(11)

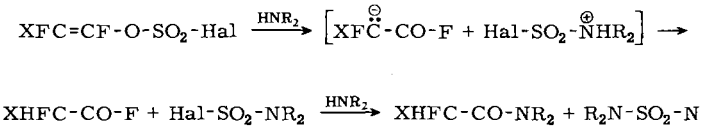
If a similar reaction is carried out in sulfuryl fluoride chloride solution—a source of fluorosulfonyl cations[85]—then α-fluorosulfonyl fluorides are formed exclusively, irrespective of which halide of fluoroalkenylsulfuric acid is used. Reaction in sulfuryl chloride (source of chlorine cations) likewise affords solely α-chloro acyl fluorides[84].



(11)

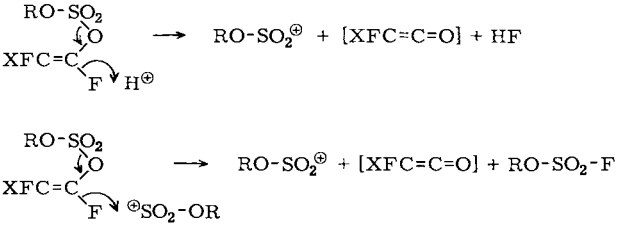
(43)

However, if a secondary amine is used to initiate decomposition of fluoroalkenyl halogenosulfates one obtains tetrasubstituted sulfamide and the amide of the corresponding carboxylic acid *(44)* having an α-hydrogen atom[77, 82].



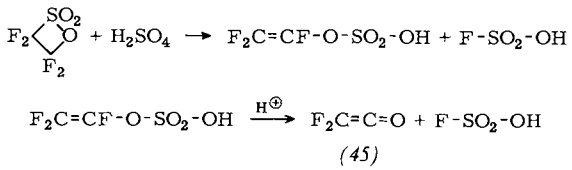
(44)

Derivatives of fluoroalkenylsulfuric acid are also very unstable in the presence of acids. Thus their esters decompose on heating with strong mineral acids (sulfuric, chlorosulfuric, and fluorosulfuric acid) to give fluorosulfates[86] in a chain reaction (Scheme 3).



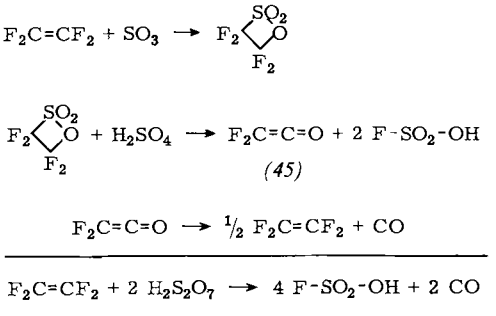
Scheme 3

The instability of trifluorovinylsulfuric acid becomes readily understandable in the light of these results. These acids, which are formed from tetrafluoroethanesultone and sulfuric acid at room temperatures, are converted into difluoroketene *(45)* and fluorosulfuric acid on heating to temperatures above 40 °C in what is probably an autocatalytic reaction.



(45)

At higher temperatures difluoroketene *(45)* decomposes to tetrafluoroethylene and carbon monoxide[86,87]. In view of these and the foregoing reactions and the conditions of β-sultone synthesis it was deduced that the processes shown in Scheme 4 take place when tetrafluoroethylene is passed through heated disulfuric acid.

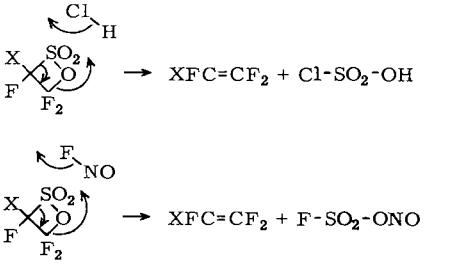


Scheme 4

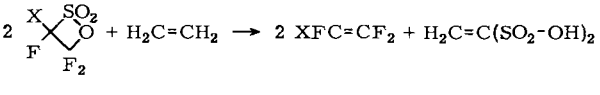
The failure of previous attempts to isolate organofluorine compounds after passage of polyfluoroolefins through oleum can presumably be explained similarly[88].

The above reactions of fluorinated β-sultones with mineral acids and their derivatives reveal the relatively labile character of the S—C bond in the sultone ring, which also determines the course of the following reactions.

Passage of dry hydrogen chloride through a cooled fluorinated β-sultone or hexafluoro-1,2-propanesultone affords chlorosulfuric acid and the corresponding olefin[89]. An analogous reaction takes place with nitrosyl fluorides[89].

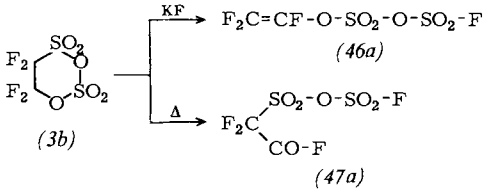


Fluoroolefins are also eliminated on passage of ethylene through β-sultones[89].



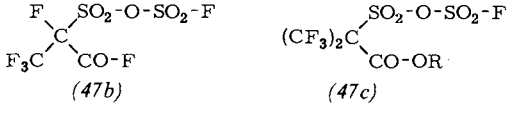
4. Fluorinated β-Disultones

Like the β-sultones, fluorinated β-disultones (1,3,2,4-dioxadithiane 2,2,4,4-tetroxides) are extremely reactive compounds. They can isomerize to sulfate- or sulfonate-type derivatives.



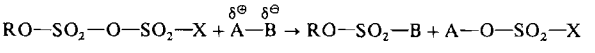
(3b) *(46a)* *(47a)*

In the case of the tetrafluoro compound *(3b)* both possible linear isomers were isolated[28]. Treatment of *(3b)* with potassium fluoride in catalytic amounts below 0 °C furnishes trifluorovinyl fluorodisulfate *(46)*; heating of *(3b)* to over 130 °C yields fluorosulfonyloxysulfonyldifluoroacetyl fluoride *(47a)*. Other fluorinated β-disultones have so far only been isomerized to derivatives of type *(47)*[23,28].

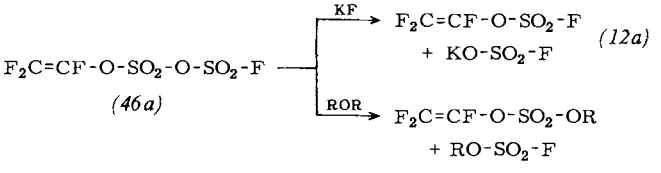


(47b) *(47c)*

Hitherto only the reactions of fluorinated β-disultones with nucleophilic compounds A-B have been studied. After ring cleavage the linear isomer sulfonylates the reagent[90].

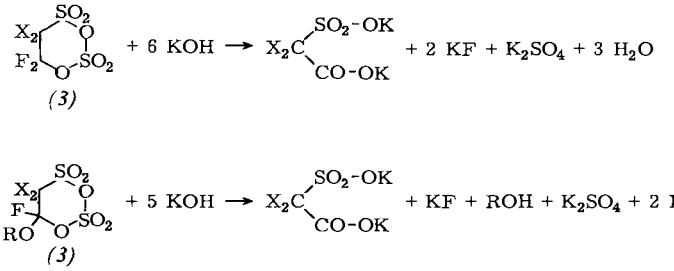


Reaction of the tetrafluoro compound *(3b)* with an excess of potassium fluoride gives potassium fluorosulfate and trifluorovinyl fluorosulfate; with ethers, alkyl fluorosulfates and alkyl trifluorovinyl sulfates are formed[28].



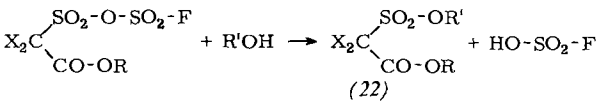
(46a) *(12a)*

Alkaline hydrolysis of compounds *(3)* also results in ring cleavage[23,24,28]. Isomerization here follows the second course. Similarly, alcoholysis initially gives a derivative of α-sulfonyloxysulfonyl carboxylic acid; the further course of the reaction depends upon the structure of the compound *(3)* and the reaction conditions.



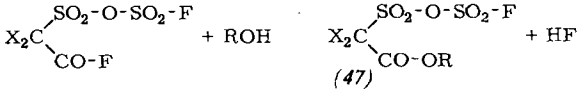
(3)

On alcoholysis of β-alkoxy derivatives ring opening is followed by sulfonylation of the alcohol and formation of the diester of the α-sulfo carboxylic acid of type *(22)*[23].



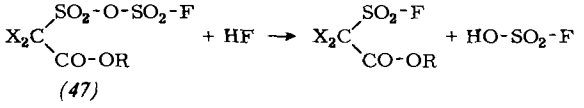
(22)

In the case of the β-fluoro derivative the alcohol is acylated to compounds of type *(47)* by the acyl fluoride formed.



(47)

The final reaction step is sulfonylation of either the alcohol (if present in excess) or the hydrogen fluoride (if insufficient alcohol is present) by compound *(47)*; depending on the conditions one obtains either the diester *(22)* or the α-fluorosulfonyl carboxylic ester[28, 91, 92].

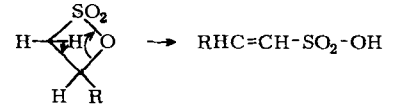


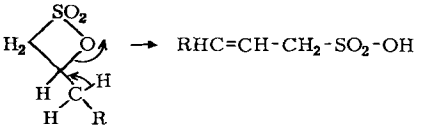
(47)

5. Transformations of β-Sultones Containing No Fluorine

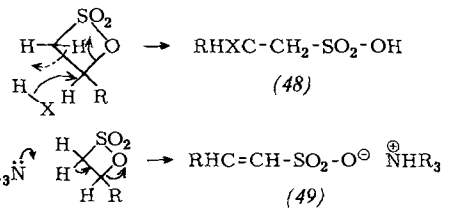
It was shown in Section 3 that the transformations of fluorinated β-sultones lead to derivatives of α-sulfo carboxylic acids or sulfuric acid. Anions play an important role in these reactions[20, 35, 73].

In contrast, β-sultones containing hydrogen atoms are characterized by their ability to undergo reactions involving proton shifts[20]. The primary products of reaction between olefins and sulfur trioxide—β-sultones, β-disultones, and δ-sultones—are known to be extremely unstable. Their transformations result from the mobility of the α-hydrogen atom in the sultone ring or of a hydrogen atom in the β-alkyl group[20]. The failure of attempts to isolate β-sultones can be explained by the ease of ring cleavage with concomitant shift of the proton to the oxygen.





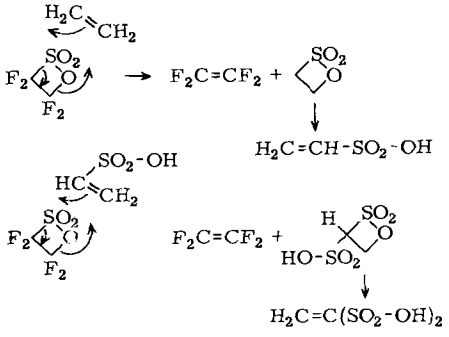
Treatment of olefin-sulfur trioxide adducts with water, hydrogen halides, alcohols, thiols, and primary or secondary amines affords β-substituted sulfonic acids *(48)*; with tertiary amines one obtains salts of α,β-unsaturated sulfonic acids *(49)*.



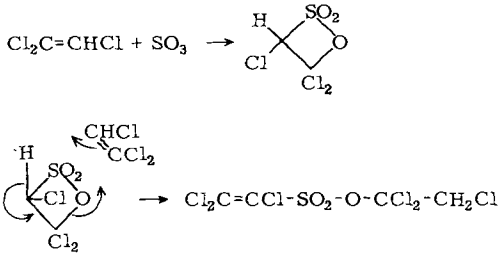
(48)

(49)

The formation of ethylenebis(sulfonic acid) on reaction of tetrafluoroethanesultone with ethylene can be interpreted in terms of the intermediacy of unsubstituted β-sultone (see Section 3.3)[89].



The reactions of bromine- and chlorine-containing olefins with sulfur trioxide can be rationalized in a similar way[11].



If a β-sultone molecule has a proton in the α-position and halogen in the β-position the reaction can, in principle, take two courses. In chlorinated or brominated β-sultones reactions involving proton shifts predominate while fluorinated β-sultones preferentially undergo reactions with participation of anions.

6. Applications

Although their study only began as late as 1957, fluorinated β-sultones have already been thoroughly investigated and numerous preparative methods have been worked out for their synthesis. Their ready accessibility prompted a search for possible applications.

Thus it has been reported that derivatives of α-sulfo polyfluoro carboxylic acids prepared from β-sultones inhibit the growth of microorganisms[15]. The derivatives *(50)* to *(53)* exhibit the greatest bactericidal effect.



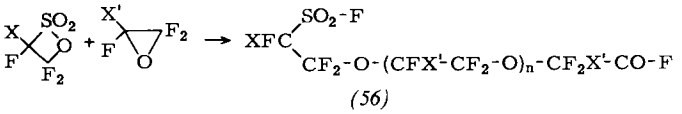
(50), R = $NH-CO-NH_2$
(51), R = $N(CH_3)C_6H_5$
(52), R = $O-CH_2-CH_2-O-CO-CF_2-SO_2-F$
(53), R = $S-C_6H_5$

Polyester and polyamides of α-sulfo polyfluoro carboxylic acids such as *(54)* and *(55)* are noninflammable polymeric materials[91].

$$[-O-SO_2-CFX-CO-O-(CH_2)_n-]_m$$
(54)

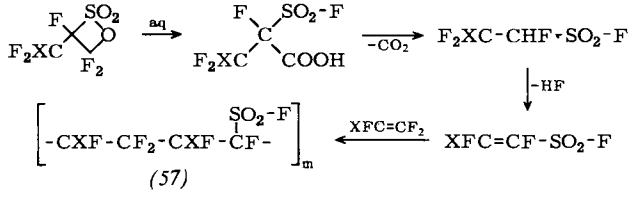
$$[-NH-SO_2-CF_2-CO-NH-(CH_2)_n-]_m$$
(55)

Telomerization products of β-sultones and fluorinated epoxides are also characterized by high thermal stability[93,94].



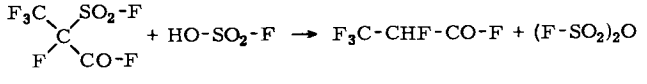
(56)

These polymers can be converted into highly stable ion-exchange resins[93]. Copolymerization of alkenesulfonyl fluorides with fluoroolefins has also been utilized to produce ion-exchange resins *(57)*[58].



(57)

A method based on desulfurization of sultones and the derivatives of α-sulfo polyfluoro carboxylic acids by the action of sulfuric, fluorosulfuric, or chlorosulfuric acid has been suggested for production of polyfluoro carboxylic acids having an α-hydrogen atom and their derivatives[86,95,96].



Finally, fluorinated β-sultones are so hygroscopic that they, and the fluoroolefins from which they are formed, can be used as stabilizers for liquid sulfur trioxide[97,98].

Further research on fluorinated β-sultones will doubtless suggest new preparative and industrial applications.

Received: April 5, 1971 [A 885 IE]
German version: Angew. Chem. *84*, 623 (1972)

[1a] *W. E. Truce* and *L. K. Liu*, Chem. Ind. (London) *1969*, 457.

[1b] *V. Regnault*, Liebigs Ann. Chem. *25*, 32 (1837).

[2] *V. Regnault*, Liebigs Ann. Chem. *27*, 11, 71 (1838).

[3] *Ch. Suter:* Chemistry of Organic Sulfur Compounds (Russian). Isdatinlit 1950, Vol. 1.

[4] *A. P. Terent'ev* and *L. A. Kazitsyna:* Reactions and Methods of Research into Organic Compounds (Russian). 1952, Vol. 2, p. 245.

[5] *E. E. Gilbert*, Chem. Rev. *62*, 549 (1962).

[6] *E. E. Gilbert:* Sulfonation of Organic Compounds (Russian). Khimiya, Moscow 1969.

[7] *M. Prudhomme*, C. R. Acad. Sci. *70*, 1137 (1870).

[8] *J. Böseken*, *J. E. Klamer*, and *J. G. de Voogt*, Rec. Trav. Chim. Pays-Bas *32*, 15 (1918).

[9] *H. Lepouse*, Bull. Soc. Chim. Belg. *34*, 133 (1925).

[10] *A. P. Terent'ev*, Zh. Org. Khim. *23*, 746 (1953).

[11] *E. E. Gilbert*, US-Pat. 2695308; Chem. Abstr. *49*, 12523 (1955).

[12] *Yang Hsi Kwei*, Acta Chim. Sinica *26*, 330 (1957); Chem. Abstr. *52*, 15493 (1958).

[13] *I. L. Knunyants, M. A. Dmitriev*, and *G. A. Sokolski*, USSR author's certificate 116578 (1958).

[14] *M. A. Dmitriev, G. A. Sokolski*, and *I. L. Knunyants*, Khim. Nauka Prom. *3*, 826 (1958); Chem. Abstr. *53*, 11211 (1959).

[15] *D. C. England* and *H. Oak*, US-Pat. 2852554 (1958); Chem. Abstr. *53*, 2253 (1959).

[16] *M. A. Dmitriev, G. A. Sokolski*, and *I. L. Knunyants*, Dokl. Akad. Nauk SSSR *124*, 581 (1959).

[17] *M. A. Dmitriev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, 847.

[18] *D. C. England, M. A. Dietrich*, and *R. V. Lindsey*, J. Amer. Chem. Soc. *82*, 6181 (1960).

[19] *C. M. Suter, P. B. Evans*, and *J. M. Kiefer*, J. Amer. Chem. Soc. *60*, 538 (1938).

[20] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, Teor. Eksp. Khim. *1*, 324 (1965).

[21] *A. P. Terent'ev* and *A. V. Dombrovskii*, Zh. Org. Khim. *19*, 1467 (1949).

[22] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1965*, 1655.

[23] *M. A. Belaventsev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1968*, 2296.

[24] *G. A. Sokolski, M. A. Dmitriev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, 1231.

[25] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, USSR author's certificate 175501 (1964).

[26] *M. A. Belaventsev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1965*, 1613.

[27] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Dmitriev*, USSR author's certificate 124435 (1959).

[28] *G. A. Sokolski, M. A. Belaventsev, L. I. Ragulin*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 2024.

[29] *M. A. Belaventsev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 2461.

[30] *F. G. Bordwell, M. L. Peterson*, and *C. S. Rondestvedt*, J. Amer. Chem. Soc. *76*, 3945 (1954).

[31] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, Dokl. Akad. Nauk SSSR *159*, 135 (1964).

[32] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1971*, 1050.

[33] *L. I. Ragulin, P. P. Ropalo, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 1754.

[34] *H. H. Gibbs* and *M. J. Bro*, J. Org. Chem. *26*, 4002 (1961).

[35] *G. A. Sokolski, M. A. Belaventsev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 1524.

[36] *G. A. Sokolski* and *M. A. Dmitriev*, Zh. Org. Khim. *31*, 1653, 2743, 3025 (1961).

[37] *G. A. Sokolski*, Zh. Org. Khim. *32*, 1310 (1962).

[38] *M. A. Belaventsev, V. B. Lukyanov, L. I. Ragulin*, and *G. A. Sokolski*, Zh. Org. Khim. *7*, 710 (1971).

[39] *G. A. Sokolski, M. A. Belaventsev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1968*, 1076.

[40] *D. P. Craig* and *E. A. Magnusson*, J. Chem. Soc. *1956*, 4895.

[41] *H. L. Roberts*, Quart. Rev. Chem. Soc. *15*, 30 (1961).

[42] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Dmitriev*, USSR author's certificate 116575 (1958).

[43] *M. A. Dmitriev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, 1035.

[44] *G. A. Sokolski, M. A. Dmitriev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 621.

[45] *I. L. Knunyants, M. A. Dmitriev*, and *G. A. Sokolski*, USSR author's certificate 116605 (1958).

[46] *M. A. Dmitriev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, 1227.

[47] *G. A. Sokolski, M. A. Dmitriev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 1055.

[48] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 813.

[49] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 1053.

[50] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 1468.

[51] *I. L. Knunyants* and *G. A. Sokolski*, USSR author's certificate 134691 (1960).

[52] *I. L. Knunyants, G. A. Sokolski, L. I. Ragulin*, and *A. I. Martynov*, USSR author's certificate 232273 (1967).

[53] *L. I. Ragulin, A. I. Martynov, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1969*, 2220.

[54] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 1289.

[55] *G. A. Sokolski, M. A. Belaventsev, L. A. Markov*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1968*, 1565.

[56] *I. L. Knunyants*, Dokl. Akad. Nauk SSSR *55*, 227 (1947).

[57] *I. L. Knunyants, O. V. Kildisheva*, and *E. G. Bychovskii*, Dokl. Akad. Nauk SSSR *57*, 49 (1949).

[58] *H. H. Gibbs* and *R. N. Griffin*, US-Pat. 3041317 (1960).

[59] *G. A. Sokolski, M. A. Belaventsev*, and *L. I. Ragulin*, USSR author's certificate 189842 (1966).

[60] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 1606.

[61] *G. A. Sokolski, L. I. Ragulin*, and *I. L. Knunyants*, Dokl. Akad. Nauk SSSR, in press.

[62] *G. A. Sokolski* and *L. I. Ragulin*, USSR author's certificate 230137 (1966).

[63] *L. I. Ragulin, P. P. Ropalo, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1968*, 1560.

[64] *R. E. Banks, G. M. Haslam, R. N. Haszeldine*, and *A. Peppin*, J. Chem. Soc. *1966*, 1171.

[65] *L. I. Ragulin, P. P. Ropalo, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1971*, 1045; *R. Fusco, S. Rossi*, and *S. Maiorana*, Chim. Ind. (Milano) *45*, 564 (1963); *R. Fusco, S. Rossi, S. Maiorana*, and *G. Pagani*, Gazz. Chim. Ital. *95*, 774 (1965).

[66] *G. A. Sokolski, L. I. Ragulin, G. P. Ovsyannikov*, and *Yu. M. Shalaginov*, USSR author's certificate 238540 (1967).

[67] *G. A. Sokolski, L. I. Ragulin, G. P. Ovsyannikov*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1971*, 1270.

[68] *I. L. Knunyants, G. A. Sokolski, M. A. Belaventsev, L. I. Ragulin*, and *P. P. Ropalo*, USSR author's certificate 232247 (1967).

[69] *T. J. Wallace*, Quart. Rev. Chem. Soc. *20*, 67 (1966).

[70] *G. Opitz*, Angew. Chem. *79*, 161 (1967); Angew. Chem. internat. Edit. *6*, 107 (1967).

[71] *G. Opitz* and *D. Bücher*, Tetrahedron Lett. *1966*, 5263.

[72] *G. Opitz, M. Kleemann, D. Bücher, O. Walz*, and *K. Rieth*, Angew. Chem. *78*, 604 (1966); Angew. Chem. internat. Edit. *5*, 1050 (1966).

[73] *G. A. Sokolski, M. A. Belaventsev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 2020.

[74] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, USSR author's certificate 166346 (1963).

[75] *G. A. Sokolski, M. A. Belaventsev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1965*, 1804.

[76] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, Izv. Akad. Nauk SSSR, Ser. Khim. *1966*, 1017.

[77] *I. L. Knunyants, M. A. Belaventsev, P. P. Ropalo*, and *G. A. Sokolski*, Izv. Akad. Nauk SSSR, Ser. Khim. *1966*, 1027.

[78] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, USSR author's certificate 167170 (1963).

[79] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, USSR author's certificate 177880 (1964).

[80] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Belaventsev*, Izv. Akad. Nauk SSSR, Ser. Khim. *1966*, 1022.

[81] *G. A. Sokolski*, Zh. Org. Khim. *2*, 951 (1966).

[82] *G. A. Sokolski, M. A. Belaventsev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1967*, 1294.

[83] *G. A. Sokolski, M. A. Belaventsev, L. I. Ragulin*, and *P. P. Ropalo*, USSR author's certificate 196760 (1965).

[84] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1970*, 373.

[85] *G. A. Sokolski*, Zh. Org. Khim. *36*, 860 (1966).

[86] *L. I. Ragulin, M. A. Belaventsev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1969*, 2220.

[87] *D. C. England* and *C. G. Krespan*, J. Org. Chem. *33*, 816 (1968).

[88] *W. Pirlson* in *Y. Saimons*: Fluorine and Its Compounds (Russian). Isdatinlit 1953, Vol. 1, p. 397.

[89] *G. A. Sokolski, M. A. Belaventsev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1970*, 625.

[90] *G. A. Sokolski*, Zh. Org. Khim. *36*, 798 (1966).

[91] *I. L. Knunyants, G. A. Sokolski*, and *M. A. Dmitriev*, USSR author's certificate 125554 (1959).

[92] *G. A. Sokolski, M. A. Dmitriev*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 617.

[93] *R. E. Putman* and *W. D. Nicoll*, US-Pat. 3301893 (1963).

[94] French Pat. 1406778 (1965), E. I. du Pont de Nemours.

[95] *L. I. Ragulin, M. A. Belaventsev, G. A. Sokolski*, and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1968*, 2304.

[96] *G. A. Sokolski, M. A. Belaventsev*, and *L. I. Ragulin*, USSR author's certificate 193474 (1965).

[97] *G. A. Sokolski* and *I. L. Knunyants*, USSR author's certificate 139308 (1960).

[98] *G. A. Sokolski* and *I. L. Knunyants*, Izv. Akad. Nauk SSSR, Ser. Khim. *1968*, 843.

Metal-Olefin and -Acetylene Bonding in Complexes

By Frank R. Hartley[*]

The molecular orbital (MO) and valence bond (VB) descriptions of the bonding in metal-olefin and -acetylene complexes are examined in relation to their ability to explain the known properties of these complexes. It is concluded that whereas there are difficulties with the valence bond description, the molecular orbital description can satisfactorily explain all the known properties of these complexes and has the necessary versatility to enable it to be readily applied to any series of metal-olefin or -acetylene complexes. It is further shown that olefin and acetylene complexes can be usefully divided into two main classes: those that resemble the platinum(II)-complexes (class S), and are either square-planar or octahedral with essentially free rotation about the metal-olefin bond; and those that resemble platinum(0)-complexes (class T) and are either trigonal planar or trigonal bipyramidal and in which there is no rotation about the metal-olefin or -acetylene bond.

1. Introduction

The metal-olefin bond is usually described in molecular orbital terms using the theory which *Dewar*[1] put forward for silver(I)-olefin complexes and which *Chatt* and *Duncanson*[2] subsequently extended to include platinum(II)-olefin complexes. The bonding, according to the Dewar-Chatt-Duncanson model essentially involves a σ-bond, from the filled $p\pi$-orbital of the olefin to an empty hybrid orbital on the metal, complemented by a π-back bond, from a filled hybrid orbital on the metal to the empty $p\pi^*$-(antibonding)-orbital of the olefin. In this bonding scheme the olefin is formally neutral and the platinum in the +2 oxidation state.

Gel'man[3] has put forward an alternative description of the bonding within the framework of the VB theory. This involves two platinum-carbon σ-bonds giving a three membered  ring. In this bonding scheme the olefin carries a formal 2− charge and the platinum is in the +4 oxidation state. Although this description of the bonding went out of favor after the Dewar-Chatt-Duncanson description was put forward, it has recently been revived to explain some of the properties of metal-olefin complexes that were apparently hard to explain on the Dewar-Chatt-Duncanson theory.

The present paper effectively falls into three parts. In the first part (Section 2) the more important properties of platinum(II)-olefin and -acetylene complexes, together, where appropriate, with their palladium(II) and nickel(II) analogs, are put forward. The molecular orbital and valence bond descriptions are then examined to see how they can explain these properties. It will then be shown that a molecular orbital description, modified slightly from the rather rigid scheme put forward initially, can explain all the presently observed phenomena and further that this description has greater flexibility than the valence bond description.

In the second part (Section 3) the same treatment is accorded to platinum(0)-olefin and -acetylene complexes, together, where appropriate, with their palladium(0) and nickel(0) analogs. Again it will be shown that all the current experimental data can be understood in terms of the molecular orbital approach, which because of this and its greater flexibility is considered to be the more useful description of the bonding.

In the third part (Section 4) the more important properties of the olefin and acetylene complexes of the other transition metals are examined and it is shown that the complexes fall into one of two classes. One class, class S, resemble the platinum(II) complexes and the other, class T, the platinum(0) complexes[*].

Throughout this paper only monoolefins and occasionally non-conjugated diolefins are considered because the bonding in conjugated polyolefin-metal complexes is considerably more complex and less well understood owing to the greater number of olefin orbitals that must be considered.

2. Platinum(II)-Olefin and -Acetylene Complexes

2.1. Experimental Observations

In this section are listed the more important experimental observations on platinum(II)-olefin and -acetylene complexes that any successful description of the bonding must be able to account for. Where appropriate the properties of the palladium(II) and nickel(II) analogs are also considered.

1. The structure of the olefin or acetylene is modified only slightly on coordination. Although platinum(II)-olefin and -acetylene complexes have been widely investigated by X-ray diffraction there are many difficulties, which have been summarized by the present author[4]. These have led

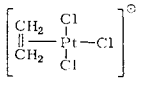
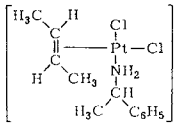
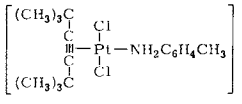
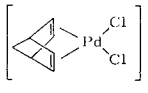
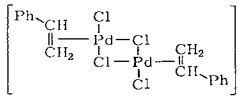
[*] Dr. F. R. Hartley
Department of Chemistry
The University
Southampton SO 9 5NH (England)

[*] These two classes and the significance of S and T are discussed in Section 4.4.

to a number of inaccurate results being published. However, a survey of the more accurate results (Table 1) suggests that on coordination there is a very slight lengthening of the multiple-bond and that the substituents are bent out of the plane of the multiple-bond away from the metal.

surprising, since it would be anticipated that with such a low energy barrier to free rotation crystal forces would lead to a distortion from 90°. The more accurate results obtained recently indicate angles slightly different from 90° (see Table 1).

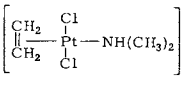
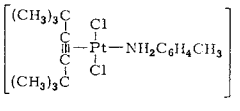
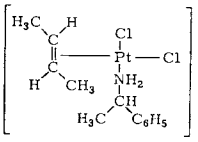
Table 1. Bond lengths and angles in olefins and acetylenes coordinated to platinum(II) and palladium(II).

Complex	Multiple bond length (Å)		Angle that alkyl substituent is bent out of the plane of the multiple bond (°)	Angle between C≡C axis and square plane (°)	Ref.
	Coord.	Free			
	1.37	1.335	—	84	[5]
	1.36	1.339	13	77	[6]
	1.24	1.20	16.5	85	[7]
	1.37		—	90	[8]
	1.32		—	89	[9]

2. The energy barrier to free rotation of the olefin about the platinum(II)-olefin bond is low[10-12], generally lying between 10 and 15 kcal/mol. This observation makes the early reports that the plane of the multiple bond is perpendicular to the square-plane surrounding the platinum atom

3. The olefin can twist slightly about the carbon-carbon double-bond axis. This is indicated by the lower ^{195}Pt-^{1}H coupling constant in the NMR spectrum of the proton *cis* to the methyl group in $[Pt(CH_3CH{=}CH_2)Cl_3]^-$ than of the *trans*-protons[13].

Table 2. Platinum-ligand bond lengths *trans* to olefins.

Metal-ligand bond	Bond length (Å)	Ref.	Comparison metal-ligand bond	Bond length (Å)	Ref.
Pt—N in 	2.02	[20]	Pt—N in *cis*-$[Pt(NH_3)_2Cl_2]$	2.01	[21]
Pt—N in 	2.10	[7]	Pt—N in *trans*-$[Pt(NH_3)_2Cl_2]$	2.05	[21]
Pt—Cl in $[Pt(dipentene)Cl_2]$	2.33	[22]	Pt—Cl in *cis*-$[Pt(NH_3)_2Cl_2]$	2.33	[21]
Pt—Cl *trans* to C_2H_4 in $[Pt(C_2H_4)Cl_3]^-$	2.33	[5]	Pt—Cl in *trans*-$[Pt(NH_3)_2Cl_2]$	2.32	[21]
Pt—Cl in 	2.35	[6]			

4. The NMR spectra show that both the *cis* and the *trans* proton-proton coupling constants of olefins decrease on coordination to platinum suggesting that the sp^2 hybridization of the carbon atoms of the free olefin has altered slightly towards sp^3 hybridization[12,14].

5. The infrared spectra indicate that the C=C stretching frequency[15,16] of olefins decreases by about 300 cm^{-1} and the C≡C stretching frequency[17] of acetylenes decreases by about 250 cm^{-1} on coordination to platinum(II). The value quoted here for olefins is that originally suggested by *Babushkin et al.*[18], but rejected by subsequent workers in favor of a decrease of about 140 cm^{-1} on coordination to platinum(II) until the recent reinvestigation of the IR and Raman spectra of Zeise's salt and its deuterated ethylene analog by *Hiraishi*[15].

6. Olefins exert a strong *trans*-effect as deduced from their influence on the substitution of ligands in the *trans*-position[19]. As mentioned above, much of the data on platinum(II)-olefin complexes obtained by X-ray diffraction is of doubtful accuracy, but the more accurate results (see Table 2) do suggest that olefins have little or no *trans*-influence as deduced from the lengths of the platinum-ligand bonds *trans* to olefins.

2.2. Description of Bonding

If the *x*, *y*, and *z* axes are those shown in Figure 1, then the original molecular orbital treatment[1,2] envisaged a σ-(olefin to platinum) bond being formed by donation of charge from the full pπ-orbital on the olefin to the empty $5d_{z^2}$ $5d_{x^2-y^2}$ 6s $6p_z$ hybrid orbital on platinum and a π-(platinum to olefin) bond being formed by back-donation of charge from the $5d_{yz}$ $6p_y$ hybrid orbital on platinum to the empty pπ*-(antibonding) orbital on the olefin. This bonding scheme required the olefin to be bound perpendicularly to the square-plane surrounding the platinum and the early X-ray structures seemed to support this[23]. However, subsequent NMR evidence suggested that the energy barrier to free rotation of the olefin about the platinum-olefin bond was low[10-12]. This can be accounted for by allowing the π-back donation to occur from either the $5d_{yz}$ $6p_y$ hybrid orbital or the $5d_{xz}$ orbital on platinum (the $6p_x$ orbital is not available for hybridization as it is involved in bonding to the *cis*-chloride ligands). Since calculations have shown[24] that d_π—p_π hybridization involving an unoccupied p-orbital can lead to a strengthened metal-ligand π-bond by increasing the overlap power of the metal

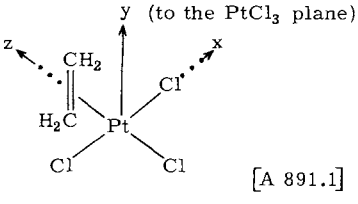


Fig. 1. Axes used in discussing platinum(II)-olefin complexes.

d_π-orbital, and that only a small amount of p character need be added to the d-orbital for this effect to be noticed, it is anticipated that the $5d_{xz}$ orbital will give less overlap with the olefin pπ*-(antibonding) orbital than the $5d_{yz}$ $6p_y$ hybrid orbital. Consequently use of the $5d_{xz}$ orbital not only accounts for the observation of rotation about the metal-olefin bond but also explains why the perpendicular arrangement of the C=C double-bond (with respect to the square-plane through the Pt atom and the Cl atom) is the most stable. This argument has recently[25,26] been put on a semiquantitative basis by calculating the total energy of the complex *trans*-$[Pt(NH_3)Cl_2(C_2H_4)]$ as a function of the angle between the C=C double-bond axis and the $PtNCl_2$ plane. The results show a deep energy minimum when this angle is 90°, which corresponds to the position necessary for maximum π-back donation from the $5d_{yz}$ $6p_y$ orbital of the platinum and a shallow minimum when the angle is 0°, which corresponds to the position necessary for maximum π-back donation from the $5d_{xz}$ orbital of the platinum.

Recent molecular orbital calculations[27,28] have indicated that the platinum 6s orbital is not significantly involved in the bonding. This has necessitated modification of the empty acceptor orbital on the metal from d^2sp to d^2p^2.

The molecular orbital treatment, as outlined above, accounts for the slight weakening of the olefinic double-bond on coordination, as required by the X-ray and IR studies, since both loss of electron density from the olefin pπ-(bonding) orbital and gain of electron density in the olefin pπ*-(antibonding) orbital will result in a weakening of the C=C double-bond.

The bonding in platinum(II)-acetylene complexes is formally similar to that in platinum(II)-olefin complexes. The two perpendicular pπ-orbitals of the acetylene interact to give a cylindrically symmetric bond[29] which forms a σ-bond in a similar way to the olefin to platinum σ-bond. The platinum to acetylene π-bond is similarly analogous to the corresponding bond in the olefin complexes.

The high *trans* effect of olefins is readily explained, as described previously by the present author[4], by the above bonding scheme in terms of the π-bonding mechanism for the *trans* effect[30]. The negligible *trans* influence of olefins, where the *trans* influence is defined as the tendency of a ligand to weaken the bond *trans* to itself[31,32], arises naturally from the bonding scheme described above, since ligands which exert their *trans* effect by a π-acceptor mechanism will only cause weakening of the *trans* bond if this bond has a π-component. If there is no π-component (*e.g.* in Pt—N) or only weak π-bonding (*e.g.* in Pt—Cl) in the *trans* bond then that bond may either not be weakened or even be strengthened[33].

The experimental material discussed so far has been that traditionally used to support the molecular orbital description of the bonding. It is important, however, to consider how the molecular orbital description accounts for (i) the bending back of substituents out of the plane of the multiple bond away from the metal, (ii) the lowering of the double-bond stretching frequency from that of an olefin to a value half-way between that of an olefin and an alkane and (iii) the reduction that occurs on coordination of the *cis* and

trans proton-proton coupling constants in the NMR spectra. All these experimental results have been used to advocate a greater or lesser modification of the sp^2 hybridization of the carbon atoms of free olefins towards sp^3 hybridization on coordination. To include these results within the molecular orbital description it is necessary to consider what the bonding scheme would look like if the olefinic carbon atoms were to be completely rehybridized to sp^3. In such a case the olefin is considered to be a dicarbanion and the platinum atom to be formally in the +4 oxidation state. Although superficially this appears to be very different from the σ-donation/π-back donation scheme discussed above, in reality the two approaches merge. This can be seen from Figure 2, which shows the effect on the distribu-

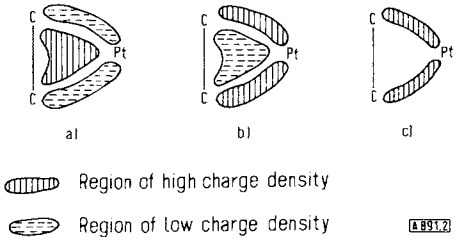


Fig. 2. Effect of varying the relative importance of the σ- and π-components of the platinum(II)-olefin bond on the density of the charge between the olefin and platinum.
(a) sp^2 hybridized carbon atoms with a strong σ-(olefin to platinum)-component and a weak π-(platinum to olefin)-component in the platinum-olefin bond. (b) sp^2 hybridized carbon atoms with a weak σ-component and a strong π-component in the platinum-olefin bond. (c) sp^3 hybridized carbon atoms.

tion of electron density in the region between the metal and the olefin when the relative importance of the σ- and π-components of the metal-olefin bond are altered. The two extremes, (a) and (c), involve a migration of electron density from inside the Pt  triangle, where it is located for sp^2 hybridized carbon atoms which give strong σ-donation and weak π-acceptance of electron density, to the edges of the Pt  triangle, where it is located for sp^3 hybridized carbon atoms. A carbon hybridization scheme mid-way between sp^2 and sp^3 would give an electron density distribution mid-way between these two extremes. This mid-way point coincides with that for an sp^2 hybridization scheme in which the π-back donation of charge (from platinum to olefin) is as important as or more important than the σ-donation of charge (from olefin to platinum). There is some evidence, such as that from stability constant studies for platinum(II)-olefin complexes[34], that the π-back donation of charge is more important than the σ-donation for the formation of a stable platinum(II)-olefin bond (*i.e.* the situation shown in Figure 2b).

The electron density distribution around the olefin shown in Figure 2b accounts for the reduced proton-proton coupling constants observed in the NMR spectra of coordinated olefins, which have been quoted as evidence for some sp^3 hybridization on the olefinic carbon atoms[12, 14]. The bonding scheme in Figure 2b can also account for the substituents R (where R = H or a more bulky group) on the multiple bond being bent out of the plane of the multiple bond away from the metal, since on going from the situation in Figure 2a to that in Figure 2b the electron density is shifted towards the C—R bonds. This will repel the C—R bond by bond-pair/bond-pair repulsion so forcing R away from the metal[35]. When this purely qualitative argument was examined semi-quantitatively using the CNDO-MO theory (Complete Neglect of Differential Overlap Molecular Orbital Theory) it was shown that for acetylenes addition of electron density to the pπ*-(antibonding) orbital of the multiple bond must cause either *cis*- or *trans*-bending of the substituents. *Cis*-bending is favored by both non-bonded interactions between the substituents and the central metal group, and by the fact that it enables the s-orbitals of the acetylene to assume the correct symmetry to contribute to the bonding[36]. Other explanations for the *cis*-bending of the substituents, that are in effect equivalent to the present one, consider the coordinated olefin or acetylene to be in an excited state[37, 38]. However, there is some disagreement as to the description of the excited state[37–39].

2.3. Summary

In conclusion, the σ-donation/π-back donation molecular orbital description of the bonding in platinum(II)-olefin and -acetylene complexes can explain all the known properties of these complexes. There is no necessity to invoke changes of hybridization of the olefinic carbon atoms from sp^2 to sp^3, since the same effect can be obtained by altering the relative importance of the σ- and π-components of the metal-olefin bond.

3. Platinum(0)-Olefin and -Acetylene Complexes

3.1. Experimental Observations

The more important experimental observations that any satisfactory description of the bonding in the zerovalent olefin and acetylene complexes of platinum, palladium and nickel must be able to explain are as follows:

1. The multiple bond is weakened and lengthened on coordination. This is indicated by the bond lengths of coordinated olefins and acetylenes as determined by X-ray diffraction (Table 3) and also by the lowering of the C≡C stretching frequency of acetylenes by about 500 cm^{-1} on coordination[47].

2. X-ray diffraction studies have shown that the axis of the multiple bond lies close to the plane containing the platinum and the other ligands. Values of between 8 and 14° have been reported for the dihedral angle α (Figure 3 and Table 3). The angle β (Figure 3) which the multiple bond subtends at the platinum atom is about 40° (Table 3).

3. X-ray diffraction studies have indicated that the substituents bound to the multiple bond are bent out of the plane of this bond away from the platinum atom (Table 3).

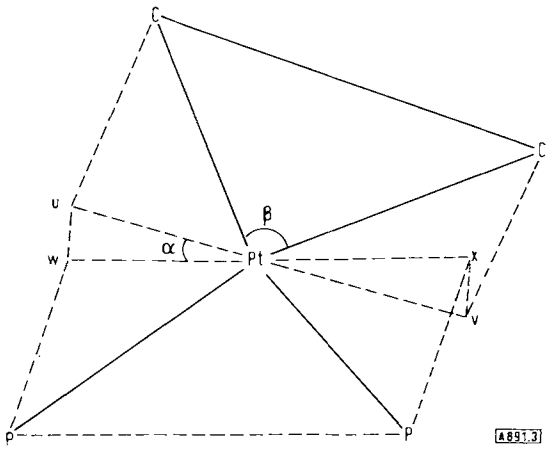


Fig. 3. The structure of olefin and acetylene complexes of platinum(0). The plane containing the points u, v, w and x together with the Pt atom is perpendicular to both the PtCC and PtPP planes.

Table 3. Results of X-ray diffraction studies of platinum(0) complexes.

Complex	C=C or C≡C Bond length (Å)		α [a]	Angle [°] β [a]	γ [b]	Ref.
	Complex	Free				
$[(PPh_3)_2Pt(TCNE)]$ [c]	1.49	1.34	8.3	41.5	32.5	[40, 41]
$[(PPh_3)_2Ni(C_2H_4)]$ [d]	1.46	1.33	12	42		[42]
$[(PPh_3)_2Pt(NC—C=C—CN)]$	1.40	1.19	8			[43]
$[(PPh_3)_2Pt(PhC\equiv CPh)]$	1.32	1.19	14	39	40	[44]
$[(^tBuNC)_2Ni(TCNE)]$ [c]	1.48	1.34	23.9	44.4	28.4	[45]

[a] See Figure 1 for definition of α and β.
[b] γ = angle by which substituents are bent out of the plane of the multiple bond away from the platinum atom.
[c] TCNE = tetracyanoethylene.
[d] Isomorphous with platinum(0) analog [46].

4. Olefins and acetylenes in which strongly electron-withdrawing substituents are bound direct to the multiple bond give more stable complexes than olefins with less electron-withdrawing substituents. This is indicated firstly by the decrease in the thermal stability of $[(PPh_3)_2Pt(R_2C=CR_2)]$ in the order R = CN (decomp. point 268—270 °C[48]) > R = F (decomp. point 218—220 °C[49]) > R = H (decomp. point 122—125 °C[50]), and secondly by studies of equilibrium (1), which showed that the position of the equilibrium favors the formation of the platinum(0) complex with the acetylene containing the most electron-withdrawing substituents (ac and ac' are substituted acetylenes)[51, 52].

$$[(PPh_3)_2Pt(ac)] + ac' \rightleftharpoons [(PPh_3)_2Pt(ac')] + ac \quad (1)$$

5. The melting-points of the complexes $[(PPh_3)_2Pt(olefin)]$, which vary from 122—125 °C for the ethylene complex to 268—270 °C for the tetracyanoethylene (TCNE) complex[53], are relatively high indicating the considerable thermal stability of the complexes.

6. The observation of two separate coupling constants between the methyl group and the phosphorus atoms in the NMR spectrum[54] of $[(PPh_3)_2Pt(PhC\equiv CCH_3)]$ and the inequivalence of the two phosphorus atoms[55] in $[(PPh_3)_2Pt(CF_2{=}CFX)]$ (where X = Cl or CF_3) both indicate that rotation of the olefin or acetylene about the platinum(0)-olefin or -acetylene bond is slow relative to the NMR time scale (*i.e.* less than 1.2 s^{-1}). Further similar NMR evidence on related complexes supports these observations[56, 57].

7. The geminal fluorine-fluorine coupling constant in the NMR spectrum of $[(PPh_3)_2Pt(CF_3—CF=CF_2)]$ is of the same order as in a saturated fluorocarbon, which suggests sp^3 hybridization of the "olefinic" carbon atoms[49].

3.2. Molecular Orbital Treatment of the Bonding

The observations firstly that olefins and acetylenes in which strongly electron-withdrawing substituents are bound direct to the multiple bond give more stable complexes than ligands with less electron-withdrawing substituents and secondly that percyano-olefins and -acetylenes, which are known to be very good π-acceptor ligands but poor σ-donors, form stable complexes with platinum(0) suggest that if the bonding in platinum(0)-olefin complexes is described in terms of the Dewar-Chatt-Duncanson model[1, 2] it would be expected that the π-bond (from platinum(0) to the unsaturated ligand) would be fairly strong whereas the σ-bond (from the unsaturated ligand to platinum(0)) would be almost non-existent. This would lead to a substantial increase in the electron density in the pπ*-(antibonding) orbitals of the olefin or acetylene which would weaken and lengthen the multiple-bond as is observed (cf. Section 3.1). Furthermore, molecular orbital calculations have shown that addition of electron density to the pπ*-(antibonding) orbital of TCNE will increase the bond-order of the C—CN bond[58]. The decrease of the C—CN bond length from 1.449 Å in free TCNE[59] to 1.41 ± 0.04 Å on coordination to platinum(0)[40, 41] is thus consistent with the Dewar-Chatt-Duncanson model. The observation that the substituents attached to the multiple bond are bent out of the plane of this bond away from the platinum atom is also consistent with a substantial electron density in the pπ*-(antibonding) orbitals of the ligand, as discussed above in connection with platinum(II) complexes.

The near planarity of platinum(0)- and nickel(0)-olefin and -acetylene complexes (see Table 3 and Figure 3) as opposed to the almost perpendicular arrangement of the multiple-bond in relation to the square-plane around the platinum atom in the divalent complexes is readily explained by the

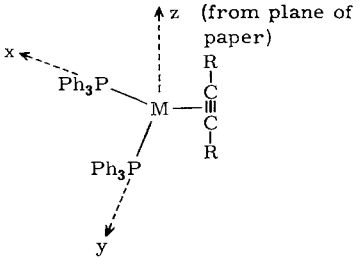
molecular orbital treatment. Zerovalent platinum complexes are tetrahedral (*e.g.* $[(PPh_3)_3Pt(CO)]$[60,61] and $[Pt(PF_3)_4]$[62]) because for a d^{10} atom there is no difference in the ligand field stabilization energies between a square-planar and a tetrahedral arrangement so that the ligands arrange themselves as far apart as possible (*i.e.* tetrahedral) to minimize bond-pair/bond-pair repulsion energies[35]. However, in an olefin or acetylene complex, where the π-back donation of charge from metal to olefin is large and the σ-donation from olefin to metal is small, there will be rather less than ten d-electrons around the platinum atom. This will lead to a Jahn-Teller distortion in which the tetrahedron is flattened, thus increasing the energy of one of the t_{2g} orbitals, which is left partly empty, and decreasing the energy of two of the t_{2g} orbitals, which are left full, relative to the energies in an undistorted tetrahedral environment[63].

The molecular orbital explanation for the observation that the geminal fluorine-fluorine coupling constant in the NMR spectrum of $[(PPh_3)_2Pt(CF_3—CF=CF_2)]$ is of the same order as in a saturated fluorocarbon is the same as advanced above for a similar observation with platinum(II) complexes (cf. Figure 2 and the related discussion).

The absence of free rotation of the olefin or acetylene about the platinum(0)-olefin or -acetylene bond arises because the platinum $6p_z$ and $5d_{z^2}$ orbitals are not readily available for back-donation to the unsaturated ligands because they are involved in back-donation to the triphenylphosphane ligands. Thus the flattened tetrahedral structure, in which the back-donation occurs from the $d_{x^2-y^2}$ orbital[27,28], is considerably more stable than any other arrangement, so preventing the occurrence of free rotation about the platinum(0)-olefin or -acetylene bond. This argument has recently[25,26] been put on a semi-quantitative basis by calculating the total energy of the complexes $[(PH_3)_2Pt(CH_3C{\equiv}CCH_3)]$ and $[(PH_3)_2Pt(C_2H_4)]$ as a function of the angle between the multiple bond axis and the PtP_2 plane. The results show a single minimum when the multiple bond lies in the PtP_2 plane. The fact that these calculations predict a minimum energy when the dihedral angle α (see Figure 3) is zero is probably an indication of the approximate nature of the calculations rather than an indication of the importance of crystal packing effects in the solid state, since crystal packing effects would be expected to vary markedly over the range of complexes shown in Table 3, whereas, with the exception of $[(t\text{-BuNC})_2Ni(TCNE)]$ the complexes show a remarkably constant value of α.

Recent molecular orbital calculations[27,28] have reinforced the conclusion mentioned above that the strength of the metal(0)-olefin or -acetylene interaction is strongly dependent on the amount of π-back donation from the metal. These calculations also indicated that the metal s-orbital was not involved to any significant extent in bonding. When group theory was used to develop a new bonding model that was consistent with this the bonding scheme in Table 4 was obtained.

Table 4. Orbitals involved in the bonding in metal(0)-olefin and -acetylene complexes.



Type of bonding	Orbitals involved in olefin complexes	Orbitals involved in acetylene complexes
σ-donation to the metal	From π-orbital of olefin to dp^2 ($d_{xy}+p_x+p_y$) hybrid on metal	(1) From π_{xy}-orbital of acetylene to dp^2 ($d_{xy}+p_x+p_y$) hybrid on metal. (2) From π_z-orbital of acetylene to d^2 ($d_{xz}+d_{yz}$) hybrid on metal.
π-back donation from the metal	From $d_{x^2-y^2}$ orbital on metal to π^*-(antibonding) orbital on olefin	(1) From $d_{x^2-y^2}$ orbital on metal to π^*_{xy}-(antibonding) orbital on acetylene. (2) From d^2 ($d_{xz}+d_{yz}$) hybrid on metal to π^*_z-(antibonding) on acetylene.

3.3. Valence Bond Treatment of the Bonding

In the valence bond description the olefin or acetylene is considered to be a dicarbanion which forms two σ-bonds to platinum, which is itself in the +2 oxidation state. This description can readily account for the following experimental observations:

1. The substituents at the multiple bond are bent away from the platinum atom on coordination. This would be an immediate consequence of the rehybridization of the carbon atoms from the sp^n to the sp^{n+1} arrangement necessary for the formation of two platinum-carbon σ-bonds ($n=1$ for acetylenes and $n=2$ for olefins). However, if the carbon atoms of the olefin are rehybridized from sp^2 to sp^3 on coordination, then the angle γ in Table 3 should be 54°44′. Since the observed values of γ (Table 3) are substantially less than 54°44′, the argument in favor of sp^3 hybridization does not appear to be warranted, particularly

in view of the ease with which the MO theory can interpret the experimentally observed values of γ.

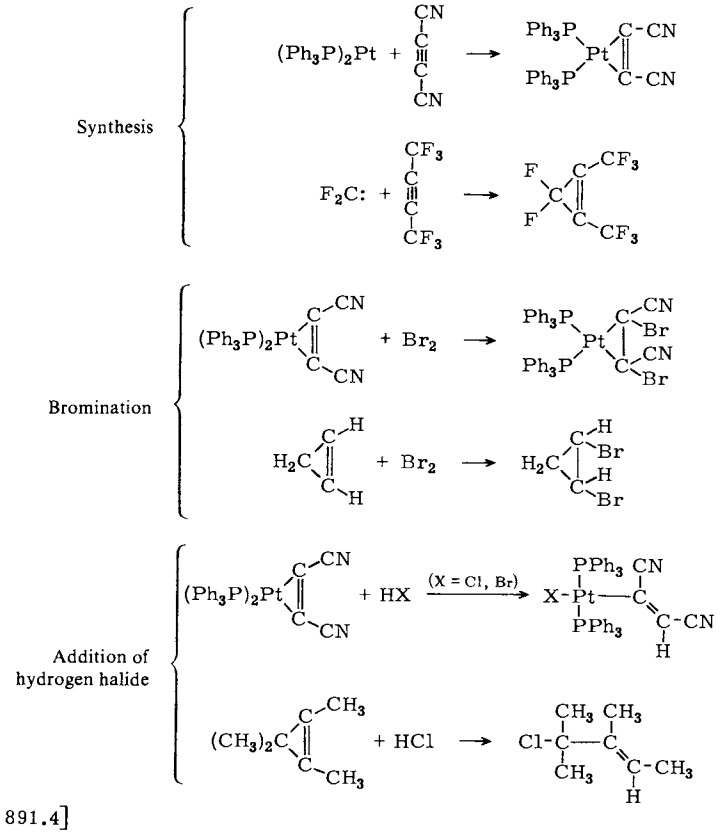
2. The geminal fluorine-fluorine coupling constant in the NMR spectrum of $[(PPh_3)_2Pt(CF_3{-}CF{=}CF_2)]$ is of the same order as in a saturated fluorocarbon, which suggests sp^3 hybridization of the "olefinic" carbon atoms and hence platinum-carbon σ-bonds[49].

3. There is no free rotation of the olefin or acetylene about the metal-olefin or -acetylene bond.

4. The VB treatment is useful in accounting for the analogies between the acetylene complexes and cyclopropenes as shown in the preparation, bromination, and addition of hydrogen halide reactions given below[64].

and rehybridization of the carbon atoms of the multiple bond[66], has recently been criticized on the grounds that the actual twisting is very small, even in $[(t\text{-BuNC})_2Ni(TCNE)]$ where the largest value of α yet observed was found[45].

2. The small values observed for the C—Pt—C angle (β in Figure 3) together with the values of about 70° observed for the C—C—Pt angle, which are in contrast to the optimum C—C—Pt angle of 109°28′ for the formation of a strong σ-bond, suggest that the three-membered  ring would be very strained. However, since the melting points of the $[(PPh_3)_2Pt(olefin)]$ complexes vary from



[A 891.4]

However, whilst the valence bond conception provides a useful way of looking at these reactions, the mechanisms of the bromination and hydrohalogenation reactions are not yet sufficiently well understood to know if the structural and mechanistic implications of the valence bond formulation are valid.

In spite of the apparent successes just listed, the valence bond description is hard pressed to account for the following experimental observations:

1. The angle α in Figure 3 generally lies between 8° and 14°. To account for this it is necessary to assume that the eclipsed position of the substituents on the multiple-bond is sufficiently unstable to cause the sp^3 hybrid orbitals to rotate towards the staggered position[65]. However, these substituents are sufficiently remote from each other for this to be rather unlikely. A suggestion, similar to the present one, that the values of α arise from a combination of twisting

122—125°C for the ethylene complex to 268—270°C for the TCNE complex[53], there would not appear to be as much strain as is suggested by these small angles.

3.4. Summary

The MO and VB descriptions of the bonding in the zerovalent complexes are equivalent in that both predict that the platinum atom has less than ten 5d-electrons (*i.e.* is formally in a positive oxidation state) and that the coordinated unsaturated ligand has a higher electron density around it than when it is free. In addition, both theories suggest that the bulk of the electron density in the platinum-olefin or -acetylene bond lies along the edges of the  triangle rather than in the center of this triangle (cf. Fig. 2c).

The MO description has two important advantages over the VB description. Firstly it can readily explain all the experimental observations reported to date for these complexes whereas the valence bond description cannot, and secondly its flexibility in terms of variations of the relative strengths of the σ- and π-components of the metal-olefin bond allows essentially the same bonding description to be used for the complexes of a whole series of metals.

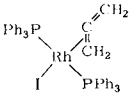
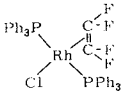
4. Olefin and Acetylene Complexes of Other Metals

In the present section the physical properties of olefin and acetylene complexes of the transition metals other than nickel, palladium, and platinum are considered. It is immediately apparent that the depth of study that has so far been accorded to these complexes is slight relative to that given to the complexes of nickel, palladium, and platinum.

4.1. X-Ray Diffraction Studies

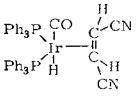
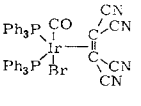
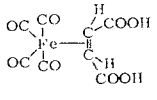
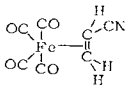
The structural data obtained from X-ray diffraction, summarized in Tables 5 and 6, is similar in its consequences for the bonding scheme to that in Tables 1 and 3. Thus in all the complexes the multiple-bond increases in length on coordination and where they have been observed the substituents attached to the multiple bond have been found to be bent out of the plane of that bond away from the metal atom. In the square-planar rhodium(I) complexes (Table 5) the olefin axis is approximately perpendicular to the ligand plane as found in the square-planar platinum(II) complexes reported in Table 1, whereas in the trigonal-bipyramidal

Table 5. Structural data on square-planar [a] rhodium(I)-olefin complexes.

Complex	Structure	Multiple bond length (Å) Complex	Free	Angle (°) between C=C axis and square plane	Ref.
$[RhI(PPh_3)_2(C_3H_4)]$		1.35	1.31 [b]	76	[67]
$[RhCl(PPh_3)_2(C_2F_4)]$		1.41	1.31 [c]	Approx. perpendicular	[68]

[a] $[RhCl(PPh_3)_2(C_2F_4)]$ is substantially distorted from square-planar towards a tetrahedral arrangement.
[b] Ref. [69].
[c] Ref. [70].

Table 6. Structural data on trigonal bipyramidal iridium(I) and iron(0) olefin complexes.

Complex	Structure	Multiple bond length (Å) Complex		Free	γ [a] (°)	Ref.
$[IrH(CO)(PPh_3)_2(FUMN)]$ [b]		1.43		—	—	[71]
$[IrBr(CO)(PPh_3)_2(TCNE)]$ [c]		1.51		1.34	35	[71]
		1.42	(racemic isomer)	1.35 [d]	—	[72]
$[Fe(CO)_4(C_4H_4O_4)]$		1.40	three crystallographically independent optically active isomers	1.35 [d]	26	[73]
		1.30		1.35 [d]	27	[73]
		1.40		1.35 [d]	37	[73]
$[Fe(CO)_4(C_3H_3N)]$		1.40		1.34	—	[74]

[a] γ = angle by which the substituents are bent out of the plane of the double-bond.
[b] FUMN = fumaronitrile.
[c] TCNE = tetracyanoethylene.
[d] Reference [75].

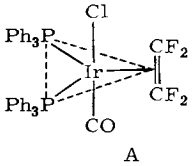
complexes (Table 6) the olefins lie in or nearly in the trigonal plane, which is similar to the arrangement in the zerovalent complexes reported in Table 3.

The X-ray diffraction studies that have been reported so far thus provide no information which cannot be accounted for in the molecular orbital description of the bonding as outlined above for divalent and zerovalent complexes of platinum.

4.2. NMR Studies

The temperature dependence of the ^{1}H-NMR spectrum of $[(\pi\text{-}C_5H_5)Rh(C_2H_4)_2]$ can best be understood in terms of free rotation about the rhodium-ethylene σ-bond axis with a rotational energy barrier of about 6 kcal/mol[76]. This can be understood in an essentially similar way to the rotation of olefins about the metal-olefin bond in platinum(II) complexes discussed above, and therefore once again does not introduce any new experimental data that the MO bonding scheme cannot accommodate.

A study of the ^{19}F-NMR spectra of the fluoro-olefin complexes of rhodium(I), iridium(I) and nickel(0) has shown that these fall into two main series[77]. In the first series, typified by $[Rh(acac)(C_2F_4)]$ and $[Ni(PPh_3)_3(C_2F_4)]$, all the fluorine atoms absorb in the same region suggesting a square-planar structure with free rotation about the metal-tetrafluoroethylene bond. This structure is of course analogous to that found for platinum(II) complexes. In the second series, typified by $[Rh(acac)(n\text{-}C_5H_{11}NC)(C_2F_4)]_2$ and $[IrCl(CO)(PPh_3)_2(C_2F_4)]$, two fluorine resonances were observed indicating the presence of two sets of fluorine atoms in chemically non-equivalent environments. By analogy with $[IrCl(CO)(PPh_3)_2(TCNE)]$ the structure of the iridium(I) complex is probably trigonal bipyramidal:



A

If the tetrafluoroethylene molecule lies in the trigonal plane and if there is no rotation about the iridium(I)-tetrafluoroethylene bond two ^{19}F-NMR signals would be expected. This structure, as already pointed out in Section 4.1, is analogous to the structure found in zerovalent platinum complexes. Thus these ^{19}F-NMR results substantiate the conclusion reached above from the X-ray diffraction results that olefin complexes fall into two main classes, those formally analogous in structure and bonding to the square planar platinum(II) complexes and those formally analogous to the platinum(0) complexes.

4.3. Infrared Studies

The IR spectra of olefin complexes indicate that the double-bond stretching frequency decreases on coordination, although, as mentioned above, the absolute magnitudes of the values which are quoted in Table 7 may be open to some doubt due to the problem of coupling of the $>CH_2$ deformation mode with the C=C stretching mode. What is certain is that there is a decrease in the C=C stretching frequency on coordination in agreement with the predictions of the MO bonding scheme.

Table 7. Stretching frequencies for the double bond of ethylene.

Metal	Complex	$\nu_{C=C}$ (cm^{-1})	Ref.
None	C_2H_4	1623	[78]
Mo	$[(\pi\text{-}C_5H_5)Mo(CO)_3(C_2H_4)]$	1511	[79]
W	$[(\pi\text{-}C_5H_5)W(CO)_3(C_2H_4)]$	1510	[79]
Mn	$[Mn(CO)_5(C_2H_4)]^{\oplus}$	1541	[80]
	$[(\pi\text{-}C_5H_5)Mn(CO)_2(C_2H_4)]$	1508	[81]
Re	*cis*-$[Re(CO)_4(C_2H_4)_2]^{\oplus}$	1539	[80]
Fe	$[Fe(CO)_4(C_2H_4)]$	1511	[82]
	$[(\pi\text{-}C_5H_5)Fe(CO)_2C_2H_4]^{\oplus}$	1527	[79]
Rh	$[Rh(C_2H_4)Cl]_2$	1520	[83]
	$[(\pi\text{-}C_5H_5)Rh(C_2H_4)_2]$	1493	[76]
	$[Rh(C_2H_4)_2(acac)]$ [a]	1524	[76]
Pd	$[Pd(C_2H_4)Cl_2]_2$	1527	[84]
Pt	$[Pt(C_2H_4)Cl_2]_2$	1516	[84]
		1239	[15]
	$[Pt(C_2H_4)Cl_3]$	1526	[84]
		1243	[15]
Ag	$[Ag(C_2H_4)]^+$	1583	[85]

[a] acac = acetylacetonate = 2,4-pentanedione.

When an olefin coordinates to $[IrCl(CO)(PPh_3)_2]$ there is an increase in the CO stretching frequency of the coordinated carbon monoxide ligand[86]. Furthermore, this increase is greatest for olefins with weak σ-donor but strong π-acceptor capacities (see Table 8). An increase in the CO stretching frequency of a metal-carbonyl complex indicates a reduction in the π-back donation of charge from the metal to carbon monoxide. Such a reduction in π-back donation accompanies the oxidation of a metal; for example $[IrCl(CO)(PPh_3)_2]$ containing iridium(I) has ν_{CO} equal to 1966 cm^{-1}, whereas $[IrCl_3(CO)(PPh_3)_2]$ containing iridium(III) has ν_{CO} equal to 2080 cm^{-1}. A series of complexes such as that shown in Table 8 demonstrates the advantages of the MO approach to metal-olefin bonding because of its built-in flexibility. It is apparent that as Table 8 is descended there is an increase in the relative importance of the π-component of the metal-olefin bond and a decrease in the rela-

Table 8. Carbonyl stretching frequencies for iridium complexes (from Ref. [86—88]).

Complex	Oxidation State	ν_{CO} (cm^{-1})
$[IrCl(CO)(PPh_3)_2]$	Ir^{I}	1955
$[IrCl(CO)(PPh_3)_2(CH_2{=}CHCN)]$		2017
$[IrCl(CO)(PPh_3)_2(NCC{\equiv}CCN)]$		2018
$[IrCl(CO)(PPh_3)_2(CF_3C{\equiv}CCF_3)]$		2025
$[IrCl(CO)(PPh_3)_2(NCCH{=}CHCN)]$		2029
$[IrCl(CO)(PPh_3)_2(F_2C{=}CF_2)]$		2040
$[IrCl(CO)(PPh_3)_2(TCNE)]$		2060
$[IrCl_3(CO)(PPh_3)_2]$	Ir^{III}	2080
$[IrI(CO)(PPh_3)_2(C_2H_4)]$		1937
$[IrI(CO)(PPh_3)_2(CH_2{=}CHCN)]$		1952
$[IrI(CO)(PPh_3)_2]$	Ir^{I}	1958
$[IrI(CO)(PPh_3)_2(NCCH{=}CHCN)]$		2020
$[IrI(CO)(PPh_3)_2(F_2C{=}CF_2)]$		2040
$[IrI(CO)(PPh_3)_2(TCNE)]$		2045
$[IrICl_2(CO)(PPh_3)_2]$	Ir^{III}	2074

tive importance of the σ-component of that bond which leads to an effective transition from iridium(I) to iridium(III) as the Table is descended. The strength of the MO approach lies in its relative disinterest in the oxidation state of the metal, whereas by contrast the VB approach can only draw the two extreme formulations shown in Figure 4, and then consider resonance between unequal amounts of these two canonical forms.



a) Iridium(I) b) Iridium(III)

Fig. 4. Extreme valence bond formulations for iridium-olefin complexes.

4.4. Summary

The physical properties of metal-olefin and -acetylene complexes just discussed suggest that they fall into two classes, class S and class T[*].

Class S Complexes are formally analogous in their properties and bonding to the square-planar complexes of platinum(II), discussed in Section 2 of this paper. It is also possible to have ligands above and below the square-plane and still have essentially the same properties. For example the room temperature proton NMR spectrum of the octahedral complex *cis*-$[Re(CO)_4(C_2H_4)_2]^+PF_6^-$ exhibits only the single proton signal[80] that would be consistent with the free rotation of ethylene about the metal-olefin bond found for other class S complexes.

Class T Complexes are formally analogous in their properties and bonding to the trigonal complexes of platinum(0) discussed in Section 3 of this paper. Again it is possible to have ligands coordinated above and below the trigonal plane giving trigonal bipyramidal complexes.

Thus class S complexes, as the name implies, involve three other ligands coordinated to the metal in the same plane as the unsaturated ligand, whereas class T complexes only have two other ligands in addition to the unsaturated ligand. One of the principal differences between the two classes of complexes is that whereas class S complexes exhibit free rotation of the olefin or acetylene about the metal-olefin or -acetylene bond, there is no such free rotation in the class T complexes.

5. Conclusions

It has been shown that the transition metal complexes of monoolefins and monoacetylenes fall into two main structural classes which are labeled S and T. An examination of of the description of the bonding in each of these two classes has indicated that the MO scheme is able to interpret all the experimental observations reported to date for these two classes whereas the VB description cannot. The MO scheme is simple to visualize and, since it is anticipated that the relative importance of the σ- and π-components will vary according to (i) the metal atom, (ii) the oxidation state of the metal atom, (iii) the nature of the olefin, and (iv) the nature of the other ligands present, this description of the bonding can readily be applied to all metal-olefin complexes. It should be pointed out that this scheme precludes any involvement of the carbon 2s orbital in the metal-olefin bond. As yet no evidence that unequivocally supports carbon 2s participation has been put forward.

I should like to thank Imperial Chemical Industries Limited for the award of a Research Fellowship during the tenure of which part of this work was carried out.

Received: May 21, 1971 [A 891 IE]
German version: Angew. Chem. *84*, 657 (1972)

[*] The letters S and T are taken from the square-planar and trigonal structures of the model platinum complexes.

[1] *M. J. S. Dewar*, Bull. Soc. Chim. Fr. *18*, C79 (1951).
[2] *J. Chatt* and *L. A. Duncanson*, J. Chem. Soc. *1953*, 2939.
[3] *A. D. Gel'man*, C. R. Acad. Sci. URSS *24*, 549 (1939).
[4] *F. R. Hartley*, Chem. Rev. *69*, 799 (1969).
[5] *J. A. J. Jarvis, B. T. Kilbourn*, and *P. G. Owston*, Acta Crystallogr. *B27*, 366 (1971).
[6] *E. Benedetti, P. Corradini*, and *C. Pedone*, J. Organometal. Chem. *18*, 203 (1969).
[7] *G. R. Davies, W. Hewertson, R. H. B. Mais, P. G. Owston*, and *C. G. Patel*, J. Chem. Soc. *A 1970*, 1873.
[8] *N. C. Baenziger, G. F. Richards*, and *J. R. Doyle*, Acta Crystallogr. *18*, 924 (1965).
[9] *J. R. Holden* and *N. C. Baenziger*, J. Amer. Chem. Soc. *77*, 4987 (1955).
[10] *A. R. Brause, F. Kaplan*, and *M. Orchin*, J. Amer. Chem. Soc. *89*, 2661 (1967).
[11] *C. E. Holloway, G. Hulley, B. F. G. Johnson*, and *J. Lewis*, J. Chem. Soc. *A 1969*, 53.
[12] *C. E. Holloway, G. Hulley, B. F. G. Johnson*, and *J. Lewis*, J. Chem. Soc. *A 1970*, 1653.
[13] *H. P. Fritz, K. E. Schwarzhans*, and *D. Sellmann*, J. Organometal. Chem. *6*, 551 (1966).
[14] *T. Kinugasa, M. Nakamura, H. Yamada*, and *A. Saika*, Inorg. Chem. *7*, 2649 (1968).
[15] *J. Hiraishi*, Spectrochim. Acta *25A*, 749 (1969).
[16] *J. Hiraishi, D. Finseth*, and *F. A. Miller*, Spectrochim. Acta *25A*, 1657 (1969).
[17] *E. O. Greaves* and *P. M. Maitlis*, J. Organometal. Chem. *6*, 104 (1966).
[18] *A. A. Babushkin, L. A. Gribov*, and *A. D. Gel'man*, Russ. J. Inorg. Chem., English Transl. *4*, 695 (1959).
[19] *F. Basolo* and *R. G. Pearson*: Mechanisms of Inorganic Reactions, 2nd Edn. Wiley, New York 1967, p. 355.
[20] *P. R. H. Alderman, P. G. Owston*, and *J. M. Rowe*, Acta Crystallogr. *13*, 149 (1960).
[21] *G. H. W. Milburn* and *M. R. Truter*, J. Chem. Soc. *A 1966*, 1609.
[22] *N. C. Baenziger, R. C. Medrud*, and *J. R. Doyle*, Acta Crystallogr. *18*, 237 (1965).
[23] *J. A. Wunderlich* and *D. P. Mellor*, Acta Crystallogr. *7*, 130 (1954); *8*, 57 (1955).
[24] *D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel*, and *L. E. Sutton*, J. Chem. Soc. *1954*, 332.
[25] *K. S. Wheelock, J. H. Nelson, L. C. Cusachs*, and *H. B. Jonassen*, J. Amer. Chem. Soc. *92*, 5110 (1970).
[26] *J. H. Nelson* and *H. B. Jonassen*, Coord. Chem. Rev. *6*, 27 (1971).
[27] *J. H. Nelson, K. S. Wheelock, L. C. Cusachs*, and *H. B. Jonassen*, Chem. Commun. *1969*, 1019.
[28] *J. H. Nelson, K. S. Wheelock, L. C. Cusachs*, and *H. B. Jonassen*, J. Amer. Chem. Soc. *91*, 7005 (1969).
[29] *C. A. Coulson*: Valence. Oxford University Press, London 1952, p. 193.

[30] *J. Chatt, L. A. Duncanson*, and *L. M. Venanzi*, J. Chem. Soc. *1955*, 4456.

[31] *A. Pidcock, R. E. Richards*, and *L. M. Venanzi*, J. Chem. Soc. *A 1966*, 1707.

[32] *L. M. Venanzi*, Chem. Britain *4*, 162 (1968).

[33] *D. M. Adams, J. Chatt, J. Gerratt*, and *A. D. Westland*, J. Chem. Soc. *1964*, 734.

[34] *R. G. Denning, F. R. Hartley*, and *L. M. Venanzi*, J. Chem. Soc. *A 1967*, 324.

[35] *R. J. Gillespie* and *R. S. Nyholm*, Quart. Rev. Chem. Soc. *11*, 339 (1957).

[36] *A. C. Blizzard* and *D. P. Santry*, J. Amer. Chem. Soc. *90*, 5749 (1968).

[37] *R. Mason*, Nature *217*, 543 (1968).

[38] *R. McWeeny, R. Mason*, and *A. D. C. Towl*, Discuss. Faraday Soc. *47*, 20 (1969).

[39] *J. N. Murrell*, Discuss. Faraday Soc. *47*, 59 (1969).

[40] *C. Panattoni, G. Bombieri, U. Belluco*, and *W. H. Baddley*, J. Amer. Chem. Soc. *90*, 798 (1968).

[41] *G. Bombieri, E. Forsellini, C. Panattoni, R. Graziani*, and *G. Bandoli*, J. Chem. Soc. *A 1970*, 1313.

[42] *C. D. Cook, C. H. Koo, S. C. Nyburg*, and *M. T. Shiomi*, Chem. Commun. *1967*, 426.

[43] *C. Panattoni* and *R. Graziani* in *M. Cais:* Progress in Coordination Chemistry. Elsevier, London 1968, p. 310.

[44] *J. O. Glanville, J. M. Stewart*, and *S. O. Grim*, J. Organometal. Chem. *7*, P9 (1967).

[45] *J. K. Stalick* and *J. A. Ibers*, J. Amer. Chem. Soc. *92*, 5333 (1970).

[46] *C. D. Cook* and *G. S. Jauhal*, J. Amer. Chem. Soc. *90*, 1464 (1968).

[47] *J. L. Boston, S. O. Grim*, and *G. Wilkinson*, J. Chem. Soc. *1963*, 3468.

[48] *W. H. Baddley* and *L. M. Venanzi*, Inorg. Chem. *5*, 33 (1966).

[49] *M. Green, R. B. L. Osborn, A. J. Rest*, and *F. G. A. Stone*, Chem. Commun. *1966*, 502.

[50] *C. D. Cook* and *G. S. Jauhal*, Inorg. Nucl. Chem. Lett. *3*, 31 (1967).

[51] *A. D. Allen* and *C. D. Cook*, Can. J. Chem. *41*, 1235 (1963).

[52] *A. D. Allen* and *C. D. Cook*, Can. J. Chem. *42*, 1063 (1964).

[53] *W. H. Baddley*, Inorg. Chim. Acta Rev. *2*, 7 (1968).

[54] *E. O. Greaves, R. Bruce*, and *P. M. Maitlis*, Chem. Commun. *1967*, 860.

[55] *M. Green, R. B. L. Osborn, A. J. Rest*, and *F. G. A. Stone*, J. Chem. Soc. *A 1968*, 2525.

[56] *J. H. Nelson, H. B. Jonassen*, and *D. M. Roundhill*, Inorg. Chem. *8*, 2591 (1969).

[57] *E. O. Greaves, C. J. L. Lock*, and *P. M. Maitlis*, Can. J. Chem. *46*, 3879 (1968).

[58] *B. R. Penfold* and *W. N. Lipscomb*, Acta Crystallogr. *14*, 589 (1961).

[59] *D. A. Bekoe* and *K. N. Trueblood*, unpublished results (1967), quoted in [45].

[60] *V. G. Albano, G. M. Basso Ricci*, and *P. L. Bellon*, Inorg. Chem. *8*, 2109 (1969).

[61] *V. G. Albano, P. L. Bellon*, and *M. Sansoni*, Chem. Commun. *1969*, 899.

[62] *J. C. Marriott, J. A. Salthouse, M. J. Ware*, and *J. M. Freeman*, Chem. Commun. *1970*, 595.

[63] *L. E. Orgel:* An Introduction to Transition Metal Chemistry. Methuen, London 1960, p. 65.

[64] *G. L. McClure* and *W. H. Baddley*, J. Organometal. Chem. *25*, 261 (1970).

[65] *E. L. Eliel:* Stereochemistry of Carbon Compounds. McGraw-Hill, New York 1962.

[66] *P. Heimbach* and *R. Traunmüller*, Liebigs Ann. Chem. *727*, 208 (1969).

[67] *T. Kashiwagi, N. Yasuoka, N. Kasai*, and *M. Kukudo*, Chem. Commun. *1969*, 317.

[68] *P. B. Hitchcock, M. McPartlin*, and *R. Mason*, Chem. Commun. *1969*, 1367.

[69] *L. E. Sutton:* Tables of Interatomic Distances and Configurations in Molecules and Ions. Chem. Soc. Special Publ. No. 18, London 1965, p. M 95s.

[70] *I. L. Karle* and *J. Karle*, J. Chem. Phys. *18*, 963 (1950).

[71] *L. Manojlović-Muir, K. W. Muir*, and *J. A. Ibers*, Discuss. Faraday Soc. *47*, 84 (1969).

[72] *C. Pedone* and *A. Sirigu*, Acta Crystallogr. *23*, 759 (1967).

[73] *C. Pedone* and *A. Sirigu*, Inorg. Chem. *7*, 2614 (1968).

[74] *A. R. Luxmoore* and *M. R. Truter*, Acta Crystallogr. *15*, 1117 (1962).

[75] *C. J. Brown*, Acta Crystallogr. *21*, 1 (1966).

[76] *R. Cramer*, J. Amer. Chem. Soc. *86*, 217 (1964).

[77] *G. W. Parshall* and *F. N. Jones*, J. Amer. Chem. Soc. *87*, 5356 (1965).

[78] *M. J. Grogan* and *K. Nakamoto*, J. Amer. Chem. Soc. *88*, 5454 (1966).

[79] *E. O. Fischer* and *K. Fichtel*, Chem. Ber. *94*, 1200 (1961).

[80] *E. O. Fischer* and *K. Öfele*, Angew. Chem. *74*, 76 (1962).

[81] *E. O. Fischer* and *M. Herberhold*, Experientia, Suppl. 9, 259 (1964); Chem. Abstr. *62*, 579f. (1965).

[82] *H. D. Murdoch* and *E. Weiss*, Helv. Chim. Acta *46*, 1588 (1963).

[83] *R. Cramer*, Inorg. Chem. *1*, 722 (1962).

[84] *M. J. Grogan* and *K. Nakamoto*, J. Amer. Chem. Soc. *90*, 918 (1968).

[85] *H. W. Quinn* and *D. N. Glew*, Can. J. Chem. *40*, 1103 (1962).

[86] *W. H. Baddley*, J. Amer. Chem. Soc. *90*, 3705 (1968).

[87] *L. Vaska*, Accounts Chem. Res. *1*, 335 (1968).

[88] *L. Vaska*, private communication.

Nuclear Magnetic Resonance in Solid-State Chemistry[**]

By Alarich Weiss[*]

Various problems of solid-state chemistry can be solved by spectroscopic investigation of the nuclear magnetic resonance (NMR and NQR methods). This progress report presents a survey of the nature of the interactions in the crystal that underlie such measurements, of the observations in the spectrum, and of the information obtainable from it. The field of application of the methods covers both static and dynamic properties of solids.

1. Introduction

During the past twenty years, nuclear magnetic resonance has acquired a dominant place in molecular chemistry as a physical method of investigation in the liquid phase. In solid-state chemistry NMR is comparable with other methods of solid-state spectroscopy, such as IR and Mössbauer spectroscopy, as a source of information.

A well-developed theory of nuclear magnetic resonance, which is substantially complete in its fundamental principles, is provided by physics[1-6]. It is only in recent years, however, that experimental advances have opened up new areas for the use of the method in the investigation of solids.

One usually distinguishes two experimental branches of nuclear resonance spectroscopy, *i.e.* nuclear magnetic resonance (NMR) and pure nuclear quadrupole resonance (NQR or PQR).

For our purposes, however, it seems more appropriate to choose a classification based on the aim of application rather than on the procedure, *i.e.* the determination of (a) static properties and (b) dynamic properties of the solid by nuclear magnetic resonance.

The possibilities offered by the application both of the NMR and of the NQR method to problems of solid-state chemistry will be discussed below with the aid of examples.

2. Physical Principles

2.1. Nuclear Magnetic Resonance (NMR)

We start with the observation that atomic nuclei in many cases have a nuclear angular momentum $\hbar\vec{I}$, which is associated with a magnetic dipole moment $\vec{\mu}$ because of the rotating charge of the nucleus. The vector of the magnetic dipole moment is parallel and proportional to the angular momentum vector:

$$\vec{\mu} = \gamma\hbar\vec{I} \tag{1}$$

γ is the magnetomechanical (gyromagnetic) ratio and $\hbar\vec{I}$ is the nuclear angular momentum vector. To determine the quantities in eq. (1), it is necessary to bring about an interaction between $\vec{\mu}$ and a second quantity in order to obtain an observable value.

If a macroscopic magnetic dipole $\vec{M}$ interacts with a magnetic field $\vec{H}_0$, the interaction energy according to classical theory is

$$E = -\vec{M}\cdot\vec{H}_0 \tag{2}$$

In the case of the magnetic moment of an atomic nucleus (or of an electron), however, certain restrictions must be imposed on the relation (2). The possible orientations of the vector $\vec{I}\hbar$ with respect to the field $\vec{H}_0$ are limited, since only certain angles are possible between $\vec{I}\hbar$ (and hence $\vec{\mu}$) and $\vec{H}_0$. The angular momentum is subject to quantum conditions. For stable nuclei, the angular momentum quantum numbers $I = 1/2, 1, 3/2, \ldots, 6$ are found in the periodic system of elements. For a nucleus with the angular momentum quantum number I there are only $2I+1$ allowed orientations of the angular momentum vector $\vec{I}\hbar$ in relation to the preferred direction $\vec{H}_0$. The energy of these states is given by

$$E_m = -m\gamma\hbar H_0 \tag{3}$$

m is the magnetic quantum number, with the values $I, I-1, \ldots, -I$, and $\hbar = h/2\pi$ represents the Dirac constant. The nuclear spin axis precesses with the Larmor frequency $\nu_0 = \omega_0/2\pi$ about the direction of $\vec{H}_0$. A transition of the nucleus from an energy state characterized by the magnetic quantum number m_a to another energy state with $m = m_b$ is allowed only if $\Delta m = m_a - m_b = \pm 1$. Thus if the energy corresponding to the energy difference between two successive levels is supplied to the system from outside, this energy can be taken up by the nuclear spin system. This "resonance energy" is given by

$$E_R = |E_{m+1} - E_m| = \hbar\omega_0 = \gamma\hbar H_0 \tag{4}$$

and one obtains the general resonance equation

$$\omega_0 = \gamma H_0 \tag{4a}$$

[*] Prof. Dr. A. Weiss
Institut für Physikalische Chemie der Universität
44 Münster, Schlossplatz 4 (Germany)
New address (since March 5, 1972):
Eduard-Zintl-Institut für Anorganische und Physikalische Chemie der Technischen Hochschule
61 Darmstadt, Hochschulstrasse 4 (Germany)

[**] Based on a lecture to the "Solid-State Chemistry" Group of the GDCh on October 1, 1970, in Bonn.

If the external magnetic field is denoted by H_0, this equation is strictly valid only if the experiment is carried out on the bare nucleus, since only then is the effective field H_0 at the position of the nucleus identical with the applied field. In all cases that can be realized in practice, however, it is necessary to modify eq. (4a):

$$\omega_0 = \gamma\left(H_0 + \sum_i H_i\right) = \gamma H_{\text{eff}} \tag{4b}$$

where the H_i may be internal magnetic fields arising from various sources. To give one example, the nuclei are surrounded by electrons, and in a magnetic field H_0, according to *Lenz*'s law, these produce a magnetic field H_i that opposes the external field. The external field is thus weakened at the position of the nucleus (diamagnetic shielding), and the effective field is $H_{\text{eff}} = H_0 - H_{\text{diamagnetic}}$.

2.2. Nuclear Quadrupole Resonance (NQR)

In addition to their electric charge some nuclei also possess electric moments of higher order, a fact which was already deduced many years ago from the study of the hyperfine structure of atomic spectra[7]. An interaction is therefore to be expected between the electric moment of the nucleus and the electric field, or more precisely its derivatives at the position of the nucleus. To calculate the electrostatic interaction of a nucleus with its environment, let us consider a nucleus having an atomic number Z, whose electric charge Ze is distributed over the entire volume of the nucleus. Let the charge density at the point $\vec{x}$ of the nucleus be $\rho_K(\vec{x})$. Let $V(\vec{x})$ be the electrostatic potential produced at the point $\vec{x}$ by all charges situated outside the nucleus in question. Taking the finite volume of the nucleus into account, one thus obtains the electric interaction energy between the nucleus and its environment:

$$\begin{aligned} W_{\text{el}} &= Ze \cdot V(0) + \vec{d} \cdot \vec{E} + \tfrac{1}{2} e\, \mathbf{Q} \cdot \nabla \vec{E} + \cdots = \\ &\text{(nuclear charge} \times \text{potential)} \\ &+ \text{(electric nuclear dipole moment} \times \text{electric field)} \\ &+ \text{(electric nuclear quadrupole moment} \times \text{electric field gradient)} \\ &+ \text{higher terms} \end{aligned} \tag{5}$$

The first term in eq. (5) is of no importance to our discussion, since it is a constant that is independent of direction, and which merely corresponds to a shift of the zero point on the energy scale. The second term (for symmetry reasons) is zero. The third term, however, is of great interest for the study of solids by NMR. The higher order terms that are also possible will be disregarded. One of the conditions for the occurrence of an interaction energy between the electric nuclear quadrupole moment and an electric field gradient at the position of the nucleus is of course the presence of an electric nuclear quadrupole moment, $e\mathbf{Q}$, where e is the elementary charge and $\mathbf{Q}$ is a 2nd rank tensor, which characterizes the symmetry of the charge distribution in the nucleus. The condition for an $e\mathbf{Q}$ different from zero is a nuclear angular momentum quantum number $I > 1/2$. The nuclear quadrupole moment tensor $e\mathbf{Q}$ can be described by the scalar moment eQ, since it may be assumed that the tensor is symmetrical and has a vanishing trace. We have: $Q \gtreqless 0$, as illustrated in Figure 1. Q is expressed in units of 10^{-24} cm^2. The second term in the product describing the interaction energy is the electric field gradient $\nabla\vec{E}$ at the position of the nucleus. It is determined by the charge distribution, *e.g.* by the electric charges, electric dipole moments, electric quadrupole moments in ionic crystals and molecular lattices, by deviations from spherical symmetry of the electron core surrounding the nucleus, by bonding electrons, *etc.*

In solid-state chemistry, knowledge of the nuclear quadrupole moment eQ will generally be assumed (this is not trivial), and conclusions concerning the bonding in the solid will be drawn from the study of the nuclear quadrupole interaction energy.

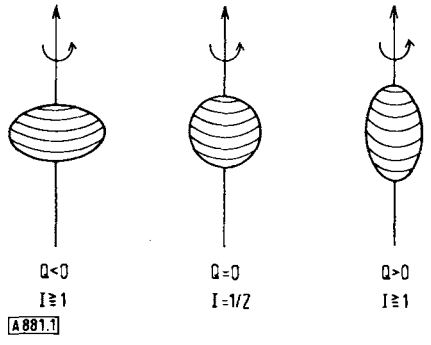


Fig. 1. Nuclear quadrupole moment and rotationally symmetrical charge distribution of nuclei.

The electric nuclear quadrupole moment is also connected with the nuclear angular momentum axis. Corresponding to the interaction energy between $\vec{\mu}$ and $\vec{H}_0$, an interaction energy arises here between $e\mathbf{Q}$ and the electric field gradient at the position of the nucleus [eq. (5)]. $\nabla\vec{E}$ is the second derivative of the potential with respect to the space coordinates at the position of the nucleus, a symmetrical tensor $\boldsymbol{\phi}$ with three principal axial components $\phi_{xx}, \phi_{yy}, \phi_{zz} : |\phi_{xx}| \leqq |\phi_{yy}| \leqq |\phi_{zz}|$. The maximum component of $\boldsymbol{\phi}$, *i.e.* ϕ_{zz}, is often expressed by eq, where e is again the elementary charge.

The interaction energy can be calculated without difficulty, and we find for the simplest case ($\phi_{xx} = \phi_{yy}$)

$$E_m = \frac{eQ}{4I(2I-1)}\left[3m^2 - I(I+1)\right]\phi_{zz} \tag{6}$$

The supply of energy quanta $h\nu$, *i.e.* the resonance experiment, is carried out in practice in the same manner as in the nuclear magnetic resonance experiment by irradiation of the sample with electromagnetic waves of frequency ν. The transition from the energy state with $m = m_a$ to a state with $m = m_b$ is again brought about by the interaction of the magnetic nuclear dipoles with the alternating magnetic field H_1 of the incident radiation.

Finally, let us consider briefly the energy level diagram for magnetic dipoles and electric quadrupoles in the magnetic field, H_0, and in the gradient of the electric field, ϕ_{zz}, respectively.

Equation (3) shows that the energy level diagram of the nuclear spin system in the magnetic field H_0 is split proportionally to the field (Fig. 2; Breit-Rabi diagram for $I = 3/2$).

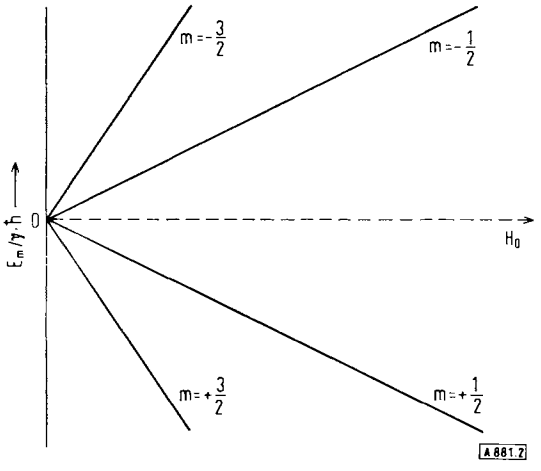


Fig. 2. Breit-Rabi diagram for the nuclear spin $I = 3/2$. The energy unit $E_m/\gamma\hbar$ is arbitrarily chosen.

In the experiment we consider only the transitions $\Delta m = \pm 1$ between two adjacent energy levels. For the case $I = 1/2$, we have $\Delta E = E_{-\frac{1}{2}} - E_{\frac{1}{2}} = \gamma\hbar H_0$. For $I = 3/2$, the transitions $\Delta E_{(-1/2 \rightleftarrows -3/2)}$, $\Delta E_{(-1/2 \rightleftarrows +1/2)}$, and $\Delta E_{(1/2 \rightleftarrows 3/2)}$ are possible; for each transition, $\Delta E = \gamma\hbar H_0$. Figure 3 shows the energy levels and the spectrum expected according to eq. (4) for $I = 1/2$ and $I = 3/2$.

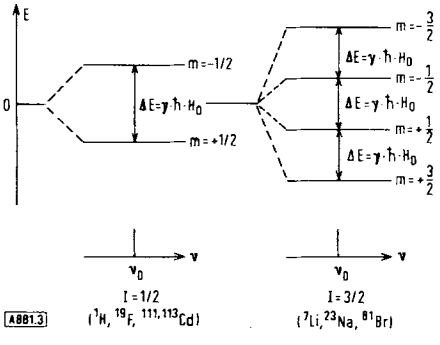


Fig. 3. Energy levels of nuclear spin systems with $I = 1/2$ and $I = 3/2$ in the magnetic field. The transitions with $I = 3/2$ are triply degenerate (energy scale arbitrary).

For the case of the interaction between the electric field gradient and the nuclear quadrupole moment, eq. (6) gives the energy level diagram illustrated *e.g.* for $I = 1$, $I = 3/2$, and $I = 5/2$ in Figure 4.

So far we have considered only resonance frequencies, *i.e.* energy states. As in all branches of spectroscopy, however, intensities and line shapes are also important in NMR spectroscopy. The effective intensities and line shapes are essentially determined by the interactions of the nuclear spins with their environment. Two parameters are important for their description, *i.e.* the spin-lattice relaxation time (longitudinal relaxation time) T_1 and the spin-spin relaxation time (transversal relaxation time) T_2. As will be shown later, the determination of

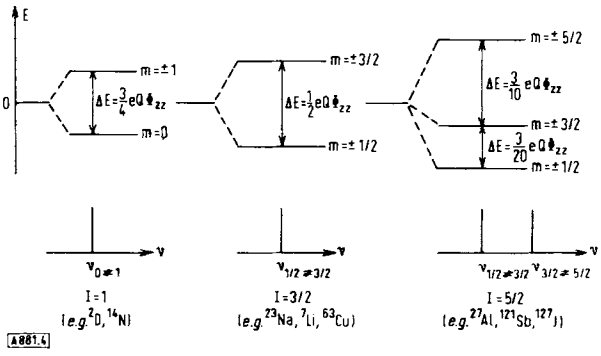


Fig. 4. Energy splitting due to nuclear quadrupole interaction ("pure nuclear quadrupole resonance", PQR) for $I = 1, 3/2$, and $5/2$. Since $E \sim m^2$, the levels are degenerate. The energy scale is arbitrary. As a limiting condition $|\Phi_{xx}| = |\Phi_{yy}| = \frac{1}{2}|\Phi_{zz}|$. The quantity $eQ\Phi_{zz}/h \equiv e^2qQ/h$ is known as the quadrupole coupling constant, and is usually expressed in hertz [Hz].

these parameters leads to results that are of interest in solid-state chemistry. However, the theory of relaxation times will not be discussed here (see *e.g.*[1],[2] or[4]).

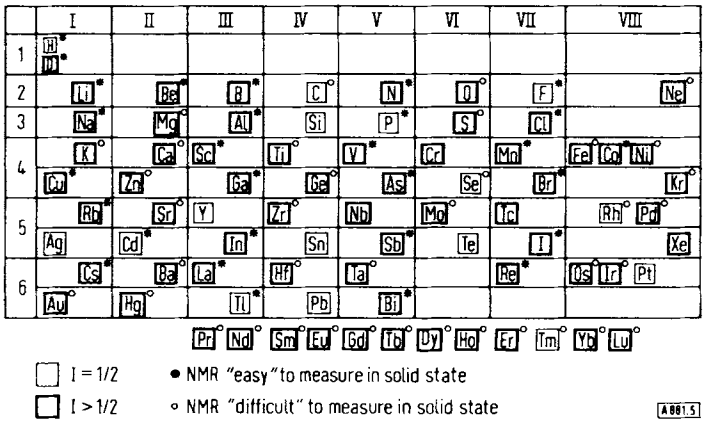


Fig. 5. Stable nuclei with $I \neq 0$ in the periodic system of the elements.

Unlike high-resolution NMR spectroscopy, NMR spectroscopy on solids is subject to only a few restrictions regarding the periodic system of the elements. Figure 5 summarizes schematically the nuclei on which NMR and (for $I > 1/2$) NQR experiments can be carried out. (Unstable nuclei with short half-lives, which escape the normal experimental methods, are not included; the statement that the NMR is "easy" or "difficult" to measure is a personal opinion, and is also strongly dependent on the relaxation times T_1 and T_2.)

3. Application of Nuclear Magnetic Resonance to the Study of Properties of Solids

3.1. Magnetic Nucleus-Nucleus Interactions in the Ideal Rigid Lattice

The simplest case, and also the first one investigated[8], of an interaction in solids that can be studied by the NMR method is the interaction between nuclear moments in a rigid lattice. The interaction energy E_{ij} of two nuclear

dipoles $\vec{\mu}_i$ and $\vec{\mu}_j$ separated by the distance vector $\vec{r}_{ij}$ is given by:

$$E_{ij} = \frac{\vec{\mu}_i\vec{\mu}_j}{r_{ij}^3} - 3\frac{(\vec{\mu}_i\vec{r}_{ij})(\vec{\mu}_j\vec{r}_{ij})}{r_{ij}^5} \qquad (7)$$

The most important case in solid-state chemistry is the interaction between two like nuclei, *e.g.* the two protons of the water molecule in crystalline hydrates. A qualitative interpretation of this interaction is that in addition to the field H_0, a field due to the magnetic moment of the proton j acts at the position of the proton i [see eq. (4b)], this second field being given by $\pm\mu r_{ij}^{-3}(3\cos^2\theta - 1)$.

Thus according to *Pake*[8], the "splitting" of the ^{1}H-NMR in the lattice is given by

$$\Delta H = 2\alpha[3\cos^2\delta\cos^2(\varphi - \varphi_0) - 1] \qquad (7a)$$

where $\alpha = \pm\frac{3}{2}\mu_p \cdot r_{ij}^{-3}$. The angles δ, φ, and φ_0 give the orientation of the vector $\vec{r}_{ij}$ joining the protons and of the magnetic field $\vec{H}_0$ with respect to each other and to a system of coordinates (Fig. 6).

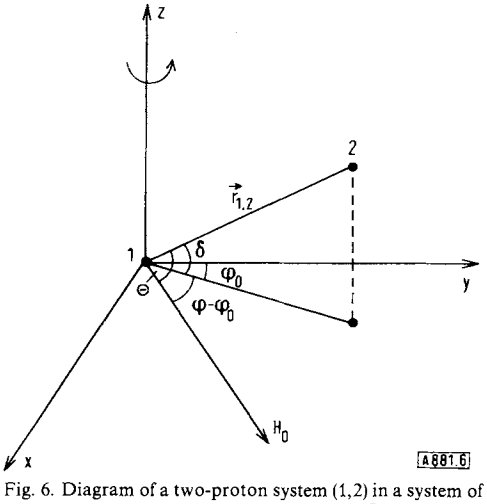


Fig. 6. Diagram of a two-proton system (1,2) in a system of coordinates x, y, z to illustrate the Pake formula [eq. (7a)].
$\vec{r}_{1,2}$ is the vector joining the pair of protons, $\varphi = \sphericalangle\,[\vec{H}_0$, reference axis $(y)]$, δ = angle between $\vec{r}_{1,2}$ and the plane containing $\vec{H}_0$ and the reference axis: $\theta = \sphericalangle\,(\vec{r}_{1,2}, \vec{H}_0)$.

The resulting NMR splitting spectrum of protons according to eq. (7a) for a two-spin system is shown in Figure 7 for $Li_2S_2O_6 \cdot 2H_2O$[12].

What information is obtainable from the spectra?

a) The splitting ΔH is very strongly dependent on the distance r_{ij}, and the H-H distance can therefore be determined very accurately.

b) The spectrum is strongly dependent on angle, and the direction cosine of the H-H vector can therefore be determined.

From the spectrum of a single crystal of a crystalline hydrate, therefore, it is possible to find the length and direction of the H-H vectors in a molecule. Further information is necessary in order to relate these vectors to the origin of the unit cell. For example if the point

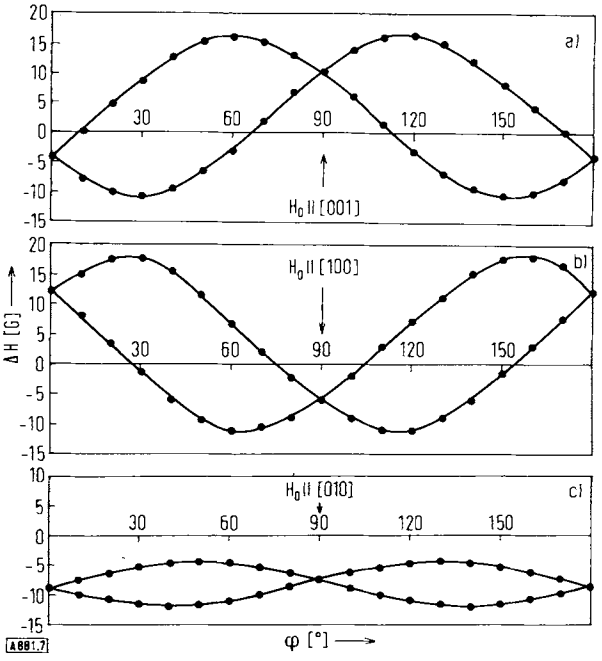


Fig. 7. Pake splitting in the ^{1}H-NMR spectrum of single crystals of $Li_2S_2O_6 \cdot 2H_2O$; after [12]. a) Axis of rotation ∥ [100]; b) axis of rotation ∥ [010]; c) axis of rotation ∥ [001].

positions of the oxygens of the water molecules in a crystalline hydrate are known, the H-H vector is fixed by the NMR experiment on the lateral surface of a cylinder. To obtain information on hydrogen bonds or on the point positions of the protons in general, therefore, it is necessary to know the angle between the two vectors O-H in the molecule, or to know the O-H distance, and to assume the direction of the hydrogen bond. Numerous NMR studies have already been carried out on the geometry of H_2O molecules in crystals (cf.[9-11]). For a complete determination of the positions of the protons, it should be sufficient in principle to know the point positions of the oxygens and to take into account the nuclear magnetic ^{1}H-^{1}H interactions of nearest and next-nearest neighbors. Owing to the strong dependence of the interaction on r_{ij}, however, the resolving power of the method is probably too low to allow a complete crystal structure determination of the proton partial lattice in this way (see *e.g.*[12, 13]).

It is often impossible to obtain suitable single crystals (which should have a size of about 1 cm^3 for classical nuclear magnetic resonance experiments) for the NMR studies. The measurements are then carried out on polycrystalline samples. For very simple cases (two-spin and three-spin systems), such a spectrum can be evaluated in accordance with eq. (7a) if an average has been taken over the angles. However, only r_{ij} can be determined from the result, while the information on the angles is lost. CH_3 groups or $(H_3O)^+$ ions in solids have been studied in this way in several investigations. A typical example is the proton resonance in crystalline $HNO_3 \cdot H_2O$, which may be regarded as $[H_3O]^+[NO_3]^-$ [14] (Fig. 8).

For a four-spin system, *e.g.* NH_4^+ or CH_4, evaluation by *Pake*'s method can no longer be used for crystalline

powders or even for single crystals. It is then necessary to use *Van Vleck*'s method, *i.e.* the "method of higher moments"[15]. Numerous examples can be found in the literature. In any case, the ^{1}H-NMR measurement is very useful as a complement to the diffraction method.

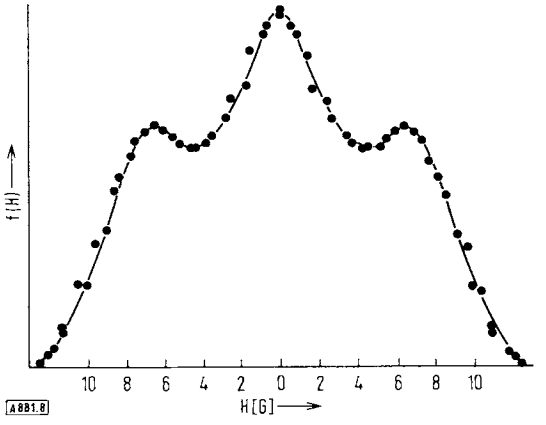


Fig. 8. ^{1}H-NMR spectrum of crystalline $HNO_3 \cdot H_2O$. The experimental data (points) were obtained at 90°K. The continuous curve was calculated from *Van Vleck*'s theory for an H_3O^+ ion (the protons are situated on a triangle having a side length of 1.72 Å). The ordinate scale is arbitrary [14].

Apart from the interaction between protons in the lattice, the only others that can be considered are those between ^{19}F and possibly between ^{31}P nuclei and $^1H \leftrightarrow {}^{19}F$, $^1H \leftrightarrow {}^{31}P$, and $^{31}P \leftrightarrow {}^{19}F$ interactions. For all other nuclei, the determination of distances (and of point positions) by means of nuclear magnetic resonance is too inaccurate to compete with the diffraction methods.

3.2. Interaction between Nucleus and Electron Cloud in the Rigid Lattice

3.2.1. The Chemical Shift

It is known that when the NMR method is used in molecular spectroscopy, two effects characterize the resonance spectrum, *i.e.* the chemical shift and the electron-coupled spin-spin interaction. The second of these effects is of practically no importance in the case of solids; the hyperfine structure produced thereby in the spectrum is masked in most cases by the line widths due to dipole-dipole interaction. However, it is possible to study the chemical shift.

As a result of an investigation of the chemical shift, we expect information about the chemical bonding. In solids, however, the chemical shifts are often superimposed by very much stronger effects, *e.g.* the dipole-dipole interactions; such shifts can therefore be easily measured only under certain conditions. For this reason we shall group these interactions on an experimental basis. It should be noted that the "overall range" of the chemical shift of the NMR is strongly dependent on the atomic number (or rather on the number of electrons in the atomic shell), the effect increasing with the number of electrons *(Lamb)*. Thus it is known from high-resolution NMR spectroscopy that the shifts, which are defined by

$$\delta = \frac{H_{sample} - H_{standard}}{H_{standard}} \times 10^6 \qquad (8)$$

cover a range of about 30 ppm for ^{1}H-NMR. This range is 150 ppm for ^{11}B, about 300 ppm for ^{19}F, about 600 ppm for ^{14}N, about 800 ppm for ^{18}O, about 2000 ppm for ^{119}Sn, and about 15000 ppm for ^{207}Pb.

3.2.2. Chemical Shift of the NMR of Nuclei with $I = 1/2$

1. *Heavy nuclei* (mass number >100): The chemical shifts here are in the region of a few 10^3 ppm, *i.e.* with a field H_0 of 10000 Oe they have values of up to 100 Oe. On the other hand, the heavy atoms and ions have fairly large radii (>1 Å), so that because of nucleus-nucleus interaction in accordance with eq. (7a), the line widths reach values of around 1 Oe (an exception is Tl metal).

The chemical shifts of the NMR in solids can thus be readily observed for the nuclei ^{207}Pb, ^{205}Tl, ^{203}Tl, ^{199}Hg, ^{195}Pt, ^{119}Sn, ^{113}Cd, ^{109}Ag, and ^{107}Ag if the spectrum is recorded against a standard in the usual manner (see *e.g.*[25, 26, 32]).

2. *Light nuclei:* The most important of these are ^{1}H, ^{19}F, and ^{31}P. Their magnetic moments are very high, and the magnetic nucleus-nucleus dipole interaction therefore leads to considerable line widths. The chemical shift, on the other hand, is small. There are two methods of suppressing the nucleus-nucleus interaction corresponding to eq. (7a) and revealing the chemical shift:

a) Rotating solid sample after *Andrew*[16] and *Love*[17]: A series of interactions in solids depend on the angle between H_0 and the direction that determines the interaction of the nuclei with their environment according to a law that contains the term $(3\cos^2\theta - 1)$ (cf. *e.g.* eq. (7a) and Fig. 6). These interactions can be partly averaged out by rapid rotation of the sample about an axis that forms the angle $\theta = 54°44'$ with the field H_0, since the value of $(3\cos^2\theta - 1)$ is then 0. However, the experimental arrangement is not simple. *Andrew et al.*[16], for example, have investigated the chemical shift of ^{31}P resonances in a number of crystalline phosphorus compounds; they obtained the results indicated in Table 1.

Table 1. Chemical shift of the ^{31}P-NMR of phosphorus compounds (δ in ppm, with respect to 85% H_3PO_4); after [16].

Substance	δ		
P_4S_3	−72,	+103	
P_4S_5	−200,	−20,	+120
P_4S_{10}	−45		
$H_4P_2O_7$	+12		
PCl_5 ($[PCl_4]^+$ $[PCl_6]^-$)	−91,	+282	
Zn_3P_2	+217,	+250	

b) Multiple pulse nuclear spin spectroscopy after *Waugh et al.*[18]: In nuclear spin pulse spectroscopy, suitable sequences of high-frequency pulses can be used to rotate the resultant magnetization vector $\vec{M} = \Sigma \vec{\mu}_i$ into certain

directions with respect to the external field $\vec{H}_0$, and undesirable interactions can thus be eliminated in the study of the chemical shift. This method is developing rapidly at present, and it remains to be seen to what extent it will prove to be of general applicability in the chemistry of solids.

3.2.3. Chemical Shift of the NMR of Nuclei with $I > 1/2$

We have to distinguish here between nuclei whose point symmetry in the lattice is cubic, *i.e.* characterized by the point groups 23, m3, 432, $4\bar{3}$m, or m3m, and those with lower point symmetry.

In the latter case the interactions between the nucleus and the environment are considerably influenced by the nuclear quadrupole interactions, and the chemical shift of the NMR can be studied only on the single crystal. (Complete information on the chemical shift for all nuclei with noncubic point symmetry is obtainable only from the single crystal, since the chemical shift is a tensor quantity.) Few complete measurements of the chemical shift of the NMR of nuclei with $I > 1/2$ and with noncubic point symmetry have been reported for diamagnetic crystals. Recent investigations have been carried out by *Spiess, Haas,* and *Hartmann*[31]. The authors investigated single crystals of cobalt(III) complexes and determined in each case the tensor of the chemical shift and the nuclear quadrupole coupling tensor. A linear relation was found between the anisotropy of the shift and the nuclear quadrupole coupling constant, and this relation was discussed in terms of the MO theory.

A series of investigations was carried out on nuclei with $I > 1/2$ in crystals with cubic point symmetry. Attention was centered mainly on the alkali metal halides and ammonium halides. Both the chemical shifts and the spin-lattice relaxation time T_1, which is related to the chemical shift by $\log T_1 = A - a \cdot \log \sigma$ (σ = shielding constant), were investigated[19–24]. The interpretation of the results is following two directions: a) assumption of a covalent bonding component, and b) consideration of the influence of the crystal potential and of the overlap effect.

The second model (b) shows satisfactory agreement between experiment and theory, and should be important to the discussion of the chemical shifts and of the bonding in ionic crystals with complicated structures.

3.2.4. Knight Shift (Chemical Shift in Metals and Alloys)

A focal point at present in the NMR spectroscopy of solids is the measurement of the chemical shift in metals and alloys. *Knight* discovered in 1949 that a shift of the nuclear magnetic resonance occurs in metals as a result of the paramagnetism of the conduction electrons. This shift, which is known as the Knight shift, has a magnitude of up to 30000 ppm (with respect to a diamagnetic salt in aqueous solution)[27]. The Knight shift K is given by

$$\frac{H_{metal} - H_{standard}}{H_{standard}} = K = \frac{8\pi}{3} \chi_p V_0 \langle |\psi(0)|^2 \rangle_F \qquad (9)$$

where χ_p is the paramagnetic spin susceptibility of the conduction electrons, V_0 is the atomic volume, and $\psi(0)$ is the wave function, normalized over the volume V_0, of an electron having the Fermi energy E_F. $\langle |\psi(0)|^2 \rangle_F$ is thus the average electron density on the nucleus for all electronic states on the Fermi surface. It is clear that quite far-reaching conclusions can be drawn from the measurement of the Knight shift K if χ_p is known (*e.g.* for the metals Li, Na, Rb, Be)[28]. The anisotropy of K in noncubic metals is also of interest, and can be studied.

Changes in the valence electron concentration, VEC, can be readily determined by measurement of K. An example is the metallic system V-Cr-H, where it has been shown that K varies in proportion to the VEC[29]. Figure 9 shows the results both for K and for $1/T_1 T$ as functions of the VEC.

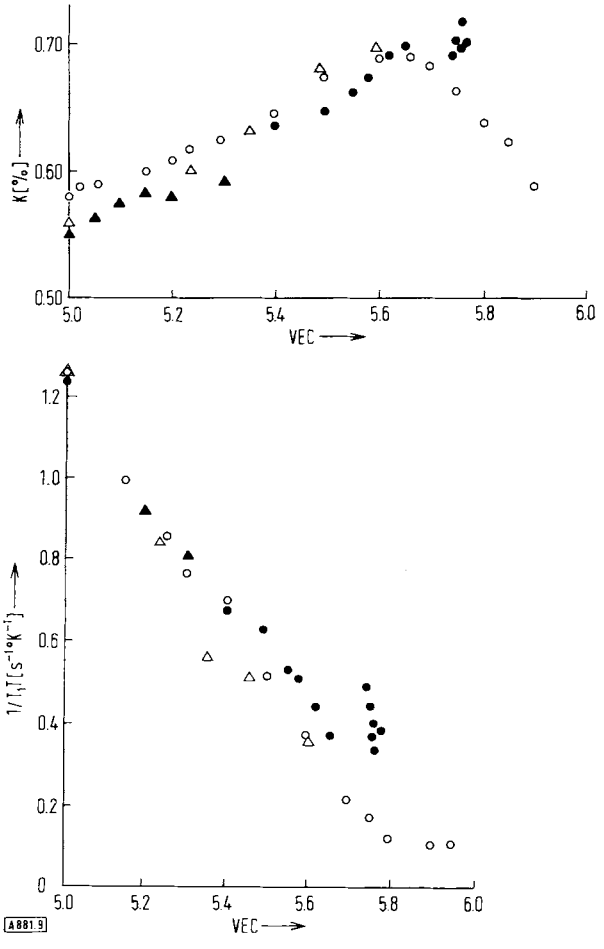


Fig. 9. ○, ▲ = $V_{(1-x)}Cr_x$; ● = $V_{(1-x)}Cr_xH_y$; △ = VH_y. Knight shift of the ^{51}V-NMR as a function of the valence electron concentration VEC in the systems V-Cr, V-Cr-H, and V-H [29].

The problems that can be tackled by nuclear magnetic resonance experiments include *e.g.* the oscillations of the conductivity electron density in metals about an impurity atom. Reviews on the Knight shift have been published by *Rowland*[27] and by *Lütgemeier*[30].

A difficulty that arises in the investigation of solids is that the chemical shift and the Knight shift often cannot be separated, since only the total effect of the internal fields

$\sum_i H_i$ is measured (cf. *e.g.*[59]). If the g factor is known for the conduction electrons, it is possible to split up δ_{total} into $\delta_{total} = \delta_{chem} + \delta_{Knight}$ ($\delta_{Knight} \equiv K$).

3.3. Nucleus-Electron Interaction in Substances with Permanent Magnetic Moments of the Individual Particles

3.3.1. Nucleus-Electron Interaction in Paramagnetic Substances

For crystals with paramagnetic ions (unpaired electrons) the internal magnetic field H_i can be studied very successfully by NMR measurements. The simplest case is that of pure dipole interaction between the electron spin at the position of the paramagnetic ion and a nuclear spin in the lattice, *e.g.* between the magnetic moment of Cu^{2+} ions and the protons in copper salts such as $CuSO_4 \cdot 5H_2O$[33], $K_2CuCl_4 \cdot 2H_2O$[34], or $CuF_2 \cdot 2H_2O$[35]. One can expect the shift of the ^{1}H-NMR frequency (after correction for the ^{1}H-^{1}H interactions) with respect to the Zeeman frequency $\omega_0 = \gamma H_0$ to be proportional to the susceptibility χ. It should be noted that this shift should be dependent upon direction. The relative shift of two groups of ^{1}H resonance lines of $K_2CuCl_4 \cdot 2H_2O$ as a function of temperature (Curie's law) is shown in Figure 10.

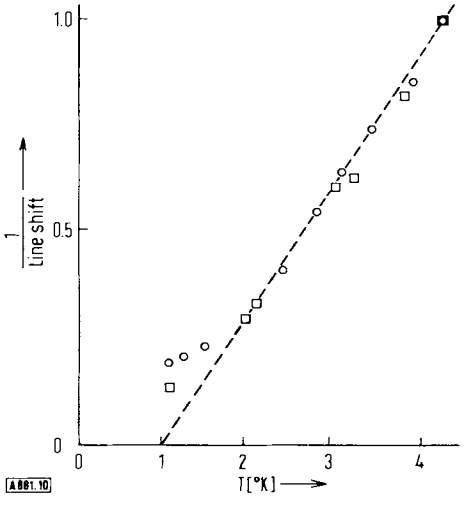


Fig. 10. Temperature dependence of the relative splitting between two groups of ^{1}H-NMR lines of $K_2CuCl_4 \cdot 2H_2O$. $H_0 \parallel [110]$. $\circ \triangleq \omega_0 = 30$ MHz; $\square \triangleq \omega_0 = 15$ MHz [34].

In many cases, however, the effect of the exchange correlation dominates the electron spin-nuclear spin coupling. This becomes clear if one examines the NMR spectra of nuclei of atoms having a covalent bonding component with the paramagnetic ion. Very strong coupling then appears. Figure 11 shows the ^{1}H-NMR spectrum and the ^{19}F-NMR spectrum of single crystals of $CuF_2 \cdot 2H_2O$ ($CuF_2 \cdot 2H_2O$ is monoclinic; the Cu^{2+} ion and two F^- ions at a distance of 1.89 Å all lie in the plane normal to the twofold axis [010]; the two oxygen atoms of the water molecules are situated on the b axis at a distance of ± 1.93 Å from the Cu^{2+} ion). Whereas the Cu^{2+}-^{1}H interaction is weak between 77 and 300°K and contains only an anisotropic component, the ^{19}F-NMR is strongly influenced, both isotropically and anisotropically, by the electron spin.

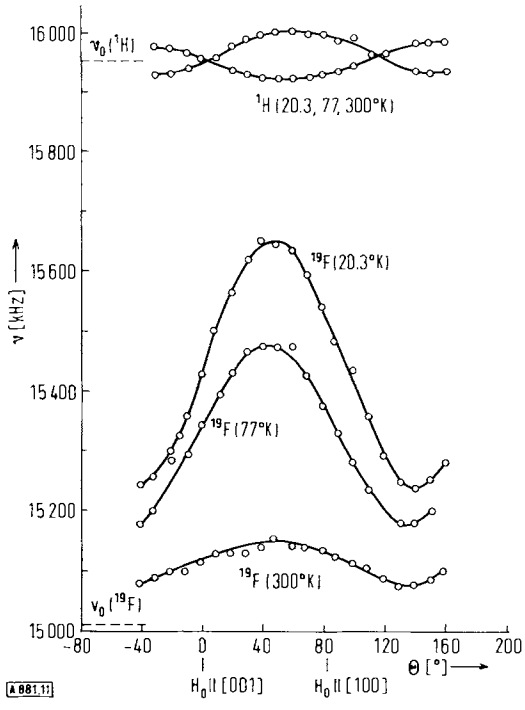


Fig. 11. Angular dependence of the ^{1}H-NMR and ^{19}F-NMR in $CuF_2 \cdot 2H_2O$ single crystals. $\vec{H}_0$ lies in the a,c plane. $\nu_0(^1H) = \gamma_H \cdot H_0/2\pi = 15.954$ MHz and $\nu_0(^{19}F) = \gamma_F \cdot H_0/2\pi = 15.001$ MHz correspond to the Larmor frequencies at field H_0 [35].

The "distribution" of the unpaired electrons over the lattice can be calculated from such measurements. *Itoh* and *Kamiya*[34] found for $K_2CuCl_4 \cdot 2H_2O$ and $(NH_4)_2CuCl_4 \cdot 2H_2O$ at $T = 4.2$°K: about 80% of the density on Cu^{2+}, 2% on each oxygen, 0.1% on each H of H_2O, less than 0.5% on the cation (K^+ or NH_4^+), and about 16% on the four Cl^-. Other examples are investigations on the nucleus-electron interaction and the susceptibility tensor by NMR measurements on ^{17}O in MnO and CoO[36] and the study of the magnetic shift tensor at the position of the Cl^- ions in $CsNiCl_3$ and $CsCuCl_3$[37].

Many investigations are concerned with the mechanism of the nuclear spin-lattice relaxation in paramagnetic substances.

3.3.2. NMR in Crystals with Collective Magnetic Behavior (Ferromagnetism and Antiferromagnetism)

Numerous investigations have shown during the past few years that NMR spectroscopy is excellently suited to the study of the magnetic structure and internal fields in crystals with collective magnetic behavior.

1. *Antiferromagnetic crystals:* Below the Néel point, ordered magnetic structures are formed, such that microscopic compensation of the spin occurs. The investigation of the NMR spectra of various nuclei in single crystals below the Néel temperature allows the determination of the magnetic field (strength and direction) at the positions of these nuclei. The magnetic structure (magnetic space group) can be obtained in this way.

Thus by a detailed study of the NMR spectra of ^{35}Cl, ^{133}Cs, and ^{1}H in $CsMnCl_3 \cdot 2H_2O$, *Spence et al.*[38] were able to determine the magnetic space group. As a typical example of the internal field at the position of the ^{1}H nuclei, Figure 12 shows $\nu(^{1}H)$ in the zero field $H_0 = 0$ as a function of the temperature.

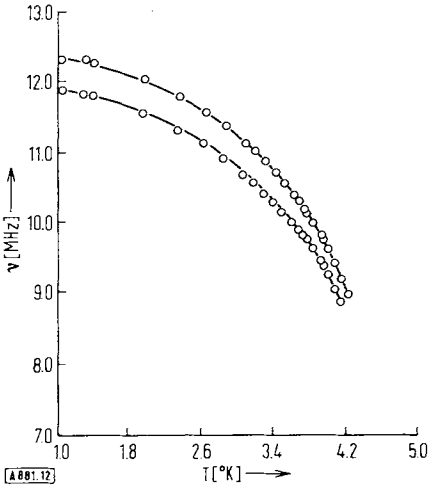


Fig. 12. ^{1}H-NMR frequencies of the protons in single crystals of $CsMnCl_3 \cdot 2H_2O$ as a function of temperature. The external field H_0 is 0 (zero-field resonance) [38].

Figure 13 shows $\nu(^{133}Cs)$ as a function of the angle θ with the field $H_0 = 5320$ Oe. The weak quadrupole interaction can be seen (example of the superposition of magnetic and

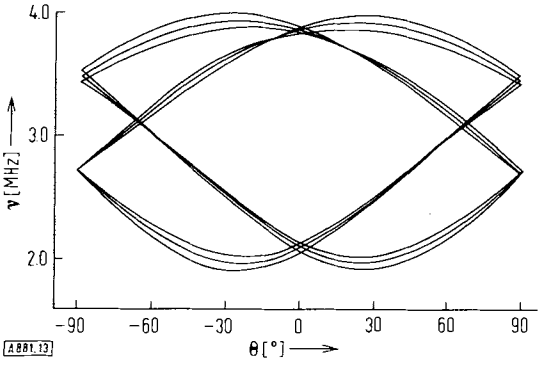


Fig. 13. Angular dependence of the ^{133}Cs resonance in single crystals of $CsMnCl_3 \cdot 2H_2O$ in an external field of 5320 Oe. At angle $\theta = 0$, $H_0 \parallel [010]$. The splitting of each curve into three lines shows the quadrupole interaction. The transitions $-\frac{1}{2} \leftrightarrow \frac{1}{2}$, $-\frac{7}{2} \leftrightarrow -\frac{5}{2}$, and $\frac{5}{2} \leftrightarrow \frac{7}{2}$ are shown. $T = 4.2$ °K; $H_i = 1.88$ kOe [38].

electric crystal fields). In any case, nuclear magnetic resonance in magnetically ordered materials is a valuable supplement to neutron diffraction.

2. *Ferromagnetic crystals:* Particularly strong magnetic fields may be expected in ferromagnetic substances. Both the NMR spectra of the nuclei with a paramagnetic electron shell and the spectra of other nuclei are observed here. The internal field is very high in many ferromagnetic materials; it is sufficient to enable the experiment to be carried out without the aid of an external field.

The most important result is probably the determination of internal fields. The pioneering work of *Gossard* and *Portis*[39] was followed by numerous other studies. As an example, Figure 14 shows the hyperfine field at the position of the ^{59}Co nucleus in iron-cobalt alloys as found by NMR experiments[40].

A review on nuclear magnetic resonance in magnetic substances has been published by *Bose*[41].

4. Use of Nuclear Resonance for the Study of Electric Fields (Crystal Fields) in Solids

The use of the NMR method for the investigation of internal magnetic fields H_i arising from various sources in crystals was discussed in the last section. Another wide field of application of the method is the study of the

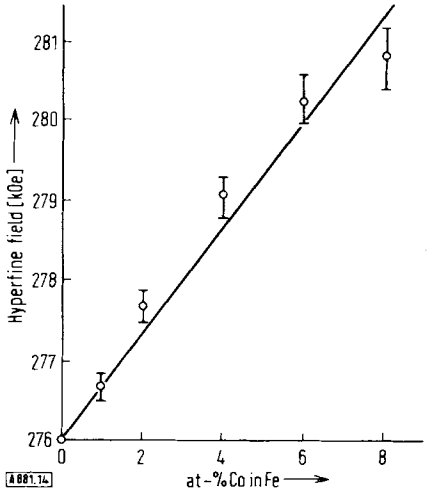


Fig. 14. Hyperfine field at the position of the ^{59}Co nucleus in Fe-Co alloys, as found by NMR measurements, as a function of the Co concentration [40].

electric field gradients in crystals by measurement of the interaction energy $eQ \cdot \phi_{zz}$ [see eq. (6)]. A condition that must be satisfied for this measurement is the presence of a nucleus with $I > 1/2$. This condition is met by a number of stable isotopes with high abundances (see Fig. 5). The use of the method for the systematic investigation of relationships in solid-state chemistry is unfortunately restricted by a quadrupole moment gap in group II (Mg, Ca, ...; exception: Be) and in group IV (C, Si, ...). Many of the NMR experiments on nuclei with $I > 1/2$ in crystals are directed toward the study of chemical bonding in molecules. The measurements are carried out on solids in this case because of the method rather than because of the problem. The main area of interest here is the investigation of ^{2}D, ^{11}B, ^{14}N, ^{35}Cl, ^{81}Br, and ^{127}I in organic molecules. The energy equation for the nuclear quadrupole interaction [eq. (6)] contains the nuclear moment eQ and the field gradient ϕ_{zz}. This gradient is due to the electric charges surrounding the nucleus:

a) the point charges, dipoles, and quadrupoles in the lattice, which produce a gradient ϕ_{zz} at the position of the atom;

b) the electron core around the nucleus in question, which may be distorted by the external fields;

c) the bonding electrons in the molecule, whose distribution around the nucleus in question deviates strongly from spherical symmetry, and which thus produce a high field gradient at the position of the nucleus.

Let us first consider case c). The electric field gradient at the position of the nucleus, and hence the coupling constant, can be used as a basis for conclusions regarding the chemical bonding. A comparison of the coupling constants with those of a standard exhibiting "pure covalent" bonding

(*e.g.* $\frac{eQ\phi_{zz}}{h}$ (XCl) compared with $\frac{eQ\phi_{zz}}{h}$ (Cl_2))

yields information on the bonding[42,43]. However, the main interest here is in the molecular properties; the solid is an "experimentally necessary evil", whose only contribution to the effects are perturbation terms, which are usually undesirable[48]. From investigations of this type it is possible to draw conclusions regarding:

1. the chemical bonding in molecules (bond strength),

2. bond angle (by measurements on single crystals—Zeeman splitting),

3. the symmetry of the bonding electrons (double bond character), by study of the components $\phi_{\nu\nu}(\nu=x,y,z)$ of the electric field gradient tensor and hence of the asymmetry parameter $\eta=(\phi_{xx}-\phi_{yy})/\phi_{zz}$; $0\leqq\eta\leqq1$,

4. symmetry elements and point position symmetry in the crystal lattice.

Detailed information on this line of investigation will be found in Refs. [42,43,46,47]

In ionic lattices or in lattices with a strong ionic bonding component between the atoms (cases a and b), the interaction between the nuclei and their environment is strongly influenced by the lattice. On the other hand, the interaction energy between the electric nuclear quadrupole and the electric field gradient is often weak here; this interaction is then investigated as a superposition over the pure Zeeman splitting. The situation in the energy level diagram for $I=3/2$ is shown in Figure 15.

A simple example of a weak quadrupole interaction with direct observation on the oscilloscope is shown in Figure 16

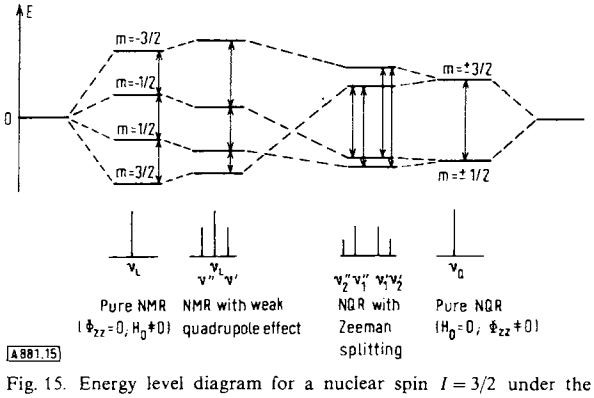


Fig. 15. Energy level diagram for a nuclear spin $I=3/2$ under the influence of an external magnetic field H_0 and a field gradient ϕ_{zz}.

for the case of the ^{23}Na-NMR in $Na_2ZnCl_4\cdot3H_2O$; Figure 17 then shows the complete "rotation diagram" of the quadrupole splitting of the NMR spectrum of ^{23}Na in this compound. In the evaluation of the experiments,

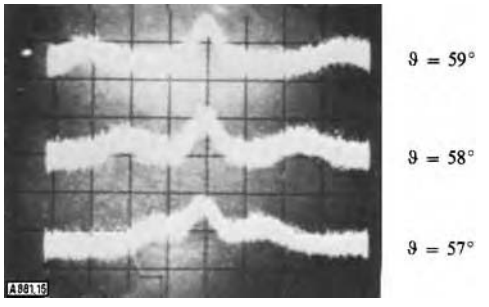


Fig. 16. ^{23}Na resonance in $Na_2ZnCl_4\cdot3H_2O$. Rotation about [100]. ϑ = angle between [001] and H_0. 1 cm (screen) ≅ 4 kHz [66].

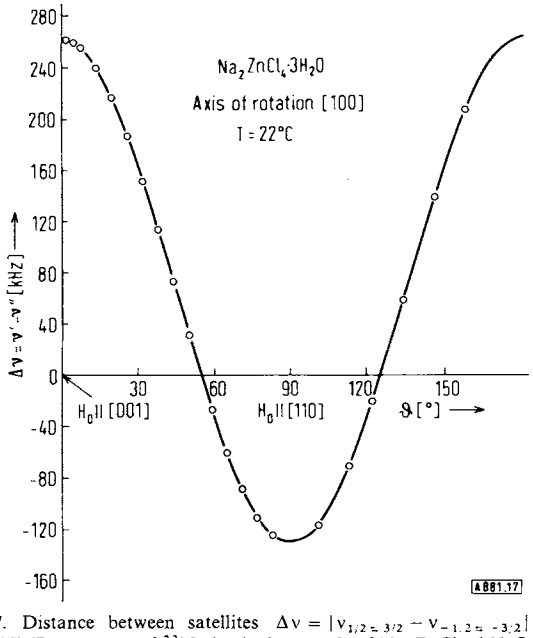


Fig. 17. Distance between satellites $\Delta\nu=|\nu_{1/2\leftrightarrow3/2}-\nu_{-1/2\leftrightarrow-3/2}|$ in the NMR spectrum of ^{23}Na in single crystals of $Na_2ZnCl_4\cdot3H_2O$ as a function of the angle between H_0 and the crystal axis [001] of the trigonal crystal [66].

however, it is often necessary to use the intermediate region of the Zeeman splitting perturbed by weak quadrupole interactions on the one hand and the pure quadrupole resonance on the other (Fig. 15). In this way one obtains the greatest possible amount of information about the solid under investigation. The arrangement of the energy levels of all possible relationships of Zeeman energy, $\nu_L=\gamma H_0/2\pi$, and nuclear quadrupole interaction energy e^2qQ/h of a nucleus with $I=5/2$ is shown in Figures 18 and 19 for the angles $\vartheta=0°$ and 60° between H_0 and ϕ_{zz}[67].

The practical evaluation of such transition states is necessary in NMR measurements on chloro complexes[37], periodates, perrhenates, *etc.*

These experiments yield information in particular on:

1. the crystal structure: the NMR experiment enables one to draw conclusions regarding the point symmetry

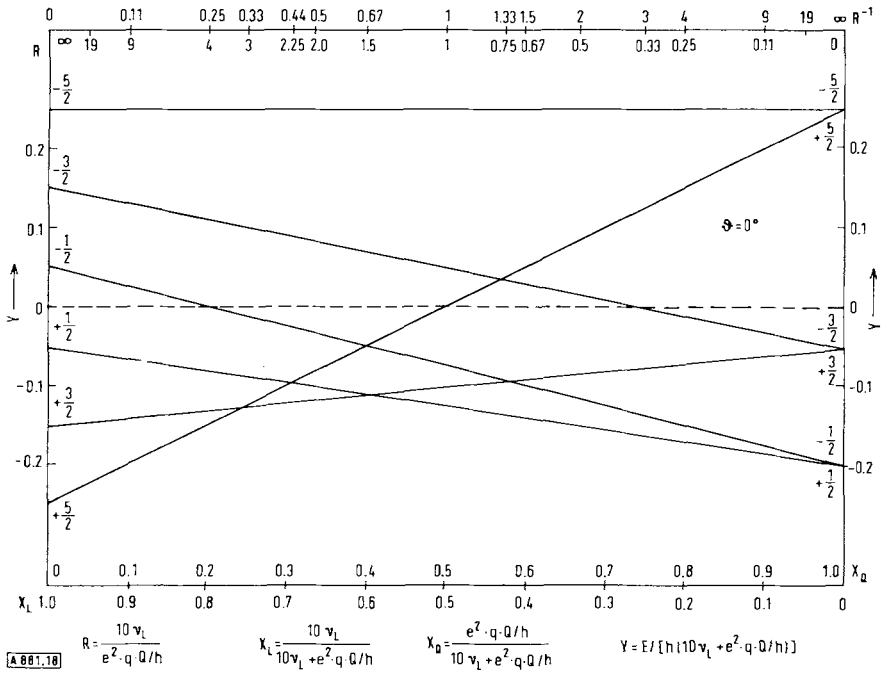


Fig. 18. Energy level diagram for a nuclear spin $I = 5/2$ under the influence of an electric field gradient and an external field H_0 for various ratios of the interaction energies $E_{Larmor}/h : e^2qQ/h$. The angle ϑ between ϕ_{zz} and H_0 is 0°.

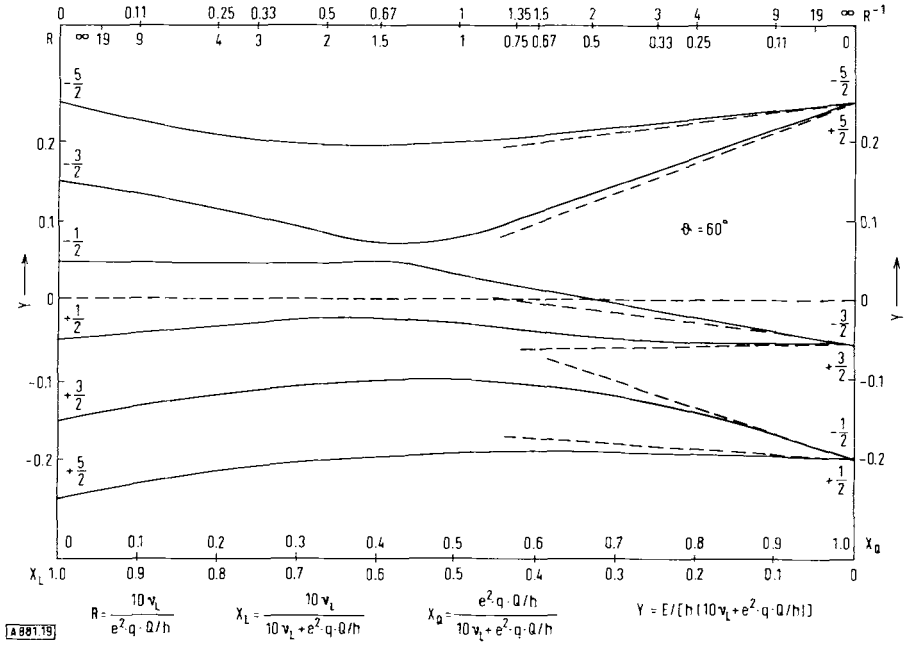


Fig. 19. Energy level diagram for a nuclear spin $I = 5/2$ under the influence of an electric field gradient and an external field H_0 for various ratios of the interaction energies $E_{Larmor}/h : e^2qQ/h$. The angle ϑ between ϕ_{zz} and H_0 is 60°.

of the nucleus in question and the symmetry elements of the unit cell (only the Laue groups influence the spectrum),

2. the charge distribution in the crystals, the arrangement of the point charges, the direction and strength of the induced dipole and quadrupole moments, *etc.*; these data are obtained indirectly from a model calculation, which can respond very sensitively to the point positions of the ions (atoms) in the lattice[45, 61],

3. the bond character (ionic component), as was mentioned earlier in connection with molecular crystals,

4. the ease of deformation of the electron core in the solid: the electric field gradient ϕ_{zz} acting at the position

of the nucleus is made up from the "external" gradient ϕ^a_{zz} and the gradient ϕ^i_{zz} induced in the core belonging to the nucleus under examination. The following relation is valid

$$\phi_{zz} = \phi^a_{zz} + \phi^i_{zz} = \phi^a_{zz}(1 - \gamma_\infty) \quad (10)$$

where γ_∞ is the Sternheimer factor. This factor, which can be found only by calculation, is very strongly dependent on the electron density distribution in the core. The NMR experiment allows a check on the quantum-mechanical calculations. For most of the ions γ_∞ is negative with values even down to -200.

The theory of quadrupole interactions in ionic crystals has been discussed at length by *Cohen* and *Reif*[44], and the literature between 1960 and 1966 is reviewed in[45]. The measurements should generally be carried out on single crystals if possible. However, the spectroscopic investigation of crystalline powders also leads to valuable though less extensive information.

One disadvantage of the interpretation of NMR studies on crystal fields is that one can usually obtain only quantitative information (after laborious calculations). Qualitative information is very difficult to obtain. This is because practically no systematic measurements on single crystals (which are fairly time-consuming) have been carried out for isotypic solids. As an example of a qualitative relationship, Figure 20 shows the linear dependence of the electric field gradient at the position of the Al^{3+} ion in alums on the radius of the monovalent cation (after[60] and literature values). Another example was provided by Mössbauer and NMR experiments on various garnets[62-65].

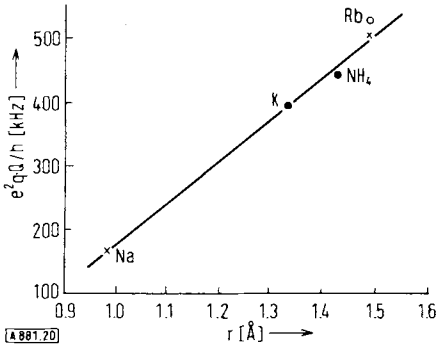


Fig. 20. Quadrupole coupling constants e^2qQ/h of ^{27}Al in sulfate alums as a function of the ionic radius $r(M^{1+})$ [60].

4.1. Crystal Defects

NMR spectroscopy is a valuable method for the investigation of lattice defects. It is mainly the electric field gradients due to defects that influence the nuclear magnetic resonance and can therefore be studied. Thus stresses due to cold working of metals affect the line widths of NMR spectra[27]. Dislocations in nonmetallic solids can also be studied in a similar manner. Very detailed information on dislocations can be obtained from measurements on single crystals[49].

Defects in solids have been intensively studied in alkali metal halides[6], and interesting and detailed results on the distortions around a foreign atom have recently been obtained by *Andersson*[50]. The development of sensitive nucleus-nucleus double resonance methods now makes it possible to study crystals with low contents of foreign atoms and thus to obtain information on crystal fields and field symmetry at the position of the nearest and next-nearest neighbors of foreign atoms (ions) (cf. *e.g.*[51]). Paramagnetic centers and their interactions with the environment can be determined from the spin-lattice relaxation time T_1 and from electron-nucleus double resonance experiments (ENDOR).

4.2. Glasses and High Polymers

It should be mentioned briefly here that the range of the interaction between nuclei and their environment is small (the electric field gradients fall off with $1/r^3$ from the point of origin). To a first approximation, therefore, the short-range order is decisive for the NMR experiment, and a glass behaves in the same manner as a crystalline powder. It has been reported that the point symmetries at the positions of alkali metal ions, Al^{3+}, B^{3+}, *etc.* in glasses can be determined in this way[52].

5. Dynamic Behavior of Solids and Nuclear Magnetic Resonance

So far we have considered only static lattices or we have assumed that the lattices are rigid. However, NMR spectroscopy is also very useful for the study of dynamic properties of solids. Both the line positions (resonance frequencies) and line shapes (line widths) as well as the relaxation behavior, particularly the spin-lattice relaxation time T_1, provide information about the dynamic behavior of solids.

5.1. Motions of Molecules and of Individual Groups on Molecules in Molecular Crystals

In molecular crystals, which are held together only by van der Waals forces, the potential barriers that hinder translation and rotation in the crystal are particularly low. The internal motions partly average out the nucleus-nucleus interactions [see eq. (7)]; as a result of motions of atoms and molecules, the NMR spectrum of a solid approaches that of a liquid. Numerous investigations have been carried out in this field. *Andrew*[54] has published a general report on motions in molecular crystals. As an example, we shall first discuss a recent investigation[53] on an organic crystal, hexamethylbenzene.

Figure 21 shows the second moment after *Van Vleck* and the spin-lattice relaxation time T_1 of the protons in hexamethylbenzene as functions of the temperature.

In the low-temperature phase I, the second moment slowly decreases with rising temperature. Its calculated value for the rigid lattice is 32.7 G^2. The difference from the values found by experiment is explained by a slow reorientation of the methyl groups, which occurs even at 2°K.

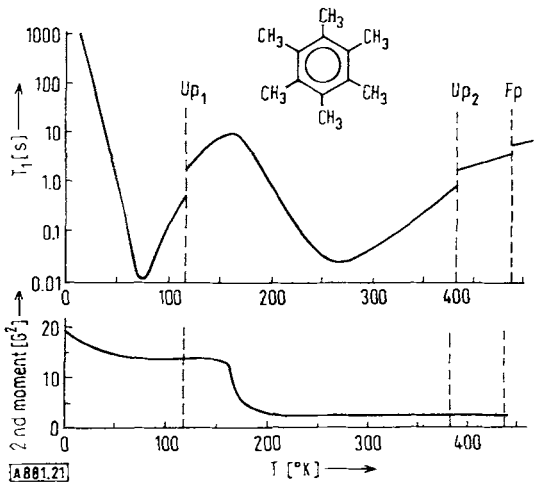


Fig. 21. Spin-lattice relaxation time T_1 and second moment of the ^{1}H-NMR of hexamethylbenzene. The substance has two transition points Up_1 and Up_2 below the melting point Fp [53].

At 50°K this reorientation becomes fast (compared with the Larmor frequency). The knowlege of the relaxation time T_1 in the region of the low-temperature phase allows the determination of the activation energy for the rotation of CH_3. T_1 is a function of the correlation time τ_c

$$T_1^{-1} \sim \left[\frac{\omega_0 \tau_c}{1+(\omega_0 \tau_c)^2} + \frac{4\,\omega_0 \tau_c}{1+(2\,\omega_0 \tau_c)^2}\right] \quad (11)$$

(ω_0 = Larmor frequency), and from the law for the activation energy of rotation (or translation):

$$\tau_c = \tau_0 \exp\{E_a/RT\} \quad (12)$$

it is possible to determine the activation energy E_a of the motion from measurements of T_1 as a function of temperature. The value found in this way for the rotation of CH_3 in $C_6(CH_3)_6$ is $E_a = 1.9 \pm 0.1$ kcal/mol. In phase II ($116\,°K \leqq T \leqq 383\,°K$), the entire molecule begins to rotate about the sixfold axis (above 150°K); the activation energy is 6.7 ± 0.1 kcal/mol. The high-temperature phase III cannot be interpreted by an additional motion.

In addition to various methylbenzene derivatives, molecules and ions having a tetrahedral structure, such as CF_4 [55], ammonium salts, and salts with BF_4^- as the anion, have been investigated.

Diffusion in solids can often be followed by NMR methods. Of the many published reports, we shall mention only the measurement of the diffusion of H and D in β-UH_3 and β-UD_3, respectively[56]. In addition to the Knight shift of the ^{1}H-NMR and the quadrupole coupling constants of ^{2}D, activation energies of 8.4 kcal/mol and 8.9 kcal/mol were found for the self-diffusion of protons and of deuterons, respectively, above 370°K.

Nuclear quadrupole resonance spectroscopy reacts very sensitively to internal motion of molecules and atoms (the ^{35}Cl resonance in $KClO_3$ has been proposed as a "thermometer"). From the temperature dependence of the resonance frequencies, it is possible to obtain information about the vibrations in the lattice, which usefully complements the findings of IR and Raman spectroscopy, as has been shown for the ^{35}Cl-NMR spectrum of K_2PtCl_6 [57]. Many studies are concerned with the elucidation of the "flipping" of the water molecules in crystal hydrates about their twofold axis by investigation of the temperature dependence of the ^{2}D-NMR spectrum.

5.2. Phase Transitions

NMR spectroscopy has frequently been used for the study of phase transitions, particularly for the investigation of ferroelectric crystals. The electric field gradients in ferroelectrics are of great interest. In the ferroelectrics characterized by hydrogen bonds, ^{2}D-NMR is an important aid in the investigation of the mechanism that leads to spontaneous polarization (see *e.g.*[58]).

6. Conclusion

The field of application of nuclear magnetic resonance in solid-state chemistry is thus large. With the aid of this

Table 2. NMR and NQR in solid-state chemistry.

Nature of the interaction	Observation in the spectrum	Information
Magnetic nuclear dipole interaction (NMR)	(a) Broadening or splitting of the resonance line as a function of the angle between the crystal axis and the external field H_0 and as a function of temperature (b) Spin-lattice relaxation time T_1	Determination of interatomic (internuclear) distances in the crystal (static); motions of atoms, groups and molecules in solids, such as translation (diffusion) and rotation
Interaction: nuclear dipole-electron (NMR)	(a) Shift of the resonance line due to internal fields H_i (b) T_1	Chemical bonding; valency state; magnetic properties such as susceptibility, fields in ferromagnetic materials, magnetic structures; metallic state (electron gas in metals)
Interaction: nuclear quadrupole-electric field gradient (NQR)	(a) Broadening and splitting in the spectrum (b) T_1	Chemical bonding; charge distribution in ionic crystals; point symmetries in the crystal (crystal structure); defects and dislocations (real structure); dynamic properties (internal degrees of freedom)

method, many partial questions can be answered, models can be confirmed, and theories supported. The simultaneous use of other methods, particularly diffraction methods, can increase the value of NMR information. A synopsis of the points discussed in this article is presented in Table 2.

I am grateful to Dr. Wolf Weyrich for critical comments on the manuscript.

Received: October 28, 1970 [A 881 IE]
German version: Angew. Chem. *84*, 498 (1972)
Translated by Express Translation Service, London

[1] *A. Abragam*: The Principles of Nuclear Magnetism. Oxford University Press, London 1961.

[2] *C. P. Slichter*: Principles of Magnetic Resonance. Harper & Row, New York 1963.

[3] *E. R. Andrew*: Nuclear Magnetic Resonance. Cambridge University Press, London 1956.

[4] *A. Lösche*: Kerninduktion. Deutscher Verlag der Wissenschaften, Berlin 1957.

[5] *H. Strehlow*: Magnetische Kernresonanz und chemische Struktur. D. Steinkopff, Darmstadt 1968.

[6] *L. Ebert* and *G. Seifert*: Kernresonanz in Festkörpern. Akademische Verlagsgesellschaft, Leipzig 1966.

[7] *H. Kopfermann*: Kernmomente. Akademische Verlagsgesellschaft, Frankfurt/Main 1956.

[8] *G. E. Pake*, J. Chem. Phys. *16*, 327 (1948).

[9] *L. W. Reeves*, Progr. Nucl. Magn. Resonance *4*, 193 (1969).

[10] *R. Chidambarum*, J. Chem. Phys. *36*, 2361 (1962).

[11] *J. W. McGrath* and *A. A. Silvidi*, J. Chem. Phys. *34*, 322 (1961).

[12] *I. Berthold* and *A. Weiss*, Z. Naturforsch. *A 22*, 1433 (1967).

[13] *M. Van Meerssche* and *J. M. Dereppe*, J. Chim. Phys. Physicochim. Biol. *63*, 17 (1966).

[14] *R. E. Richards* and *J. A. S. Smith*, Trans. Faraday Soc. *47*, 1261 (1951).

[15] *J. H. Van Vleck*, Phys. Rev. *74*, 1168 (1948).

[16] *E. R. Andrew*, Proc. XIV. Colloq. AMPERE, p. 388 (1967); Proc. Roy. Soc. (London), Ser. *A 291*, 257 (1966).

[17] *I. J. Love*, Phys. Rev. Lett. *2*, 285 (1959).

[18] *J. S. Waugh, C. H. Wang, L. M. Huber*, and *R. L. Vold*, J. Chem. Phys. *48*, 662 (1968); *U. Haeberlen* and *J. S. Waugh*, Phys. Rev. *175*, 175 (1968); *J. S. Waugh* and *L. M. Huber*, J. Chem. Phys. *47*, 1862 (1967). *J. D. Ellett, Jr., M. G. Gibby, U. Haeberlen, L. M. Huber, M. Mehring, A. Pines*, and *J. S. Waugh*, Advan. Magn. Resonance *5*, 117 (1971).

[19] *H. S. Gutowsky* and *B. R. MacGarvey*, J. Chem. Phys. *21*, 1423 (1953).

[20] *N. Bloembergen* and *P. P. Sorokin*, Phys. Rev. *110*, 865 (1958).

[21] *R. Baron*, J. Chem. Phys. *38*, 173 (1963).

[22] *J. Itoh* and *Y. Yamagata*, J. Phys. Soc. Jap. *13*, 1182, 1232 (1958); *14*, 225 (1959); *17*, 481 (1962); J. Chem. Phys. *24*, 621 (1956).

[23] *J. Kondo* and *J. Yamashita*, J. Phys. Chem. Solids *10*, 245 (1959).

[24] *Y. Yamagata*, J. Phys. Soc. Jap. *19*, 10 (1964).

[25] *L. H. Piette* and *H. E. Weaver*, J. Chem. Phys. *28*, 735 (1958).

[26] *R. Freeman, R. P. Gasser*, and *R. E. Richards*, Mol. Phys. *2*, 301 (1959).

[27] *T. J. Rowland*, Progr. Mater. Sci. *9*, 3 (1961).

[28] *R. T. Schumacher* and *C. P. Slichter*, Phys. Rev. *95*, 1089 (1954); *101*, 58 (1956); *R. T. Schumacher* and *W. F. Vehse*, J. Phys. Soc. Jap. *17*, Suppl. B-I, 460 (1962).

[29] *D. Rohy* and *R. M. Cotts*, Phys. Rev. *31*, 2070 (1970).

[30] *H. Lütgemeier*, Z. Angew. Phys. *24*, 246 (1968).

[31] *H. W. Spiess, H. Haas*, and *H. Hartmann*, J. Chem. Phys. *50*, 3057 (1969).

[32] *D. A. Anderson*, J. Chem. Phys. *40*, 1168 (1964).

[33] *N. Bloembergen*, Physica (Utrecht) *16*, 95 (1950).

[34] *J. Itoh* and *Y. Kamiya*, J. Phys. Soc. Jap. *17*, Suppl. B-I, 512 (1962).

[35] *R. S. Shulman* and *B. J. Wyluda*, J. Chem. Phys. *35*, 1498 (1962).

[36] *D. E. O'Reilly* and *T. Tsang*, J. Chem. Phys. *40*, 734 (1964).

[37] *H. Rinnenberg, H. Haas*, and *H. Hartmann*, J. Chem. Phys. *50*, 3064 (1969).

[38] *R. D. Spence, W. J. M. de Jonge*, and *K. V. S. Rama Rao*, J. Chem. Phys. *51*, 4694 (1969).

[39] *A. C. Gossard* and *A. M. Portis*, Phys. Rev. Lett. *3*, 164 (1959); *A. M. Portis* and *A. C. Gossard*, J. Appl. Phys. (Suppl.) *31*, 205 (1960).

[40] *R. C. La Force, S. F. Ravitz*, and *G. F. Day*, J. Phys. Soc. Jap. *17*, Suppl. B-I, 99 (1962).

[41] *M. Bose*, Progr. Nucl. Magn. Resonance *4*, 335 (1969).

[42] *E. A. C. Lucken*: Nuclear Quadrupole Coupling Constants. Academic Press, New York 1969.

[43] *T. P. Das* and *E. L. Hahn*, Solid State Phys. Suppl. *1*, 1 (1958).

[44] *M. H. Cohen* and *F. Reif*, Solid State Phys. *5*, 321 (1957).

[45] *A. Weiss*, Proc. XIV. Colloq. AMPERE, p. 1076 (1967).

[46] *W. Van Bronswyk*, Struct. Bonding (Berlin) *7*, 87 (1970).

[47] *G. A. Jeffrey* and *T. Sakurai*, Progr. Solid State Chem. *1*, 380 (1963).

[48] *D. Biedenkapp* and *A. Weiss*, Ber. Bunsenges. Phys. Chem. *70*, 788 (1966).

[49] *O. Kanert* and *M. Mehring*: NMR, Basic Principles and Progress. Springer, Berlin 1971, Vol. 3.

[50] *L. O. Andersson*, Proc. XIV. Colloq. AMPERE, p. 1101 (1967).

[51] *P. R. Spencer, H. D. Schmid*, and *C. P. Slichter*, Phys. Rev. B *1*, 2989 (1970).

[52] *P. J. Bray* and *A. H. Silver*, Mod. Aspects Vitreous State *1*, 92 (1960).

[53] *P. S. Allen* and *A. Cowking*, J. Chem. Phys. *47*, 4286 (1967).

[54] *E. R. Andrew* and *P. S. Allen*, J. Chim. Phys. Physicochim. Biol. *63*, 85 (1966); *E. R. Andrew*, J. Phys. Chem. Solids *18*, 9 (1961).

[55] *L. Niemelä* and *M. Niemelä*, Ann. Acad. Sci. Fenn., Ser. A *6*, No 341 (1970).

[56] *J. Grundzweig-Genossar, M. Kuznietz*, and *B. Meerovici*, Phys. Rev. B *1*, 1958 (1970).

[57] *R. L. Armstrong, G. L. Baker*, and *K. R. Jeffrey*, Phys. Rev. B *1*, 2897 (1970).

[58] *R. Blinc*, Advan. Magn. Resonance *3*, 141 (1968).

[59] *M. Schlaak* and *A. Weiss*, Solid State Commun. *8*, 1241 (1970).

[60] *N. Weiden*, Diplomarbeit, Universität Münster 1970.

[61] *P. Schmidt*, Diplomarbeit, Universität Münster 1969.

[62] *K. C. Brog, W. J. Jones, Jr.*, and *C. M. Verber*, Phys. Lett. *20*, 258 (1966).

[63] *W. J. Nicholson* and *G. Burns*, Phys. Rev. A *133*, 1568 (1964).

[64] *V. H. Schmidt* and *E. D. Jones*, Phys. Rev. B *1*, 1978 (1970).

[65] *E. D. Jones* and *V. H. Schmidt*, J. Appl. Phys. *40*, 1406 (1969).

[66] *A. Weiss* and *A. Wüst*, unpublished results.

[67] *W. Weyrich*, Dissertation, Technische Hochschule Darmstadt 1971.

The Study of Prehistoric Metallurgy

By Axel Hartmann and Edward Sangmeister[*]

The puzzle we have to solve is: How did prehistoric man live? Archeologists and scientists, chemists and prehistorians have now joined forces in applying much imagination and painstaking effort to the search for a solution. Some of the fruits of their cooperation are presented in this progress report.

1. Scientific Methods

Archeology is now able to provide us with an—admittedly still rather sketchy—picture of prehistoric man, his way of life, customs, and environment. The more we see and learn of his utensils, jewellery, and tools, the more pressing becomes the question of how all these objects were made, *i. e.* the question of the technical knowledge, aptitude, and scope of prehistoric man. This field is to some extent the precinct of the archeologist himself. However, as far as the study of prehistoric metallurgy goes, *i. e.* the working of metals and their extraction from ores in prehistoric times, it is clear that close cooperation between archeologists and scientists is very necessary. The aim of such studies should be, on the one hand, a metallographic investigation of the structure of prehistoric metal finds, and, on the other, a chemical investigation of such finds to ascertain their quantitative composition. It is primarily the second aim that has been pursued during the last twenty years by the "Study Group for Ancient Metallurgy of the Central Roman-Germanic Museum" with whose work the present article is largely concerned. With the support of the Deutsche Forschungsgemeinschaft such studies have been carried out at the Württemberg State Museum in Stuttgart, this work now having become the main research activity of the physical chemistry laboratory.

At Stuttgart attention was first directed to the analytical study of a large number of prehistoric copper and gold specimens rather than metallographic texture investigations, since:

1. Analytical studies require only a small sample of material; the object itself can remain in the museum. This aspect becomes particularly important when considering specimens in the possession of foreign museums. Textural studies, on the other hand, require that the object of investigation be transported to the laboratory.

2. Analytical studies also promised to reveal trading routes and connections between prehistoric cultures whenever it is possible to detect differing degrees of skill in alloying metals or to distinguish between metallic materials of different origin according to the various constituents present and to recognize historical and geographical boundaries. The eventual goal is to elucidate the direction and rate of spreading of ancient methods of metal extraction and working.

In contrast, textural studies mainly yield information about the technical details of the way in which the metal was worked to give the finished product, *e. g.* whether is was beaten, cast, annealed, or quenched. It would certainly be most interesting to be able to follow the dissemination of this technical knowledge too; however, chemical analysis appeared more promising and more practicable.

For the reasons mentioned in point 1 above, it was not so much a matter of finding a completely non-destructive method of analysis—as might initially be thought—but of choosing a method capable of providing a complete quantitative analysis with a small sample of material, in which the possible concentrations of minor components may range over several powers of ten. Bearing in mind that an examination of several thousand objects, and not just random samples, was intended (over 20000 prehistoric copper finds and about 3300 gold ones have so far been analyzed), it becomes clear that time-consuming micro or semimicro wet analyses had to be ruled out immediately. Emission spectroscopy offered a working compromise between the time and effort invested, size of sample, and costs incurred on the one hand and accuracy and sensitivity of analysis on the other.

An additional factor influencing our choice was the existence of earlier spectral analyses of prehistoric copper objects by *Winkler*[1], *Otto* and *Witter*[2], and *van Doorselaer*[3]. *Scheufele*[4] utilized the available experience to develop a method requiring 40 mg of substance that was suitable for routine analyses. However, the technique requires calibration alloys containing all likely minor components Sn, As, Sb, Ni, Bi, Ag, Pb, *etc.*, which are not always easy to prepare.

It was only after several years' experience in the analysis of about 10000 Early Bronze Age copper objects producing some encouraging results that the question arose of extending such studies to prehistoric gold finds.

The particular value of the objects involved makes it all the more important to work with samples that are as small as possible. A method was successfully developed[5] that permits spectral determination of minor components down to 0.01% or less in a 2-mg sample of gold. Above all it proved possible to avoid use of calibration alloys of gold/silver/copper containing possible minor components by

[*] Dr. A. Hartmann
Chemisch-physikalisches Laboratorium
Württembergisches Landesmuseum
7 Stuttgart 1, Schillerplatz 6 – Altes Schloss (Germany)

Prof. Dr. E. Sangmeister
Institut für Ur- und Frühgeschichte der Universität
78 Freiburg, Adelhauser Strasse 33 (Germany)

applying drops of the dissolved sample to graphite electrodes. Calibration then only requires gold solutions containing the same minor components in known concentrations.

In this way it was possible to include even highly valuable collections from German and foreign museums in our studies and to dispel any original misgivings.

2. Interpretation of Copper Analyses[6]

As mentioned above, spectral analyses of prehistoric copper objects can be interpreted in two ways. Firstly, the kinds of alloys can be determined and technical advances traced; secondly, it appears possible, on the basis of characteristic impurities, to establish the ore used and thereby the deposits from which prehistoric man obtained the raw materials for certain utensils. The distribution of the utensils and their distance from the source of raw materials should then permit further conclusions to be drawn regarding trading in the period concerned and thus also regarding the direction and rate of propagation of techniques for extraction and working of metals.

However, whereas the determination of the kinds of alloys gave rise to no significant difficulties, ascertainment of the ore deposits proved less simple than originally envisaged since the deviations between the deposits are hardly sufficient to provide more than rough indications. Moreover, comparison of presently accessible ore samples with analyses of prehistoric finished articles is beset with problems. The ore samples come largely from modern underground mines and their composition may differ widely from those surface outcrops accessible to prehistoric man. In addition, we have no knowledge of the smelting processes used at the dawn of history to extract metals from their ores; the technical details—*e.g.* temperature control alone—of the process would certainly affect the composition of the final product.

The direct question of ore deposits was therefore dropped by the Stuttgart group and some indication of origin sought instead by comparison of analyses of prehistoric objects. Such comparisons require a method capable of sifting through large amounts of analytical data for material whose uniform composition can be attributed to the same raw material and corresponding technical processes. The method of choice was a statistical model previously described by *Klein*[4]. Its use permitted classification of materials having the same combinations of elements to a first approximation as so-called "material groups". The material groups can be localized geographically and chronologically, as will be seen from the maps in Figures 1—4.

The distribution of a material group A indicates the area in which this material has been most frequently used and those in which it remained unknown, it can also be seen in which prehistoric periods it first featured in trading, when it dominated the market, and when it disappeared again. Although the exact origin of the raw material is not established, a definite contribution is made to the history of commerce. And if it also proves possible to demonstrate that the material in question is endowed with characteristic qualities that render it suitable or unsuitable for one purpose or another, then reasons can also be given for its popularity or decline.

Copper and its alloys and gold were chosen for our studies. A factor in their choice was that these two materials are the first metals to have been used by man. This is not altogether surprising since they both occur as the native metal. Prehistoric man will have been more readily confronted with them than with, *e.g.* iron, which occurs native only in meteorites.

It is important to realize the full meaning of the sentence: "Man was confronted with these materials." In the course of prehistory we see man constantly searching for materials—this searching is therefore by no means limited to the industrial age—and subjecting all new substances to familiar technical procedures. For instance, we know that during the Neolithic age, in which the first copper and gold was found, man had mastered the following techniques: hewing, chipping, grinding, perforation of soft stones and bones; hewing and grinding of flint; all kinds of woodworking with stone tools; firing of clay (ceramics). On application of these techniques to native gold or copper he will have seen how to shape these materials by beating and thus discover "cold forging". After overcoming his initial disappointment about the lack of any hardening effect akin to that clay when the metals were heated in an open fire or in a simple potters kiln, he will have found that they are more readily shaped while hot ("hot forging"). He must also have seen the melting of these metals although unable to utilize it because of the inadequate temperatures reached in his simple pottery kiln. Such temperatures only became accessible in the kilns available in the Mesopotamian cultures of the 4th millenium BC. Although there was no copper in Mesopotamia itself such a state of culture had been reached in the 4th millenium that raw materials could be transported from deposits in the surrounding mountainous country. The demand arose when the Mesopotamian cultures began to fashion precious materials into amulets, statuettes, jewellery, *etc.* Polished malachite was one such material used for adornment. It is conceivable that fire testing in a pottery kiln gave the first smelted copper, although we shall never be able to prove it. We can be sure, however, that the first copper artifacts come from the 4th millenium in Mesopotamia, as do the oldest gold objects known. The exploitation of the malleability as a characteristic metal property marks the beginning of metallurgy.

Our reasons for not studying objects from hither Asia are of a purely practical nature. It would simply have been too costly to obtain sufficient analytical samples from relevant finds, for we were fully aware that only extensive series of samples could provide conclusive results in view of the statistical method of evaluation necessary. We therefore began our investigations on prehistoric finds from Europe although we knew that we were dealing with a kind of "developing area" where the first techniques of metalworking were introduced as established procedures. However, we may assume that then, as now, nobody would freely

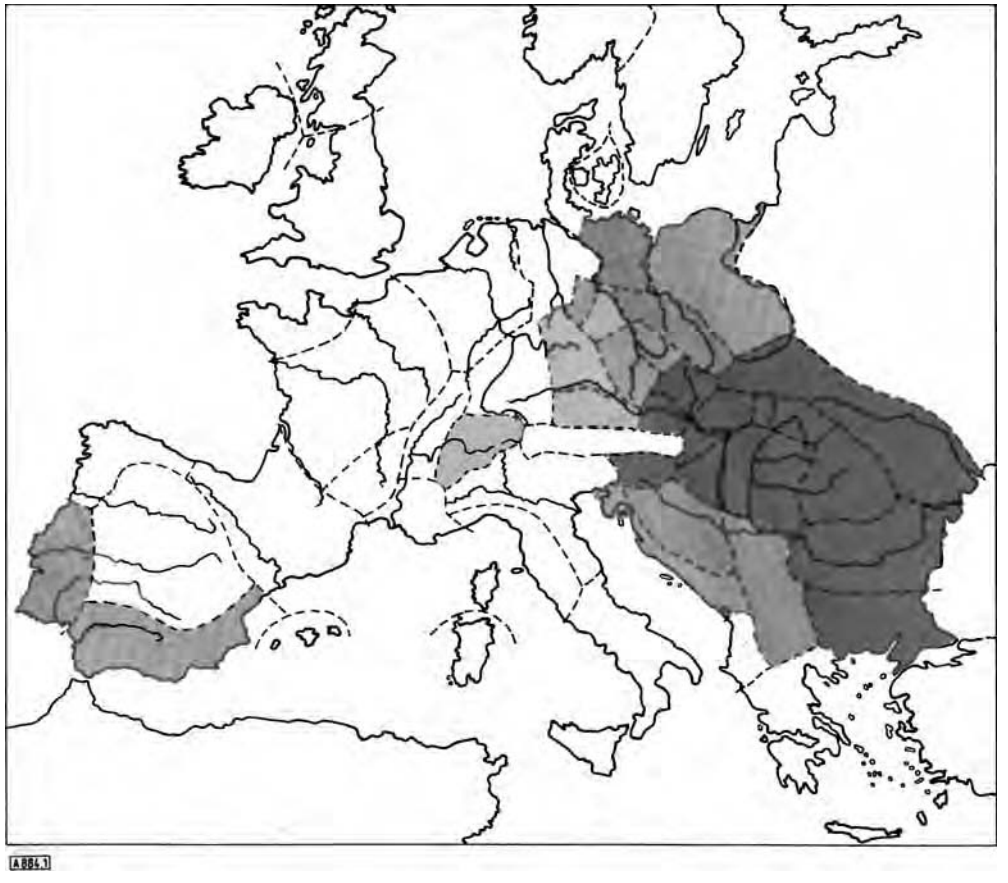


Fig. 1. Distribution of material group copper E 00 during the Copper Age at the end of the 3rd and beginning of the 2nd millenium BC. The material is free from impurities except for small quantities of silver. The map shows the first regions of copper-working in Europe and the directions in which it spread. It is assumed that the requisite knowledge was transmitted from the Near East. The areas of densest distribution are most heavily shaded and those of less dense distribution correspondingly lightly.

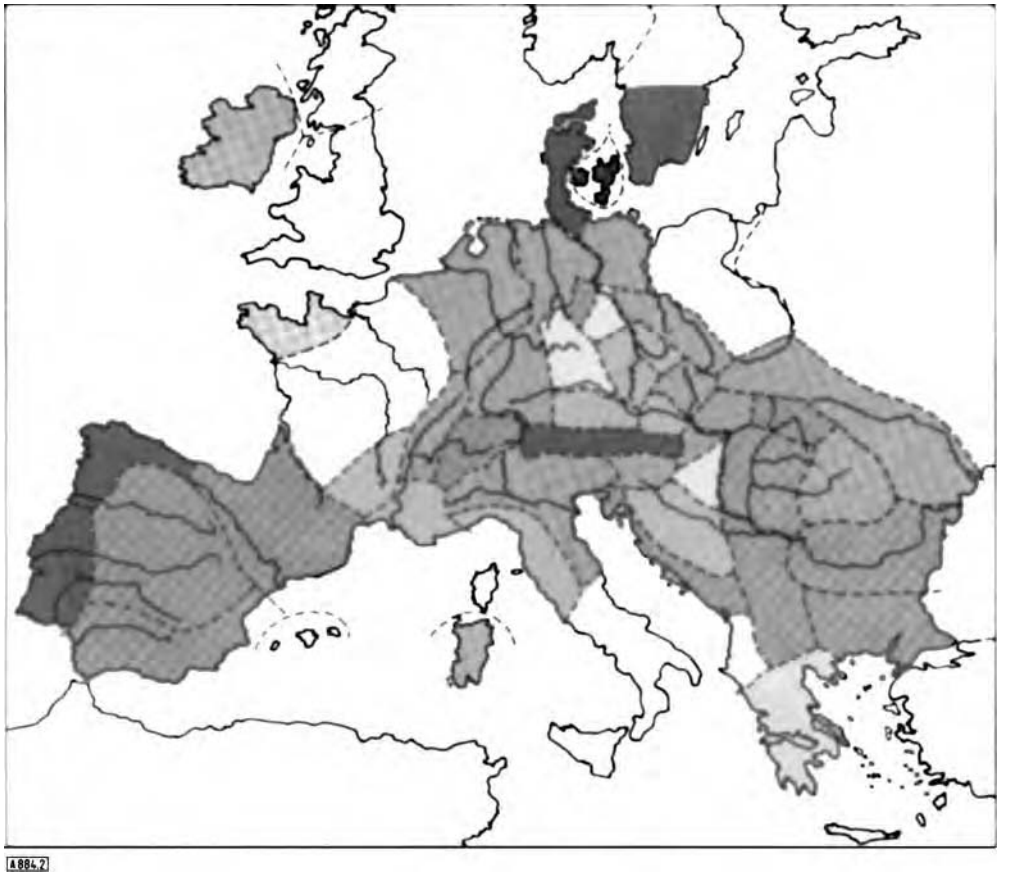


Fig. 2. Centers and distribution of the first arsenic bronze (material group copper E 01 A). Arsenic bronze seems to have been discovered in the Aegean and then produced in areas possessing the raw material. From these areas it was traded over large distances during the later Copper Age at the beginning of the 2nd millenium BC. The material shown contained no impurities other than arsenic (up to about 7%) and small amounts of silver. For meaning of shading see Fig. 1.

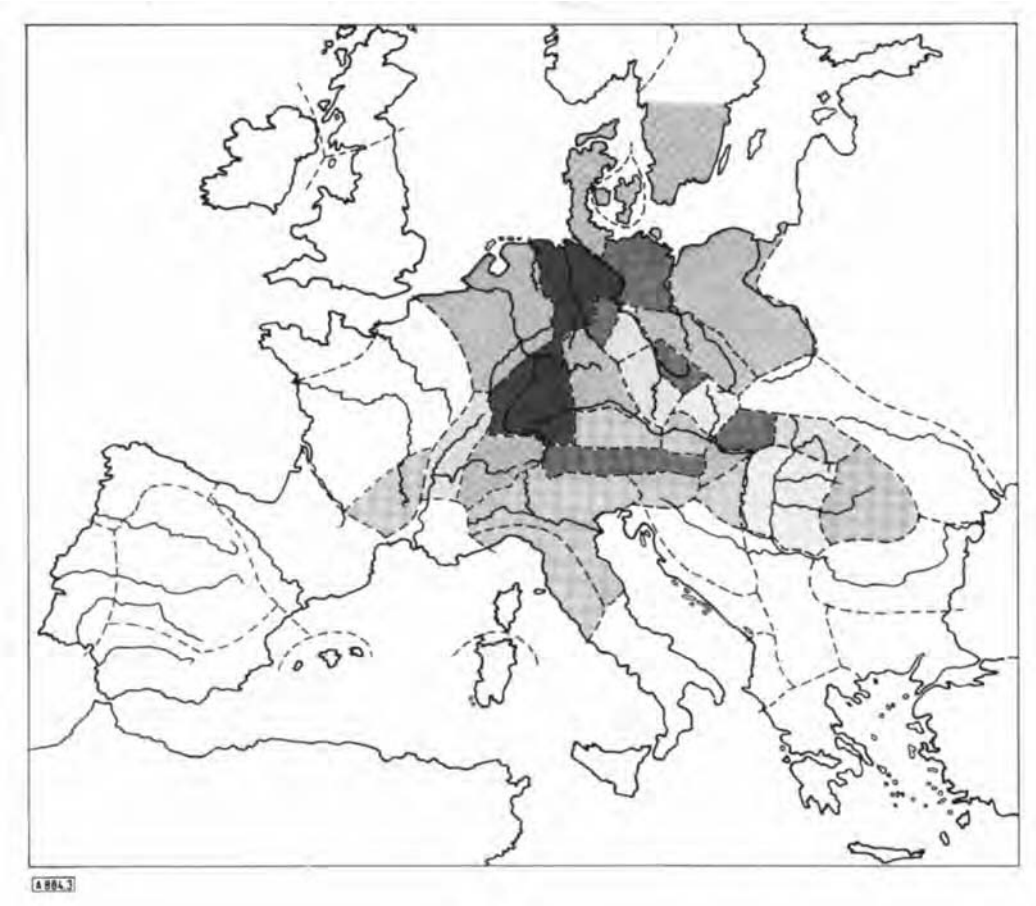


Fig. 3. Distribution of material group copper A during the Early Bronze Age, 18/17th century BC. The material is characterized by high contents of arsenic, antimony, silver, and nickel and by the complete absence of bismuth. Antimony and nickel often reach several per cent. For meaning of shading see Fig. 1.

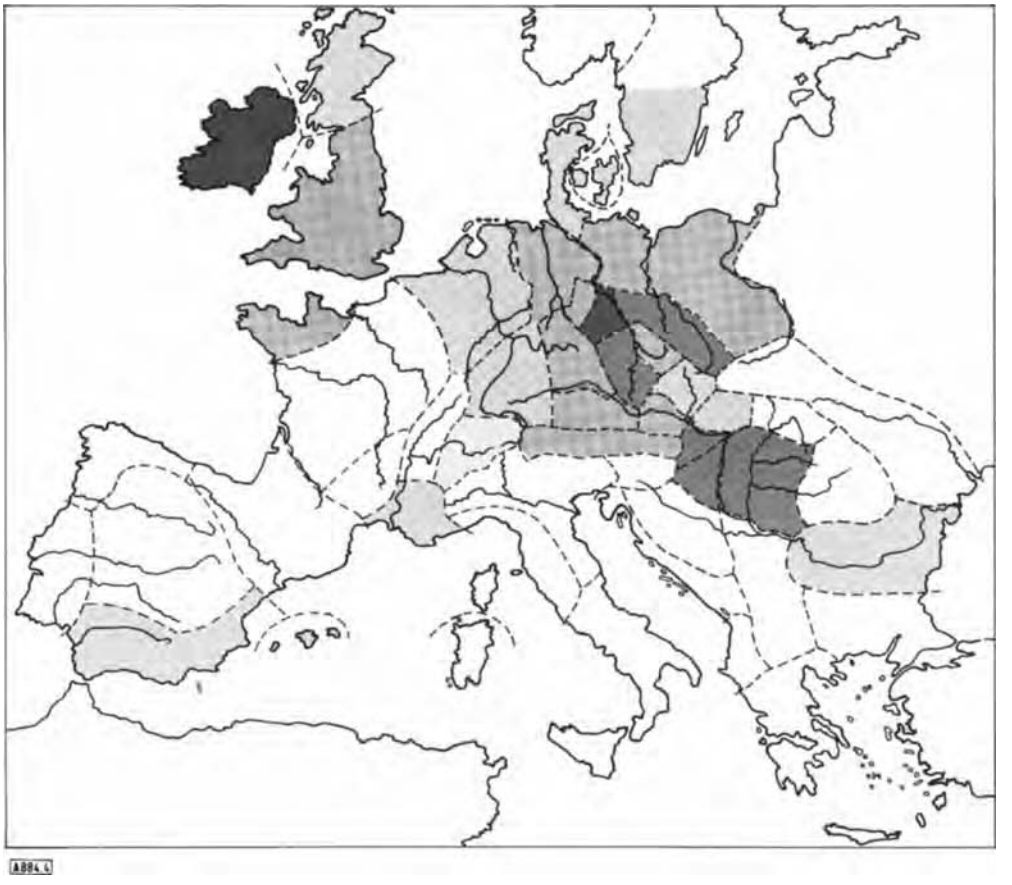


Fig. 4. Distribution of material group copper E 11 B, characterized by contamination with arsenic, antimony, and silver, by the absence of nickel, and by the presence of less than 0.02% of bismuth. The material was used exclusively during the Early Bronze Age, 18/17 century BC, although apparently discovered later than A. For meaning of shading see Fig. 1.

broadcast the secrets of working a new material. Rather, attempts will have been made to satisfy home demand from foreign deposits without revealing too much secret knowledge.

3. Results of Copper Studies[6]

After preliminary evaluation of about 20000 analyses of prehistoric copper and bronze objects we can now provide the following picture regarding Europe.

In the middle of the 3rd millenium BC certain communities having a farming economy and living in permanent settlements in present-day Bulgaria, Romania, and southern Yugoslavia came to know copper. They used it to produce simple utensils and jewellery such as awls, needles, and wire and sheet rings. The copper is almost completely free from impurities and probably partly native copper and partly won from surface outcrops of ore. Possible sources are deposits in the neighborhood of Niš in Yugoslavia and in the Carpathians. This copper is very different from that used during the same period in the eastern Mediterranean and Anatolia, in so far as suitable analytical samples were at our disposal. This seems to confirm the assumption that copper-seekers from the Near East traveling to the Carpathians and the region of Niš passed on a knowledge of rudimentary metallurgical processes to the local inhabitants.

The picture changes about 100 years before the beginning of the 2nd millenium. It appears that large scale exploitation then began of the copper deposits throughout the whole Carpathian basin, the material being worked for local requirements and for export. The utensils, axes, axe-adzes, hammer axes, *etc.*, are characterized by their large size, thickness, and corresponding weight. They were possibly also used as a source of raw material in the same way as the later ring ingots. They are frequently found, like the latter, in large numbers where they had apparently been hoarded. This would also suggest that a special closed guild of metalworkers provided the farming settlers with an established supply of utensils. Utensils produced in these parts traveled as far as the Baltic in the north and Bavaria in the west. The copper of this period is practically free from impurities and was therefore probably still obtained largely from oxide ores. The large amounts worked preclude any large contribution by native copper.

An analogous process probably took place in west Europe during the same period. Originating from the Cyclades or from Syria, the copper seekers seem to have established a series of fortified factories along the coast of Spain and Portugal. They probably again initially used oxide ores from surface outcrops, as is apparent from the complete lack of impurities in the oldest artifacts. A little later, evidence is found for all stages of copper extraction and working; crude ore was in places transported more than 40 km from the deposits to the factories where it was smelted on a small scale and made into ingots, utensils, and jewellery, and prepared for transport and stored. Some of the objects resemble those from the eastern Mediterranean, as does the composition of the material in a number of cases, thus suggesting a certain degree of mutual trading. The metal concerned is characterized by the, presumably natural, presence of antimony, arsenic, and bismuth.

Thanks to its arsenic content the eastern Mediterranean copper produced during this period—at the dawn of the 2nd millenium BC—could readily be cast in one- or two-piece molds, as have also been found. It would also seem probable from the suggested trading that searches were instigated for copper ore having a similar arsenic content and the same good casting properties on the Iberian peninsula. Such deposits were found in abundance and formed the basis for the production of "arsenic bronze" in which copper-arsenic alloys having 5—8 % As were manufactured by raising the proportion of arsenic, possibly even by addition of the native element.

Arsenic bronze, equally familiar in the western and the eastern Mediterranean, then spread throughout the whole of Europe. Interestingly, the first metal-saving utensils, *e.g.* small sharp-edged axes, appear simultaneously with arsenic bronze. The material clearly competed with other kinds of copper produced at the same time in southeast Europe. However, the latter were technically inferior to arsenic bronze because the impurities they contain—antimony, silver, in some cases bismuth too—do not enhance its properties, at least in the proportions present.

A further metallurgical improvement occurred in the 18th century BC when new ores were worked and production began using central European ores from the eastern Carpathians to the Harz Mountains, and possibly even those from the Hardt region in southwest Germany. These ores are characterized by a varying high content of arsenic, antimony, nickel, silver, and bismuth. They yield at least five readily distinguishable kinds of copper and explain the abundance of metal objects in particular groups of societies, an abundance that led archeologists to speak of "Bronze-Age" cultures. It is only since the advent of chemical analysis that we know the frequently light-colored products to be neither arsenic- nor tin bronzes but that their light color is often attributable to their content of silver and nickel, the impurities amounting to 5 to 10% in many cases.

The production of these kinds of copper is associated with a whole new range of utensils and jewellery. It appears that the ring ingots were then first used as currency. They are open neck rings with recoiled ends which, after surface finish, were worn as adornment, and also represented the trading form of the metal. Hoards of several hundred such ring ingots have been discovered. They usually still carry direct evidence of the casting process.

Each variety of copper in this period has its own area of distribution from which the production and marketing regions can be deduced as exemplified by the distribution maps in Figures 3 and 4. Thus Figure 3 depicts the rather narrow distribution of the variety of copper denoted as material group A, while Figure 4 shows the much larger export distribution of another variety of copper (E 11 B) from central Europe. Such exports traveled to areas that had hardly been reached before, for instance Ireland and England, and areas, such as northern Germany, where they were in direct competition with the established

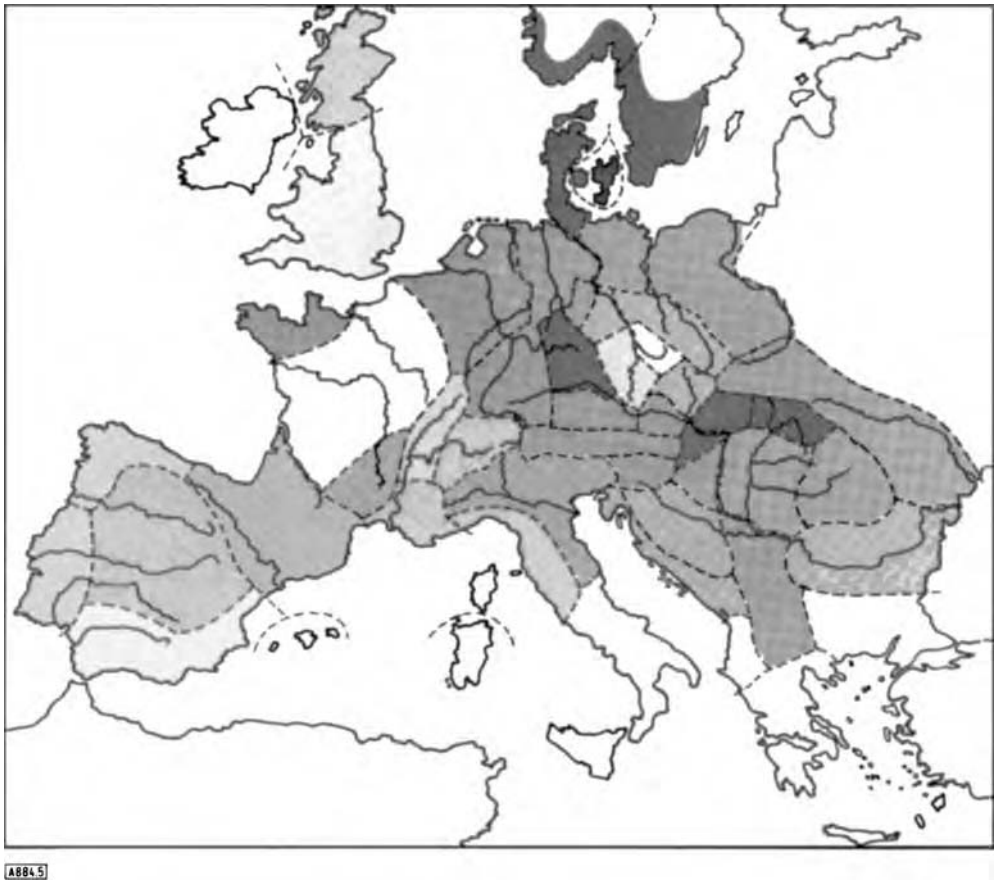
southern European suppliers (cf. Fig. 1). This trade also extended to the south, namely to Italy, where it counteracted local trade not discussed here. It even penetrated the old exporting regions of southeast Europe, without going much farther to the east or south, however, than the Carpathians. Southwest Europe was hardly affected by these exports, for production of the extremely useful arsenic bronze was continued there (Fig 2).

One of the export routes mentioned above assumed particular importance because it initiated the next step in metallurgy, for this period of central European copper manufacture witnessed the crucial step of alloying with tin, to produce the genuine tin bronze which played a dominating role for many centuries until finally ousted by iron.

Even today we still cannot say where and when alloying with tin was discovered. It appears that tin bronze was known in the orient during the 3rd millenium BC although it is still mysterious from which deposits the tin came. We do know that the tin bronze that suddenly appeared in central Europe in the 17th century BC was manufactured from typically central European varieties of copper. It therefore appears reasonable to think of a rediscovery of bronze in these regions, particularly since one of the few accessible tin deposits was located in the frontier mountains between Saxony and Czechoslovakia. Copper seekers and -workers could have come across a mixture of copper and tin ores and thus become acquainted with the tin alloy which was even superior in its casting and hardening properties to arsenic bronze. Possessing such experience, concentrated searches for tin ores could now be made.

Alloying with tin opened up further technical possibilities. Reuse of older material, which could be rendered suitable for producing all kinds of castings by admixture of tin, became more important. As a result new varieties of copper dating from about 1600 BC and thereafter can be legitimately suspected to have been manufactured from previously worked material. Hoarded older material—belonging to scrap collectors— features far more often in archeological finds from this time than deposits of bars (Fig. 5).

Understandably, it becomes difficult in these circumstances to find really informative material groups on analysis of prehistoric objects. We have to content ourselves with distinguishing between groups obtained from raw materials and those produced from salvaged material or from a mixture of scrap and ore. It already appears possible to make a preliminary statement on this topic: In the Mediterranean regions, from the Greek Archipelago *via* Italy to southern France, and also in Switzerland, recourse was apparently again made to ore deposits affording uncontaminated copper; or perhaps the first success at refining can be placed in this period. In southeast, central, and north Europe, however, it must remain an open question to what



A884.5

Fig. 5. Distribution of material group copper FB 1. The material appears to have dominated the central and north European market from the 16th century BC onwards. Arsenic and antimony are present in small to average quantities ($\approx 0.05\%$), and the nickel concentration is invariably $> 0.1\%$. It is possible that different kinds of older material were melted down together. For meaning of shading see Fig. 1.

extent local ore was worked together with scrap material from the whole region. We do know, though, that underground mining of copper had already begun by this time (as found in the Austrian Alps). The metal produced probably contained nickel as the sole impurity.

It may be of interest in conclusion to dwell for a moment on the effect of the smelting and working of copper on the social structure of European regions. Whereas copper-working played a subordinate role in the cultures of the Near East and Crete at the end of the 3rd and beginning of the 2nd millenium BC, it seems at least to have contributed to a change in social structure in Europe before the middle of the 2nd millenium. At this time, a socially superior class can be detected in many parts of Europe whose graves were richly provided with noble metal objects and other valuables. It is certainly significant that they are found in the Aegean commercial and cultural center, in the shaft graves of Mycenae, and in the copper production region of, *e.g.* Transylvania, the western Carpathians, the Harz Mountains, and in west Switzerland. They likewise occur in the tin producing areas of Brittany and the south of England. Applying all caution it is probably valid to assume a mutual connection between the appearance of this socially privileged class and a prosperity due to production of and trading in metal.

4. Interpretation of Gold Analyses

Many parts of Europe have no natural gold deposits at all. As examples we can consider the whole north German plain, the Netherlands, Belgium, and Denmark. Nevertheless, these regions abound in archeological gold specimens dating from prehistoric times; indeed, Denmark can be regarded as particularly rich in such finds. The material used to produce the gold bracelets, dishes, beakers, *etc.* must therefore have originated from other parts, it remaining an open question whether the gold was transported and traded as the raw material or as finished jewellery. Analysis of the material can clearly provide no answer; each case must be treated individually on the basis of archeological considerations of style and similar characteristics.

Location of natural gold deposits, which were worked in prehistoric times and which produced such high yields as to supply regions devoid of gold, should prove easier than the search for corresponding copper deposits, since the number of gold deposits is far smaller. Only sources of elemental gold—primary or secondary deposits—need be considered. No prehistoric smelting process involving modification of impurities and accompanying elements took place; moreover, the deposits themselves—at least as regards those of a secondary nature—are much more uniform in their composition.

An attempt to characterize significant natural gold deposits on the basis of accompanying elements, and thus to retrace the routes by which the gold was transmitted to regions far and near in prehistoric times, could therefore be undertaken with considerable hope of success. It has so far proved possible to distinguish, with a fair degree of certainty, two of the European gold sources according to their minor components and to recognize this gold in prehistoric finds.

Even if it proves impossible to ascribe the gold in prehistoric objects to particular natural deposits according to analyses of accompanying elements, *i.e.* the question of the origin of the gold must remain unanswered, it will still be possible to correlate gold finds on the basis of characteristic contaminants and to class them as so-called material groups, as in the case of copper. A material group comprises all those objects made of material whose content of accompanying elements is the same with regard to quality and quantity (within certain limits of variation). It is assumed that the gold occurring in all finds belonging to the same material group come from the same natural deposit, even if it has yet to be located.

Nevertheless, it will have to be borne in mind when considering such material groups that two distant natural deposits may well yield gold whose composition varies so little that the resulting objects are assigned to the same material group. The greatest caution must be exercised when a material group embraces widely differing periods and cultures and particularly when the nature and amounts of accompanying elements are not very characteristic.

5. Results of Gold Studies

We shall first consider a number of observations made with natural gold. Copper and silver are regularly found in natural gold, although in very different concentrations. The silver content is at least about 2% and can reach values of 40%. In contrast, only 0.01% of copper is often present and is reported never to exceed 1.5%[7]. Apart from these two elements we found that more than 30 samples of native gold from the Rhine and its tributaries, Transylvania, Bohemia, Ireland, Wales, and Scotland all contain mercury, sometimes only in traces of less than 0.01% but usually in the order of 0.1%, irrespective of whether the samples come from primary or secondary deposits.

Platinum and tin, however, two elements frequently encountered in prehistoric gold finds, are completely absent in gold from primary deposits. Our studies on alluvial gold concentrates revealed them to regularly contain tin and in some cases platinum too. However, these two elements are not incorporated in the grains of gold present in the concentrate but are enriched owing to their density—tin in the form of cassiterite[8,9] and platinum as the native metal[9]. Both elements will readily have gone into the gold regulus during prehistoric recovery operations and now witness to the production of the gold from placer deposits. Results of studies on about 3300 European gold finds dating from the Bronze Age to the beginning of our era indicate that placer gold was the only gold available, for, with very few exceptions, all these finds contain some tin[*].

[*] Exceptions can arise owing to the presence of large nuggets in alluvial gold; such nuggets will readily be separable from accompanying minerals and are thus no longer associated with tinstone. Nevertheless, with regard to the other compounds, this gold exhibits the same composition as the stanniferous, finely divided material from alluvial deposits and is treated as such in our studies.

Mining for gold was apparently unknown in prehistoric Europe and seems to have been gradually introduced in Roman times.

Strikingly, it is precisely the earliest prehistoric European gold finds that are made from tin-free material which may well have been mined, although this naturally cannot be proved since alluvial deposits free from tinstone are perfectly conceivable. However, when it is remembered that this tin-free gold (which, moreover, generally has a silver content of less than 10% and rarely as much as 15%) is limited specifically to the earliest Metal Age—and disappears in the Middle Bronze Age—some justification may be seen for assuming that this material was imported from the eastern Mediterranean region where the cultures of Asia Minor are known to have engaged in the mining of ores as long ago as the 3rd millenium BC. When local extraction from alluvial deposits got under way in Europe there was no longer any need for these imports. This would provide a ready explanation for the disappearance of the tin-free material in the Middle Bronze Age.

Further support for this conception comes from the distribution of the tin-free gold we have designated "B", as shown in Figure 6. Each prehistoric gold object having this composition is indicated by a point at its place of discovery. It is clearly seen that such finds have been registered particularly frequently in coastal regions, again suggesting that they were imported, especially since the south coast of Spain and Portugal is known beyond doubt from the fortified factories established by copper seekers (Section 3) to have been exposed to the influence of the eastern Mediterranean. Non-coastal locations of such finds lie almost exclusively in the region of the lower Danube and possibly mark an inland import route. Of course, a distribution map of this kind should not be consulted without remembering the respective gaps in research, applying in this case to the regions covered by present-day Greece, Italy, Bulgaria, and Romania. Closing of these gaps by future investigations will undoubtedly do much to clarify the situation.

Utilization of the tin-free material B coincides in the Early Bronze Age with that of the slightly later material "A_3" having a considerably higher silver content (on average 26% Ag) whose distribution is shown in Figure 7. The map clearly shows the high frequency of finds in the middle reaches of the Danube. This would possibly suggest some connection with the well-known gold deposits near Brád in Transylvania. Unfortunately, we had no comparison samples of alluvial gold from this region at our disposal, but samples of gold from recent mining operations in the neighborhood of Brád also exhibit an average silver content of about 25% Ag[10]. It may therefore be assumed that during the Early Bronze Age material A_3 was obtained from alluvial deposits in a wide area surrounding the primary deposits of Transylvania (shown as hatched trapezium). This local gold displaced the imports of material B and was doubtless also exported since it is encountered in individual Bronze Age gold finds in Scandinavia, the Netherlands, and Germany, and even a flat gold ring found in Brittany appears to have been made of Transylvanian material. So far we are completely ignorant of the extent to which Transylvanian gold found its way to Mycenaean Greece, to the Hittite Kingdom in Asia Minor, and to

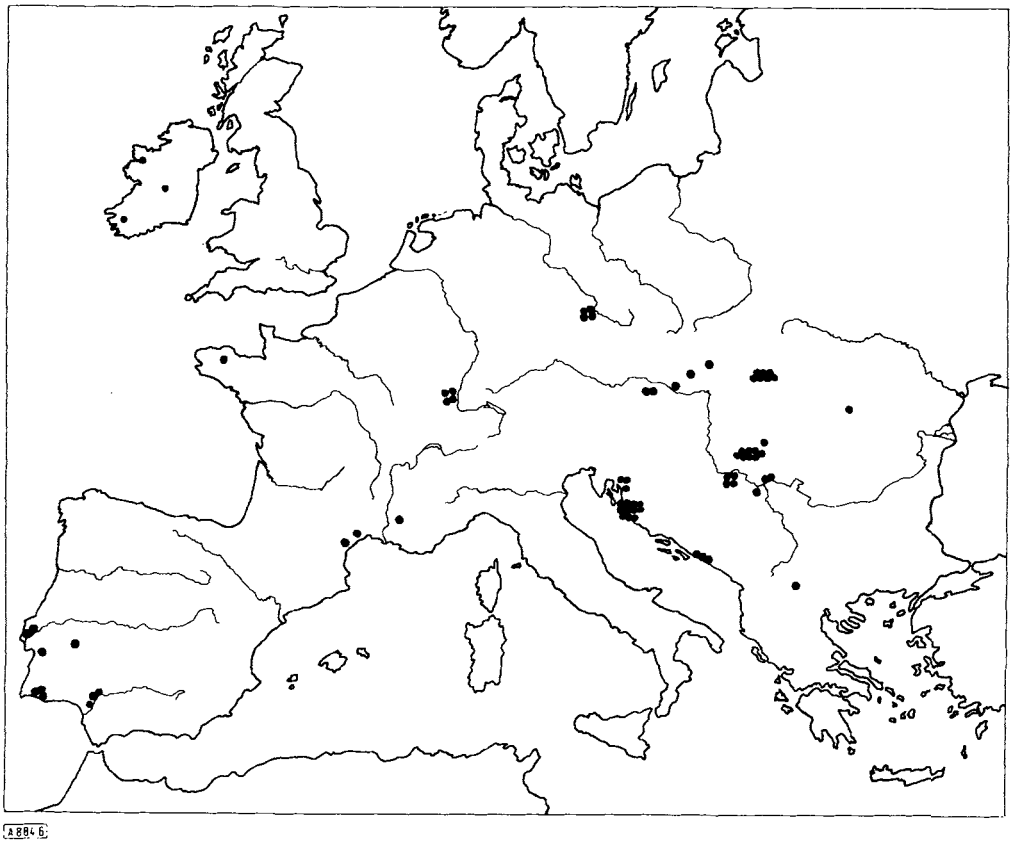
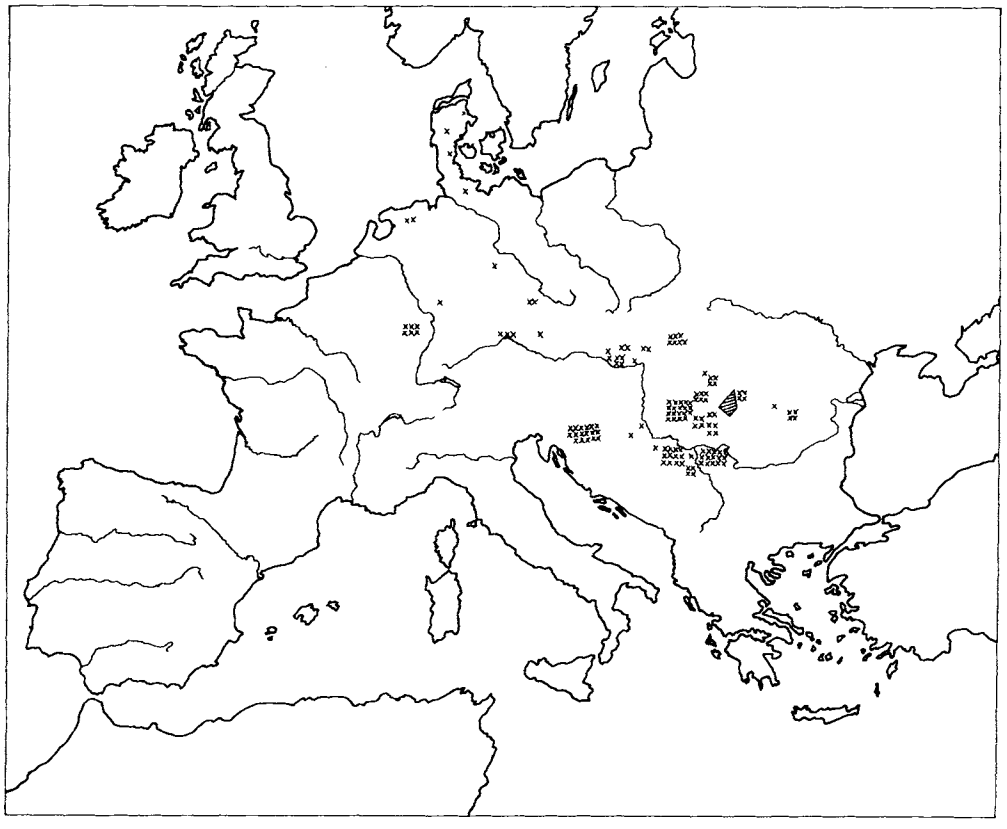
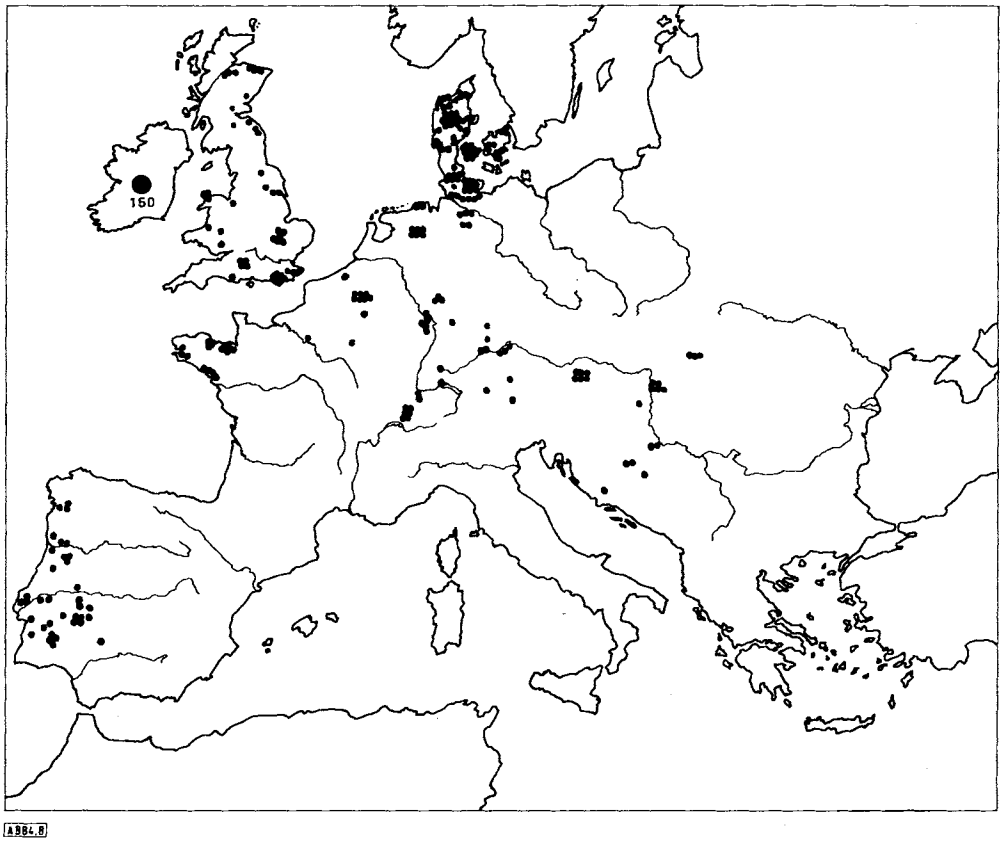


Fig. 6. Distribution of material group gold B.



A884.7

Fig. 7. Distribution of material group gold A_3. Natural gold deposits in Transylvania shown as hatched area.



A884.8

Fig. 8. Distribution of material group gold N. More than about 150 objects found in Ireland belong to this group. Little work has so far been done on specimens from England (British Museum, London) and Denmark.

Troy. However, it is our hope that future research will shed some light upon these questions.

Towards the close of the Bronze Age in Central Europe—around the turn of the 2nd to the 1st millenium BC—a particularly widely distributed variety of gold appears whose tin content clearly points to its alluvial origin. Figure 8 shows how this material, hitherto unencountered in the geographical area studied, was in use from the Balkans to Spain and Ireland. The centroid of the distribution of this gold, which we have designated "N" and which is characterized by its relatively high tin content (>0.1%) and high copper content (≈2%)[*], appears to lie in present-day Schleswig-Holstein/Denmark, the British Isles and the areas of Brittany accessible therefrom, and the western part of the Iberian peninsula. There is a temptation to regard the finds in the extreme west of Europe as comprising local gold of fortuitously identical composition; however, archeological excavations provide unequivocal evidence for extensive trading and cultural ties, particularly between Portugal/west Spain, Brittany, and the British Isles, going back far earlier than the period discussed in this report. It is therefore justifiable to relate this unexpectedly widely distributed variety of gold with a single source whose location we cannot yet define. However, the extent of this source seems so considerable that we can hardly expect to find it in west or central Europe. Furthermore, the appearance of N-type gold in central Europe coincides with that of the Urnfield culture in a period marked by significant folk migrations, and the time graduation of these folk movements from east to west is also reflected in the occurrence of N-type gold. Further conclusions will hardly be possible until the research gaps in the GDR, Poland, and Romania have been remedied. We would therefore like to do no more than cautiously express the tentative conjecture that this gold stems from somewhere in east Europe and was traded—as adequately shown by Figure 8—by a maritime route *via* the Baltic, the North Sea, and the Atlantic. Maritime trading routes must therefore have played a very important role at this time, as in the Mediterranean 1000 years previously (Fig. 6), a fact that is still not sufficiently appreciated. However, there remains some uncertainty as to what goods and valuables can have figured as objects of exchange in such a widely distributed gold trade.

This period, *i.e.* the dawn of the last millenium BC, also witnessed the first large-scale adulteration of gold with copper, particularly in the case of N-type gold. The amounts of copper found generally fluctuate in the order of up to 10% and only occasionally exceed this value. The gold assumes a particularly warm, golden-yellow color and its hardness also increases. Indeed, it is really rather surprising that this device was discovered so late: it soon became common practice in the British Isles but found somewhat less following on the European mainland. Considering that the art of alloying copper with tin had been known for half a millenium, one is forced to the conclusion that certain mythical-religious concepts had hitherto prevented abasement of the pure native gold with copper.

Finally, this is a fitting place to take a stand on a question that has long occupied archeologists. The alluvial gold deposits along the Upper Rhine were actively worked until modern times, and the assumption that gold was obtained from this source in prehistoric times, and at least those prehistoric finds excavated in the neighborhood of the Upper Rhine Valley were made from Rhine gold, appeared not entirely without foundation. Since concentrates from gold-bearing Rhine sands are still accessible today we had no difficulty in following up this proposition and were able to confirm the composition of Rhine gold—low Ag content below 10% and, in the lower reaches of the Upper Rhine, mainly accompanying platinum—as found in early analyses. However, comparison with prehistoric gold finds, primarily from southwest Germany, showed that Rhine gold was not worked until the La Tène period, *i.e.* in the last centuries BC, and that gold extraction from the deposits of the Rhine was not practiced at all, or only to an insignificant extent, before this time. The low number of La Tène objects that are made of Rhine gold also emphasizes that the production of Rhine gold can never be compared with that from the Transylvanian deposits or possibly with that of material N discussed above.

The final problem dealt with stresses once again how indispensable the application of scientific methods is for investigations of prehistoric metallurgy when any serious attempt is made to engage in successful studies of this topic, which is so important for the history of technology as a whole. That the methods employed in the natural sciences are merely aids open to continuous improvement hardly needs demonstrating to the readership of this journal.

Received: July 8, 1971 [A 884 IE]
German version: Angew. Chem. *84*, 668 (1972)

[*] Although this copper content exceeds the upper limit given by Gmelin [7], we still consider it unlikely that the copper content was intentionally raised but rather that the natural copper content of this variety of gold was enhanced by the copper minerals in the secondary deposits.

[1] *J. Winkler:* Quantitative spektralanalytische Untersuchungen an Kupferlegierungen zur Analyse vorgeschichtlicher Bronzen. Veröffentl. Landesanstalt Volkheitskunde Halle, No. 7 (1935); Z. Anorg. Allg. Chem. *218*, 149 (1934).

[2] *H. Otto* and *W. Witter:* Handbuch der ältesten vorgeschichtlichen Metallurgie in Mitteleuropa. J. A. Barth, Leipzig 1952; *H. Otto*, Spectrochim. Acta *1*, 381 (1940).

[3] *M. van Doorselaer*, Verhandel. Koninkl. Vlaam. Acad. Wetenschap. Belg. Kl. Wetenschap. *12*, No. 35 (1950).

[4] *S. Junghans, H. Klein*, and *E. Scheufele:* Untersuchungen zur Kupfer- und Frühbronzezeit Süddeutschlands. 34. Bericht der Römisch-Germanischen Kommission 1951–53, pp. 77ff.

[5] *A. Hartmann:* Prähistorische Goldfunde aus Europa. Studien zu den Anfängen der Metallurgie, Vol. 3. Gebr. Mann Verlag, Berlin 1970.

[6] *S. Junghans, E. Sangmeister*, and *M. Schröder:* Metallanalysen kupferzeitlicher und frühbronzezeitlicher Bodenfunde aus Europa. Studien zu den Anfängen der Metallurgie, Vol. 1. Gebr. Mann Verlag, Berlin 1960; Kupfer und Bronze in der frühen Metallzeit Europas. Studien zu den Anfängen der Metallurgie, Vol. 2. Gebr. Mann Verlag, Berlin 1968.

[7] Gmelins Handbuch der anorganischen Chemie: System No. 62, 8th Edit., p. 43. Verlag Chemie, Weinheim 1954.

[8] *F. Kirchheimer:* Über das Rheingold. Jh. geol. Landesamt Bad.-Württ. *7*, 77 (1965).

[9] *P. Ramdohr:* Rheingold als Seifenmineral. Jh. geol. Landesamt Bad.-Württ. *7*, 92 (1965).

[10] *F. Schumacher:* Die Golderzlagerstätten und der Goldbergbau der Rudaer Zwölf-Apostel-Gewerkschaft zu Brád in Siebenbürgen. Verlag M. Krahmann, Berlin 1912, p. 56.

Pentafluoroorthoselenic Acid

By *Konrad Seppelt*[*]

Compounds of fourth-row non-metals (As, Se, Br) generally resemble their homologs from the third row, whereas an increase in coordination number is often observed on going to the fifth row, *e.g.* SO_4^{2-}, SeO_4^{2-}, $H_4TeO_6^{2-}$. Thus selenium oxide tetrafluoride, analogous to sulfur oxide tetrafluoride, should be capable of existence; tellurium, on the other hand, is found to give pentafluoroorthotelluric acid[1].

However, all attempts to prepare $SeOF_4$ have been unsuccessful. Fluorination of seleninyl fluoride $SeOF_2$ with halogen fluorides (ClF_5, IF_7) gives only selenium tetrafluoride; treatment with elemental fluorine under pressure affords selenium hexafluoride.

Surprisingly, the latter reaction yields the hitherto unknown pentafluoroorthoselenic acid *(1)*, alongside a large amount of selenium hexafluoride, when carried out in the presence of hydrogen fluoride.

$$SeOF_2 + F_2 + HF \rightarrow \underset{(1)}{HOSeF_5}$$

Occasional explosions in the autoclave, which is slightly above room temperature, introduce a certain element of risk. Synthesis from selenyl fluoride[2] proved less dangerous:

$$SeO_2F_2 + 2HSO_3F + KHF_2 \rightarrow \underset{(1)}{HOSeF_5} + H_2SO_4 + KSO_3F$$

This reaction is carried out in a large excess of fluorosulfuric acid. Compound *(1)*, contaminated with SeO_2F_2 and HF, distills over in a yield of about 30% on heating the reaction mixture. The product can be purified by distillation and fractional crystallization. Yields of less than 10% are obtained in the following reactions:

$$BaSeO_4 + 5HSO_3F + 2HF \rightarrow (1) + 3H_2SO_4 + Ba(SO_3F)_2$$
$$H_2SeO_4 + 3HSO_3F + 2HF \rightarrow (1) + 3H_2SO_4$$
$$SeO_2F_2 + SeF_6 + 2HF \rightarrow 2\,(1)$$
$$SeO_2F_2 + SOF_4 + HF \rightarrow (1) + SO_2F_2$$

Compound *(1)* is a colorless crystalline solid having a high vapor pressure (0°C: 76 torr; 15°C: 186 torr); m.p. 38°C, b.p. 44°C. The empirical formula was established by molecular weight determination according to *Dumas*, from the mass spectrum [*m/e* 188—194 (F_5SeOH 0.5%), 171—177 (F_5Se 3.8%), 168—174 (F_4SeO 3.8%), 149—155 (F_3SeO 6.5%), 133—139 (F_3Se 9%), 130—136 (F_2SeO 100%), 114—120 (F_2Se 5.3%), 111—117 (FSeO 74%), 95—101 (FSe 3.8%), 92—98 (SeO 13%); 75 eV] and elemental analysis. Compound *(1)* sublimes extremely readily and exhibits a strongly depressed melting point in the impure state—typical properties of spherically shaped molecules.

[*] Dr. K. Seppelt [**]
Anorganisch-chemisches Institut der Universität
69 Heidelberg, Im Neuenheimer Feld 7 (Germany)

[**] I wish to thank Dr. *R. Geist* for recording the mass spectrum and Farbenfabriken Bayer AG, Leverkusen, for the fluorosulfuric acid.

The IR spectrum [gas phase: 3609 (s, νOH), 1171 (s, δOH), 750 (vs, νSeF), and 436 cm^{-1} (s, δSeF)] is surprisingly simple; its interpretation, which is based on a slightly perturbed octahedral model, is only tentative. The ^{19}F-NMR spectrum, a complex multiplet between −65 and −85 ppm (in $CFCl_3$ as internal standard, 56.4 MHz) which can be unequivocally interpreted as an AB_4 spectrum[3], is particularly informative: $\delta_{F_A} = -77.9$, $\delta_{F_B} = -68.3$ ppm; $J_{F_A-F_B} = 224$ Hz; $R = J/\Delta\delta = 0.395$. In addition, sidebands arising from the isotope ^{77}Se can also be observed: $J_{^{77}Se-F} = 1300 \pm 5$ Hz. The ^1H-NMR spectrum exhibits a sharp singlet ($\delta = 7.65$ ppm in $CFCl_3$, TMS as external standard).

Compound *(1)* is a strong, oxidizing acid that immediately liberates chlorine in an exothermic reaction with sodium chloride. It attacks glass and metals; this corrosivity is possibly promoted by the presence of traces of hydrogen fluoride. Teflon and, to a lesser extent, quartz are resistant. The existence of pentafluoroorthoselenic acid and its detailed resemblance to pentafluoroorthotelluric acid represents an interesting exception to the much more frequently encountered analogy between the chemistries of sulfur and selenium.

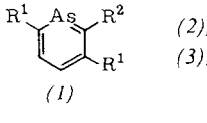
Received: October 25, 1971 [Z 557 IE]
German version: Angew. Chem. *84*, 212 (1972)

[1] *A. Engelbrecht* and *F. Sladky*, Angew. Chem. *76*, 379 (1964); Angew. Chem. internat. Edit. *3*, 383 (1964).
[2] *A. Engelbrecht* and *B. Stoll*, Z. Anorg. Allg. Chem. *292*, 20 (1957).
[3] *R. K. Harris* and *K. J. Parker*, J. Chem. Soc. *1961*, 4736.

X-Ray Structure Analysis of 2,3,6-Triphenylarsenin

By *F. Sanz* and *J. J. Daly*[*]

A recent report[1] describes a general synthetic route to substituted arsenins *(1)* by a carbene insertion into an arsolene. The spectral data (MS, NMR, UV, and IR) of the compounds obtained from this reaction were consistent with the presence of an aromatic C_5As heterocyclic ring system. The synthesis of arsenin *(2)*, the arsenic analog of pyridine, has recently been accomplished[2]. We have used single crystal X-ray methods to determine the structure of 2,3,6-triphenylarsenin, *(3)*, and thus to ascertain the geometrical characteristics of the arsenin ring.



(1)

(2), $R^1 = R^2 = H$
(3), $R^1 = R^2 = C_6H_5$(=Ph)

The small, colorless, air-stable crystals[3] of *(3)* are monoclinic, space group C2/c with $a = 31.768$, $b = 10.456$, $c = 10.543$ Å, $\beta = 94.6°$, there are eight molecules of $C_{23}H_{17}As$ in the unit cell, The arsenic and carbon atom positions were found from the three dimensional Patterson function and, after some refinement, the hydrogen atoms were found from a difference synthesis. Further least squares refinement of

[*] Dr. F. Sanz and Dr. J. J. Daly
Monsanto Research S. A.
CH-8050 Zürich, Eggbühlstrasse 36 (Switzerland)

1623 diffractometer data gave a final R ($=\sum|\Delta|/\sum|F_o|$) value of 0.085.

The bond lengths and angles in the arsenin ring are shown in Figure 1. This six-membered ring is, within the limits of experimental error, planar and has mm2 (C_{2v}) symmetry. The arsenic-carbon bond length of 1.872 Å (average) is less than the sum of the covalent bond radii[4] (1.98 Å) and the standard[5] As—C single bond length (1.96 Å). The carbon-carbon bond lengths in the heterocyclic ring have an average length of 1.405(20) Å and this may be compared with the corresponding lengths in pyridine[6] (1.394 Å) and in 2,6-dimethyl-4-phenylphosphorin[7] (1.388 Å). The arsenin ring angles show large deviations from 120° but they are subject to geometrical constraints[7]; only five parameters are required to define this ring if it has mm2 (C_{2v}) symmetry. These parameters may be chosen as As—C1 = 1.872 Å, C1—C2 = C2—C3 = 1.405 Å, ring angles at C1 = 122.1° and at C2 = 121.5°, and may be used to calculate the ring angles at As, 101.6°, and at C3, 131.1°. Thus deviations of ring angles from 120° are a consequence of non-equality of the As—C and C—C bond lengths in the ring. The observed geometry of the arsenin ring is consistent with a delocalized 6π electron system.

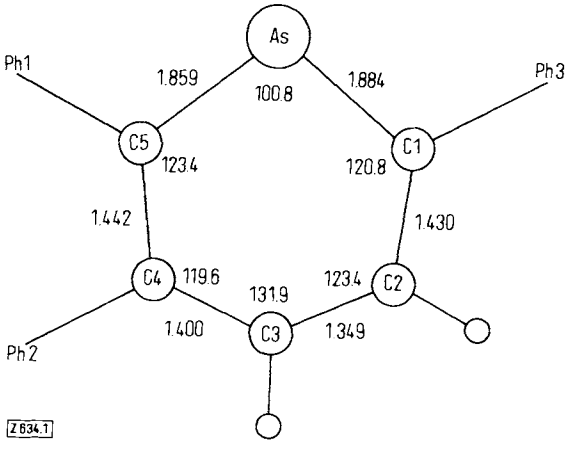


Fig. 1. Bond lengths (Å) and angles in the arsenin ring of 2,3,6-triphenylarsenin. Standard deviations: As—C, 0.014; C—C, 0.02 Å; C—As—C, 0.6; As—C—C, 1.0; C—C—C, 1.3°.

The phenyl groups are attached to the arsenin ring by essentially equal carbon-carbon bonds of average length 1.482(20) Å. These groups are individually planar with an average carbon-carbon bond length of 1.388 Å and the angles between these planes and that of the heterocyclic ring are 63, 47, and 36° for Ph(1), Ph(2), and Ph(3) respectively.

Received: February 7, 1972 [Z 634 IE]
German version: Angew. Chem. *84*, 679 (1972)

[1] *G. Märkl, H. Hauptmann,* and *J. Advena,* Angew. Chem. *84*, 440 (1972); Angew. Chem. internat. Edit. *11*, 441 (1972).

[2] *A. J. Ashe,* J. Amer. Chem. Soc. *93*, 3293 (1971).

[3] We thank Prof. Dr. *G. Märkl* who kindly supplied us with a sample of this substance.

[4] *L. Pauling:* The Nature of the Chemical Bond, 2nd. Edition, Cornell University Press, New York 1940.

[5] "Interatomic Distances Supplement", Special Publ. No. 18, The Chemical Society, London 1965.

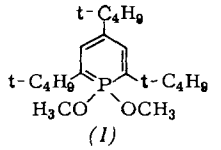
[6] *B. Bak, L. Hansen-Nygaard,* and *J. Rastrup-Andersen,* J. Mol. Spectry. *2*, 361 (1958).

[7] *J. C. J. Bart* and *J. J. Daly,* J. Chem. Soc. *A 1970*, 567.

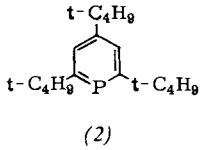
Unusual Sequence of the Two Highest Occupied π-Molecular Orbitals in the Phosphorin System[1]

By *Armin Schweig, Werner Schäfer,* and *Karl Dimroth*[*]

In a previous paper[2] we postulated that the highest occupied molecular orbital (HOMO) in the λ^3-phosphorus system[**] is the π-MO with non-zero coefficient, $\pi_1(s)$[3], and not the π-MO with its node, $\pi_2(a)$[3], on the phosphorus atom. Meanwhile we have proved this hitherto unique MO sequence by means of the photoelectron spectrum of a λ^5-phosphorin, namely 2,4,6-tri-*tert*-butyl-1,1-dimethoxyphosphorin[4] *(1)*.



(1)



(2)

Each methoxyl-oxygen atom in *(1)* has two lone pairs, one of them oriented along the C_{2v} axis and the other perpendicular thereto. The former is described by an n(s)-MO, the latter by an n(a)-MO. The interaction of the dimethoxy system with the π-MO's of the phosphorin system can arise only by linear combinations, antisymmetric with respect to the molecular plane, of the n(s)-MO's on the one hand and the n(a)-MO's on the other. In this process $\pi_1(s)$ couples with the n(s)-linear combination and $\pi_2(a)$ with the n(a)-linear combination in an antibonding manner. Coupling can be effective only in the first case, since $\pi_1(s)$ has a non-zero coefficient on the P atom. Thus it is to be expected that the HOMO $\pi_1(s)$ will be raised by a large amount. In the second case, because of the node on the phosphorus atom in $\pi_2(a)$, there remains only the possibility of a spiro-conjugative interaction, which, however, can only be slight[5]. Thus it is to be expected that $\pi_2(a)$ is only slightly raised by the action of the dimethoxy system.

These predictions were fully confirmed by experiment, as comparison of the PE spectra of *(1)* and 2,4,6-tri-*tert*-butylphosphorin *(2)* shows (Fig. 1)[6]. Band 1, which in *(2)* we had assigned to $\pi_1(s)$[2], is shifted in *(1)* by 1.3 eV to

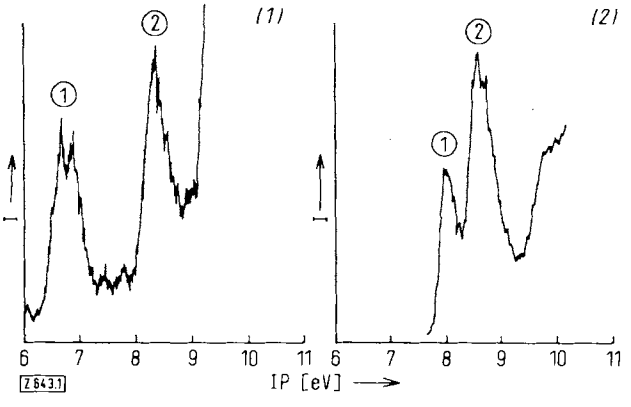


Fig. 1. Photoelectron spectra of 2,4,6-tri-*tert*-butylphosphorin *(2)* and 2,4,6-tri-*tert*-butyl-1,1-dimethoxyphosphorin *(1)*. The vertical ionization potentials of the two first bands of *(1)* are 6.7 and 8.4 eV.

[*] Prof. Dr. A. Schweig and Dipl.-Chem. W. Schäfer
Fachbereich Physikalische Chemie der Universität
355 Marburg, Biegenstrasse 12 (Germany)
Prof. Dr. K. Dimroth
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

[**] λ^3 = trivalent phosphorus atom; λ^5 = quinquevalent phosphorus atom.

smaller IP values, while band 2 remains almost unchanged. In *(2)*, because of the measured intensity ratio band 1: band 2 = 1:2, we had assigned band 2 to π_2(a) and the n-MO that describes the lone electron pair on the P atom[2]. Since this n-MO is not present in *(1)*, the intensity ratio must there be approximately 1:1, as was confirmed by experiment. These findings prove that the assignment made for *(2)* is correct. They also prove that the unusual and hitherto unique MO sequence (π-MO with non-zero coefficient on the hetero atom higher in energy than the π-MO with node on the hetero atom) actually occurs in the phosphorin system.

Received: March 28, 1972 [Z 643 IE]
German version: Angew. Chem. *84*, 636 (1972)

[1] Part 10 of Theory and Application of Photoelectron Spectroscopy. — Part 9: [5]. — We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work and the Deutsches Rechenzentrum, Darmstadt, for carrying out the calculations.

[2] *H. Oehling, W. Schäfer*, and *A. Schweig*, Angew. Chem. *83*, 723 (1971); Angew. Chem. internat. Edit. *10*, 656 (1971).

[3] All the MO's are classified relative to the symmetry plane perpendicular to the molecular plane (s: symmetric; a: antisymmetric).

[4] Prepared according to directions of *C. Mach*, Dissertation, University of Marburg, 1968.

[5] *U. Weidner* and *A. Schweig*, Angew. Chem. *84*, 551 (1972); Angew. Chem. internat. Edit. *11*, 537 (1972).

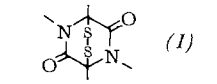
[6] The He-I (584 Å) photoelectron spectra were measured on a PS-16 photoelectron spectrometer from Perkin-Elmer, Beaconsfield, England.

X-Ray Structural Analysis of *N,N'*-Dimethyl-3,6-epitetrathio-2,5-piperazinedione [**]

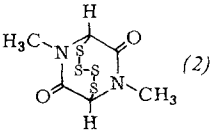
By *Betty R. Davis, Ivan Bernal*, and *Ulrich Schmidt*[*]

The structural fragment common to gliotoxin[1,2a], virus inhibiting antibiotics of the aranotin type[3], sporidesmins[2b,4] and the cancerostatic antibiotic chaetocin[5] is a 2,5-piperazinedione ring with an epidithio bridge *(1)*. A study of methods for the direct insertion of sulfur functions (such as S_n, with $n=2,3,4$, *etc.* ...) has been reported previously[6]. *Benedetti et al.*[7] have previously reported that the supposedly "rigid" diketopiperazines are surprisingly flexible. We are interested in establishing the systematics of the stereochemistry of the piperazinedione fragment and the S_n bridge as a function of the length of the polysulfide chain.

The title compound crystallizes in the orthorhombic space group Fdd2 with $a=15.352(5)$, $b=20.432(7)$, and $c=6.635(2)$ Å; $V=2081.2(8)$ Å^3; $d_{obs.}=1.72(2)$ gm cm^{-3}, $d_{calc.}$ ($Z=8$) $=1.71$ gm cm^{-3}. The data were collected with a computer controlled diffractometer using monochromatic $Mo_{K\alpha}$ ($\lambda=0.71069$ Å) radiation. Data of the form hkl and $\bar{h}kl$ were collected to $2\theta \leq 69.8°$, resulting in 2856 reflections of which 1326 were unique. The 1135 independent reflections for which $F_0^2 > 3\sigma(F_0^2)$ were used to refine the structure. No absorption correction ($\mu=8.71$ cm^{-1}) has been applied to the observed structure amplitudes. A least-squares refinement in which the hydrogen atoms were added as a fixed contribution to the structure factors ($B=3.06$ Å^2) and all the other atoms were assigned anisotropic thermal parameters, converged at values of $R_1=0.033$ and $R_2=0.052$, with an error in an observation of unit weight of 1.72 electrons.



(1)



(2)

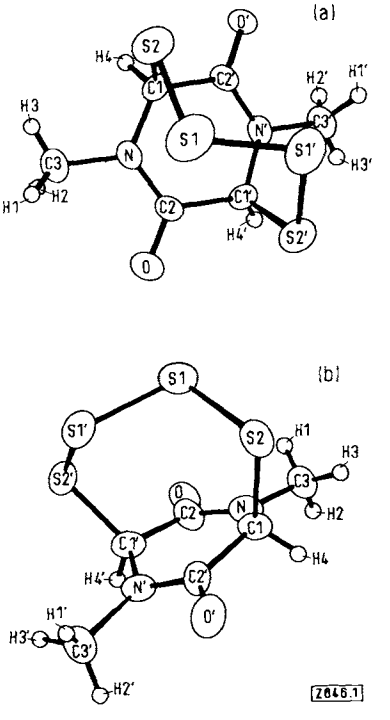


Fig. 1. Crystal structure of *N,N'*-dimethyl-3,6-epitetrathio-2,5-piperazinedione. (a) View approximately down the two-fold axis of symmetry which bisects the S1—S1' bond. (b) View along an arbitrary line of sight chosen to emphasize the three-dimensionality of the tetrasulfide chain and the non-planarity of the piperazinedione ring.

Two views of the molecule[9] are shown in Figure 1. View (a), down the crystallographic two-fold axis of symmetry, shows the geometry of the S_4 fragment projected onto the piperazinedione ring. The primed and unprimed labels on the atoms are chosen to emphasize the two-fold axis relationship between the two molecular halves. View (b) shows more clearly the three-dimensional character of the epitetrathio link and also the non-planarity of the piperazinedione ring at positions 3 and 6 (=Cl and Cl'). The dihedral angle between planes defined by C2—N—C2'—N' and C2'—Cl—N is 18.07°. In 2,5-piperazinedione[10] and in *trans*-3,6-dimethyl-2,5-piperazinedione[9], the rings are planar, while in *cis*-3,6-dimethyl-2,5-piperazinedione, the

[*] Prof. Dr. I. Bernal and B. R. Davis
Department of Chemistry, Brookhaven National Laboratory
Upton, N. Y. 11973 (USA)
Prof. Dr. U. Schmidt
Organisch-Chemisches Institut der Universität
A-1090 Wien, Währingerstrasse 38 (Austria)

[**] Part 1 of: The Crystal Structure of 2,5-Piperazinediones Having Sulfur Bridges Between C-3 and C-6. — A portion of this research (BRD and IB) was carried out under the auspices of the US Atomic Energy Comission. — We thank Mr. *John Smith* for technical assistance and Dr. *H. Poisel* for preparing the crystals.

Table 1. Bond lengths and bond angles in a few 3,6-epioligothio-2,5-piperazinediones.

Compound	Bond lengths (Å) [a]							Bond angles (°)					Ref.
	N—C1	C1—C2	N—C2	C2—O	C1—S2	S2—S1	S1—S1′	C2—C1—N	N—C2—O	C1—C2—O	C1—C2—N	C1—N—C2	
N,N′-Dimethyl-3,6-epitetrathio-2,5-piperazinedione	1.431	1.513	1.348	1.229	1.867	2.023	2.083	115.4	122.2	119.5	118.3	122.4	
Gliotoxin ($C_{13}H_{14}O_4N_2S_2$)	1.46	1.51	1.35	1.23	1.88		2.08	110.6	125.5	120.7	113.2	117.5	[2a]
Sporidesmin ($C_{19}H_{21}O_6N_3S_2Cl\cdot CH_2Br_2$)	1.46	1.52	1.39	1.20	1.90		2.08	110.5	122.8	123.2	113.5	115.1	[2b]
	1.35	1.59	1.35	1.27	1.91			114.0	124.7	125.4	111.0	121.7	[2b]
LL-S88α ($C_{22}H_{20}N_2O_8S_2$)	1.446	1.537	1.346	1.216	1.882		2.082		127.0	122.0	111.0	119.0	[11]
2,5-Piperazinedione	1.449	1.499	1.325	1.239				115.1	122.6	118.5	118.9	126.0	[10]
trans-3,6-Dimethyl-2,5-piperazinedione	1.462	1.470	1.325	1.240				112.8	122.9	117.8	119.2	127.9	[9]
cis-3,6-Dimethyl-2,5-piperazinedione	1.462	1.534	1.323	1.218				112.0	122.0	120.1	117.4	126.3	[7]
	1.457	1.512	1.344	1.244				109.9	124.8	120.4	115.1	127.1	[7]
$(C_{10}H_{12}O_2S_4)_2$						2.028	2.066						

[a] Maximum error: 0.005 Å

deviation from planarity is 8°. A comparison of the most important bond lengths and angles of the compound we studied with those of chemically related molecules is given in Table 1.

Received: April 17, 1972 [Z 646 IE]
German version: Angew. Chem. *84*, 640 (1972)

[1] *M. R. Bell, J. R. Johnson, B. S. Wildi,* and *R. B. Woodward,* J. Amer. Chem. Soc. *80*, 1001 (1958).

[2] a) *J. Fridrichsons* and *A. Mc L. Mathieson,* Acta Cryst. *23*, 439 (1967); b) *ibid. 18*, 1043 (1965).

[3] *R. Nagarajan, N. Neuss,* and *M. M. Marsh,* J. Amer. Chem. Soc. *90*, 6518 (1968).

[4] *R. L. M. Synge* and *E. P. White,* Chem. Ind. (London) *1959*, 1546; *S. Safe* and *A. Taylor,* J. Chem. Soc. *C 1970*, 432.

[5] *D. Hauser, H. P. Weber,* and *H. P. Sigg,* Helv. Chim. Acta *53*, 1061 (1970).

[6] *H. Poisel* and *U. Schmidt,* Angew. Chem. *83*, 114 (1970); Angew. Chem. internat. Edit. *10*, 130 (1971); Chem. Ber. *104*, 1714 (1971), *105*, 625 (1972); *E. Öhler, H. Poisel, F. Tataruch,* and *U. Schmidt, ibid. 105*, 635 (1972).

[7] *E. Benedetti, P. Corradini, M. Goodman,* and *C. Pedone,* Proc. US Nat. Acad. Sci. *62*, 650 (1969).

[8] *J. S. Ricci* and *I. Bernal,* J. Chem. Soc. *B 1971*, 1928; *B. R. Davis, I. Bernal,* and *H. Köpf,* Angew. Chem. *83*, 1018 (1971); Angew. Chem. internat. Edit. *10*, 921 (1971).

[9] *E. Benedetti, P. Corradini,* and *C. Pedone,* J. Phys. Chem. *73*, 2891 (1969).

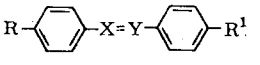
[10] *R. Degeilh* and *R. E. Marsh,* Acta Cryst. *12*, 1007 (1959).

[11] *D. B. Cosulich, N. R. Nelson,* and *J. H. van den Hende,* J. Amer. Chem. Soc. *90*, 6519 (1968).

Nematic Liquids with Positive Dielectric Anisotropy[1]

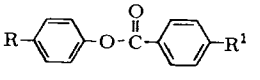
By *Ralf Steinsträsser*[*]

According to the *Gruler-Meier* model[2], nematic liquid crystals show the dynamic scattering effect described by *Heilmeier*[3] only if their dielectric anisotropy has a negative sign, *i.e.* if the dielectric constant ε_1 measured in the direction of the long molecular axis of a nematic single crystal is smaller than the constant ε_2 measured perpendicular thereto[4]. Nematic phases of this type are known at room temperature; they have the general formula *(1)*, in which the —X=Y— bridge is —CH=N—[5,6],



(1)

—N=NO—[7] or —CH=CCl—[8]. Low-melting nematic liquids having a negative dielectric anisotropy and thus capable of dynamic scattering were recently described[9] also among esters of type *(2)*[12].



(2)

Nematic liquid crystals with positive dielectric anisotropy ($\varepsilon_1 > \varepsilon_2$) cannot be excited to dynamic light scattering simply by electric fields, but they can find use as electro-optical detection systems[10] or for electrically-controllable color filters[11] that can be used in polarized light.

By lengthening the central part of the molecule of esters *(2)* by a further benzoyloxy group one obtains the diesters *(3)*[12], some of which are listed in Table 1.

Unlike the esters *(2)*, the compounds *(3)* show very broad enantiotropic mesophases extending over *ca.* 100 °C. It is interesting that even the phenol *(3)*, $R = C_4H_9$, $R^1 = OH$ (m.p. 177 °C, cl.p. 218 °C) can still form a stable nematic phase.

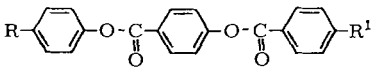
The influence of the substituents R and R^1 on the mesomorphic properties is less marked with the diesters *(3)* than with the monoesters *(2)* in which the nature and chain length of the substituents is decisive for appearance or absence of nematic phases.

The melting points of the compounds *(3)* are too high for their practical applications as nematic dielectrics to be of interest. However, the melting points fall when the com-

[*] Dr. R. Steinsträsser
Zentrallabor für Industriechemikalien,
Abteilung Forschung der Firma E. Merck
61 Darmstadt, Postfach 4119 (Germany)

[**] Application of an electric field can disorientate the molecules of a nematic liquid that contains ionic impurities. Molecular 'turbulences' arise that become scattering centers. This effect is described as dynamic scattering.

pounds are mixed. Thus the eutectic from *(3)*, $R=R^1=C_4H_9$ (60%) and *(3)*, $R=C_4H_9$, $R^1=OCH_3$ (40%), melts at 54 °C (clear pt. 204 °C). Nematic phases are obtained at room temperature if two substances of type *(3)* and one or several low-melting esters *(2)* are melted together. With some of these mixtures crystallization does not occur even on storage for many hours at temperatures well below 0 °C.



(3)

As an example of such a system, a mixture of 25% of *(3)*, $R=R^1=C_4H_9$, 25% of *(3)*, $R=C_4H_9$, $R^1=OCH_3$, 15% of *(2)*, $R=OCH_3$, $R^1=C_4H_9$, and 35% of *(2)*, $R=C_4H_9$, $R^1=OCH_3$, may be cited. This mixture has a clearing point of 110 °C and is liquid even at −80 °C. Differential thermal analysis did not show a melting point; it was also impossible to determine whether this was a eutectic mixture and thus a thermodynamically stable liquid, because mixtures of the same components in other proportions also showed no melting point.

Measurement[13] of the dielectric anisotropy gave a positive $\Delta\varepsilon$ ($\varepsilon_1 > \varepsilon_2$), so that the non-occurrence of dynamic scattering can be understood. However, the detection principle described by *Schadt* and *Helfrich*[10] could be readily demonstrated for this mixture.

Table 1. Melting points and clearing points of phenyl *p,p'*-disubstituted *p*-(benzoyloxy)benzoates *(3)*.

(3) [a] R	R^1	M.p. (°C)	Cl.p. [b] (°C)	*(3)* [a] R	R^1	M.p. (°C)	Cl.p. [b] (°C)
C_2H_5	OCH_3	136	230	C_4H_9	$O{-}CO{-}C_5H_{11}$	96	207
C_3H_7	OCH_3	110	236	CH_3O	C_2H_5	134	230
C_4H_9	C_2H_5	93	189	CH_3O	C_4H_9	134	224
C_4H_9	C_4H_9	89	183	CH_3O	OCH_3	146	273
C_4H_9	OCH_3	107	235	$C_6H_{13}O$	C_4H_9	92	187
C_4H_9	OC_4H_9	113	212	$C_6H_{13}O$	C_6H_{13}	89	177
C_4H_9	$OC_2H_4OC_2H_5$	99	170	$C_6H_{13}O$	OCH_3	112	227
C_4H_9	$OC_{10}H_{21}$	91	172	$C_6H_{13}O$	OC_4H_9	91	215
C_4H_9	$O{-}CO{-}CH_3$	124	236	$C_6H_{13}O$	OC_6H_{13}	93	206
C_4H_9	$O{-}CO{-}C_3H_7$	107	225				

[a] Unbranched chains.
[b] Clearing points: anisotropic-isotropic transition points.

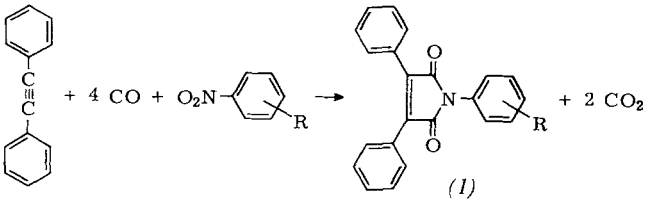
Received: November 5, 1971 [Z 644 IE]
Publication delayed at author's request
German version: Angew. Chem. *84*, 636 (1972)

[1] Part 6 of Nematic Systems. — Part 5: see Ref. [9].
[2] *H. Gruler* and *G. Meier*, Mol. Cryst. Liqu. Cryst. *12*, 289 (1971).
[3] *G. H. Heilmeier*, Sci. Amer. *222*, (4), 100 (1970).
[4] *W. Maier* and *G. Meier*, Z. Naturforsch. *16a*, 1200 (1961).
[5] *H. Kelker* and *B. Scheurle*, Angew. Chem. *81*, 903 (1969); Angew. Chem. internat. Edit. *8*, 884 (1969).
[6] *R. Steinsträsser* and *L. Pohl*, Z. Naturforsch. *26b*, 87 (1971).
[7] *R. Steinsträsser* and *L. Pohl*, Tetrahedron Lett. *1971*, 1921.
[8] *W. R. Young, A. Aviram*, and *R. J. Cox*, Angew. Chem. *83*, 399 (1971); Angew. Chem. internat. Edit. *10*, 410 (1971).
[9] *R. Steinsträsser*, Z. Naturforsch., in press.
[10] *M. Schadt* and *W. Helfrich*, Appl. Phys. Letters *18*, 127 (1971).
[11] *G. H. Heilmeier, J. A. Castellano*, and *L. A. Zanoni*, Mol. Cryst. Liqu. Cryst. *8*, 293 (1969).
[12] German patent applied for.
[13] Dr. *G. Meier*, Institut für Angewandte Festkörperphysik, Freiburg.

The Catalytic Deoxygenation of Aromatic Nitro Compounds by Carbon Monoxide in the Presence of Diphenylacetylene[1]

By *Abul F. M. Iqbal*[*]

Reactive species occurring in the deoxygenation of nitro compounds by carbon monoxide have been trapped by aldehydes[2, 3] and protic solvents[4, 5] to give a variety of products. We now report the interaction of diphenylacetylene with carbon monoxide and aromatic nitro derivatives in the presence of catalytic quantities of hexadecacarbonylhexarhodium $[Rh_6(CO)_{16}]$ to afford high yields of the corresponding *N*-aryl-2,3-diphenylmaleimides *(1)*.



(1)

Apparently, carbon monoxide performs here the dual function of a reducing and carbonylating agent. No maleimide is formed in the absence of catalyst. The reaction is fairly selective and conveniently carried out in a steel autoclave. Tertiary amines (such as pyridine, *N*-methylpyrrolidine *etc.*) are used as solvents. In benzene, a small amount of a brick-red polymer is formed which was not further examined.

Some results are presented in Table 1. All products have been characterized by mixed melting point, elemental analysis, and IR and NMR spectroscopy. Compounds *(1a)* and *(1b)* have previously been prepared by an independent route[6].

Since formation of amines and isocyanates cannot be excluded under the given conditions[2, 3], the question arises whether they play a role in the formation of the diphenylmaleimide derivatives *(1)*. This has been checked by performing under analogous conditions the reaction of di-

[*] Dr. A. F. M. Iqbal
Monsanto Research S. A.
Eggbühlstrasse 36
CH-8050 Zürich (Switzerland)

phenylacetylene with aniline and phenylisocyanate, respectively. In the former case, *N*-phenyl-2,3-diphenylsuccinimide (20—30%) is obtained as major product apart from a trace amount of *(1a)*, while from the latter conversion the only product thus far isolated consists of a high melting (> 300 °C) crystalline compound, which has not yet been identified.

Table 1. Compounds prepared by the reaction of diphenylacetylene with aromatic nitro compounds and carbon monoxide in the presence of carbonyl rhodium.

	R	Yield (%) [a]	M.p. (°C) [b]	IR (ν_{CO}) (μ) [c]	^{1}H-NMR Chemical Shift δ(ppm) [d] aromatic	methyl
(1a)	H	75	175 [e]	5.67 5.85	6.85–7.7	–
(1b)	*p*-CH_3	77	192–194 [f]	5.68 5.85	7.0 –7.7	2.38
(1c)	*m*-CH_3	77	160–161	5.70 5.88	6.9 7.7	2.37
(1d)	*m*-Cl	75	145–146	5.68 5.83	7.0 –7.7	
(1e)	*p*-OCH_3	50	188–189	5.68 5.85	6.85–7.7	3.78
(1f)	*p*-C_6H_5	80–85	244–246	5.70 5.87	7.2 –7.9	–

[a] Crude yield, based on diphenylacetylene.
[b] Melting points are uncorrected.
[c] KBr disc.
[d] Measured in $CDCl_3$.
[e] 174—175 °C after Ref. [8].
[f] 192 °C after Ref. [6].

In view of these findings we tend to rule out intermediacy of amine or isocyanate in the direct formation of *(1)* from diphenylacetylene and nitro compounds. In analogy to related cases[2, 3, 5] we believe in intervention of some sort of a nitrenoid species originating from the nitro component.

N-(p-Biphenylyl)-2,3-diphenylmaleimide (1f):

A solution of diphenylacetylene (0.005 mol), *p*-nitrobiphenyl (0.0055 mol) and hexadecacarbonylhexarhodium[7] (10^{-5} mol) in anhydrous pyridine (6 ml) was allowed to react with carbon monoxide (150 atm) in a stainless steel autoclave (30 ml capacity) at 165—170 °C (external temperature) for 3 hours. After cooling to room temperature, the autoclave was discharged and pyridine removed *in vacuo* at 50 °C. The residue was swirled with 10—15 ml of *(1f)* in 80—85% yield, m.p. 244—246 °C.

Received: February 1, 1972 [Z 647 IE]
German version: Angew. Chem. *84*, 641 (1972)

[1] Part 4 of Catalytic Deoxygenation of Organic Compounds by Carbon Monoxide. — Part 3: [2].

[2] *A. F. M. Iqbal*, Helv. Chim. Acta *55*, 798 (1972).
[3] *A. F. M. Iqbal*, J. Org. Chemistry, in press.
[4] *T. Kajimoto* and *J. Tsuji*, Bull. Chem. Soc. Japan *42*, 827 (1969).
[5] *A. F. M. Iqbal*, Tetrahedron Lett. *1971*, 3385.
[6] *G. Gysae*, Ber. dtsch. chem. Ges. *26*, 2478 (1893), cf. also [8].
[7] *B. L. Booth*, *M. J. Else*, *R. Fields*, *H. Goldwhite*, and *R. N. Haszeldine*, J. Organometal. Chem. *14*, 417 (1968).
[8] *R. Anschütz* and *P. Bendix*, Liebigs Ann. Chem. *259*, 65 (1890).

MO Calculations on the Insertion Reactions of Vinyl Cations[**]

By *Herbert Kollmar* and *Harry O. Smith*[*]

The chemistry of vinyl cations and related species[1] is characterized by rearrangements and additions to unsaturated systems[2, 3]. MO calculations, however, predict that such ions should also be able to participate in insertion reactions, in analogy to the well-known insertions of carbenes. The simplest example of such a reaction is the addition of the vinyl cation to the hydrogen molecule to form the ethyl cation:

$$C_2H_3^+ + H_2 \longrightarrow C_2H_5^+ \qquad (1)$$

The reverse of (1) is observed in mass spectrometry as a fragmentation reaction[4]. We have studied this example in some detail.

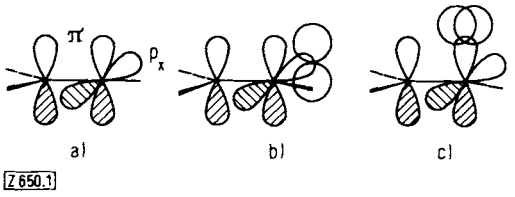
A modified[5] CNDO[6] method was used which allows the complete minimization of the energy of a molecule with respect to its geometry and thus is particularly well suited to the calculation of reaction coordinates[7].

The vinyl cation has an almost empty p orbital (p_x in Fig. 1a) perpendicular to the π bond orbital. The π orbital is strongly polarized; hence the vinyl cation can be described as a methylene with CH_2^+ as a substituent. Various modes of H_2 addition are conceivable in reaction (1). For instance, the H_2 molecule could approach the occupied π orbital of the $C_2H_3^+$ ion from the side (Fig. 1c). This is a very

[*] Dr. H. Kollmar
Battelle-Institut e. V.
6 Frankfurt 90, Postfach 900160 (Germany)
Dr. H. O. Smith
Max-Planck-Institut für Medizinische Forschung
69 Heidelberg, Jahnstrasse 29 (Germany)

[**] First communication of MO calculations on electrophilic reactions.

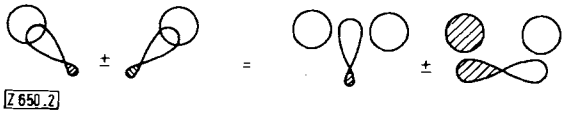
unfavorable reaction path because two occupied orbitals are forced to interact with each other. (Assuming C_s symmetry, this path is forbidden according to the Woodward Hoffmann rules[14]). On the other hand, the approach of H_2 along the empty p_x orbital (Fig. 1 b), leading initially to a three-center bond, should be energetically more favorable[8, 9].



Z 650.1

Fig. 1. Addition of H_2 to the vinyl cation.

The ethyl cation formed, of course, normal C—H bonds and not three-center bonds. As demonstrated in Fig. 2, however, two *vicinal* C—H bonds can be described by a linear combination of two three-center bonds. The calculations show that these three-center bonds are formed consecutively during the course of the reaction.



Z 650.2

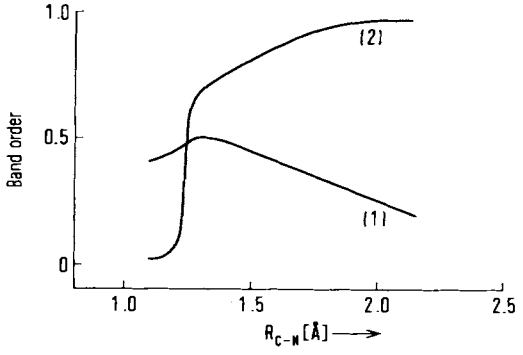
Fig. 2. Representation of C—H bond orbitals as a linear combination of three-center bonds.

The detailed results of the calculations of the reaction path for reaction (1) are as follows: The reaction proceeds with relatively little activation energy (9 kcal/mol at a C—H distance of 2.3 Å). ΔH_0 for the addition is calculated to be 46 kcal/mol (experimental value 60 kcal/mol[10]). An interesting result is that the reaction proceeds in two easily discernable steps:

1. In the first step a three-center bond is formed between the H atoms and the empty p_x orbital ("electrophilic phase of the reaction"). This step is analogous to the electrophilic addition of carbenium ions to saturated C—H and C—C bonds, which can be observed in highly acidic solutions[9]. The prototype reaction is the addition of H_2 to CH_3^+ to form the CH_5^+ cation, which, according to MO calculations, should proceed without activation energy[11].

2. In the second step, beginning at a C—H distance of about 1.3 Å, the antibonding orbital of H_2 combines with the occupied π orbital of the vinyl cation to form the second three-center bond. The H—H distance becomes larger and the geometric structure of the product is obtained. This phase of the reaction corresponds to the characteristic breaking of the bond of the substrate during an insertion process (the "nucleophilic phase", involving the occupied π orbital of the vinyl cation).

The two-phase mechanism is reflected in the changes of the parameters describing the electronic structure along the reaction coordinate. Figure 2 shows the change in the bond order between the originally empty p_x orbital of the vinyl cation and the 1s orbital of an approaching H atom as a function of the C—H distance. During the formation of the first three-center bond, this bond order increases from 0 at infinite distance to about 0.5 at a C—H distance of 1.3 Å. The decrease at smaller distances is due to rehybridization. Similarly, the bond order between the two H atoms of the approaching H_2 molecule sinks continuously from 1 at infinite distance to 0.6 at 1.3 Å. At this point it then drops sharply to almost 0 due to the admixture of the antibonding H_2 orbital to an occupied orbital in the second phase of the addition.

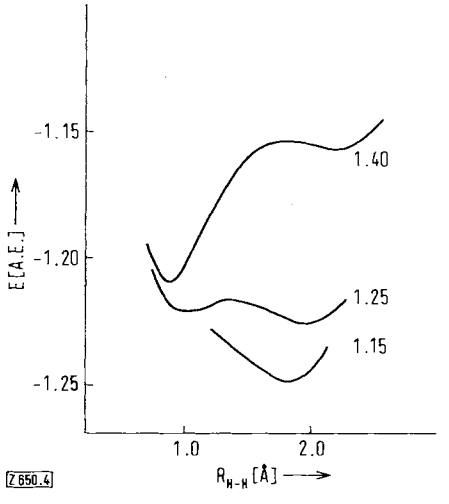


(1) p_x-H
(2) H-H

Z 650.3

Fig. 3. Changes in the electronic structure during reaction (1).

The reaction coordinate is also affected by the two-phase mechanism (Fig. 4). The H—H distance remains relatively small (0.9 Å) down to a C—H distance of 1.3 Å and then increases rapidly with further shortening of the new C—H bond to the final value of 1.85 Å. At intermediate C—H distances (1.25—1.4 Å) there exist two local energy minima at different H—H distances. Above 1.3 Å the minimum with a short H—H bond is energetically more favorable. This order is reversed at shorter C—H distances ($\leq$1.25 Å).



Z 650.4

Fig. 4. The energy as a function of the H—H distance at constant C—H distances.

The two-phase mechanism does not entail any steric consequences (and thus chemical repercussions) in this case. Such effects become important in the analogous insertion reactions of carbenes[12, 13].

Received: February 18, 1972 [Z 650 IE]
revised: March 17, 1972
German version: Angew. Chem. *84*, 680 (1972)

[1] *G. Modena* and *U. Tonellato*, Advan. Phys. Org. Chem. *9*, 185 (1971).

[2] *A. E. Lodder, H. M. Buck*, and *L. J. Oosterhoff*, Recl. Trav. Chim. Pays-Bas *89*, 1229 (1970); *H. Hogeveen* and *C. F. Roobeek*, Tetrahedron Lett. *1971*, 3343.

[3] *H.-U. Wagner* and *R. Gompper*, Tetrahedron Lett. *1971*, 4061, 4065.

[4] *M. Vestal* and *J. H. Futrell*, J. Chem. Phys. *52*, 978 (1970).

[5] *H. Fischer* and *H. Kollmar*, Theoret. Chim. Acta *13*, 213 (1969).

[6] *J. A. Pople, D. P. Santry*, and *G. A. Segal*, J. Chem. Phys. *43*, S 129 (1965).

[7] *H. Kollmar*, Battelle Inform. *1971*, No. 10, 10.

[8] *H. Kollmar* and *H. O. Smith*, Theoret. Chim. Acta *20*, 65 (1971).

[9] *G. A. Olah, Y. Halpern, J. Shen*, and *Y. K. Mo*, J. Amer. Chem. Soc. *93*, 1251 (1971).

[10] *J. L. Franklin et al.*: Ionization Potentials, Appearance Potentials and Heats of Formation of Gaseous Positive Ions. National Bureau of Standards, Nat. Stand. Ref. Data Svcs., No. 26, Washington 1969.

[11] *H. Kollmar* and *H. O. Smith*, Chem. Phys. Lett. *5*, 7 (1970).

[12] *R. C. Dobson, D. M. Hayes*, and *R. Hoffmann*, J. Amer. Chem. Soc. *93*, 6188 (1971).

[13] *H. Kollmar*, Tetrahedron, in press.

[14] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

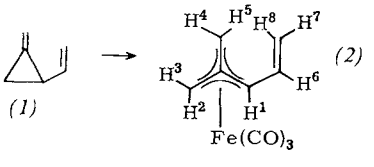
Dimethylene(2-propenylidene)methanetricarbonyliron[1]

By *W. Edward Billups, Lee-Phone Lin*, and *Otto A. Gansow*[*]

Reactions of carbonyliron complexes with compounds whose structural features incorporate the vinylcyclopropane *or* methylenecyclopropane grouping are of current interest.

Thus the reaction of $Fe_2(CO)_9$ with cyclopropylstyrene[2a,b] or spiro[2.4]hepta-4,6-diene[2c] gives substituted 1,3-diene-$Fe(CO)_3$ complexes, whereas bullvalene[2e] and semibullvalene[2f] give complexes resulting from cleavage of the cyclopropane ring with formation of both a π-allyl and a σ component bound to the $Fe(CO)_3$ unit. Methylenecyclopropane[2d] also gives a low yield of butadienetricarbonyliron upon reaction with $Fe_2(CO)_9$; however, methylenecyclopropanes bearing a phenyl or methyl substituent on C-2 give trimethylenemethane-coordinated products[2d].

Methylene(vinyl)cyclopropane *(1)*[3] is a molecule that incorporates *both* these functionalities and the present communication reports on a stable iron complex dimethylene(2-propenylidene)methanetricarbonyliron *(2)* derived from *(1)* and $Fe_2(CO)_9$.



(1) *(2)*

Complex *(2)* is prepared (43% yield) by stirring a 1:1 mixture of *(1)* and $Fe_2(CO)_9$ in benzene at 35—40 °C for 2 h. After removal of benzene, bulb to bulb distillation at 92 °C/2.5 torr gives *(2)* as a deep green oil whose composition was shown to be $C_6H_8Fe(CO)_3$ by its mass spectrum (parent molecular ion *m/e* 220). The infrared spectrum shows C≡O absorptions at 2048 and 1984 cm^{-1}. The ^{1}H-NMR spectrum (Table 1) of *(2)* provides convincing evidence for the proposed structure. In addition, the decoupled ^{13}C-NMR spectrum of *(2)* at ambient probe temperature shows seven distinct signals (Fig. 1). Two ^{13}C resonances may be immediately identified as due to the carbonyl carbon and the central carbon of the trimethylene-methane ligand by simple chemical shift[4] and signal intensity considerations. The two methylene resonances at −51.9 and −52.5 ppm are quite near those observed for trimethylenemethanetricarbonyliron[4], while those at −137.6 and −118.7 ppm are near the resonances of the vinyl group of compound *(1)*.

Table 1. ^{1}H-NMR parameters of *(2)* determined at 60 MHz and relative to TMS.

	δ(ppm)	J(Hz)
H-1	3.67 (d, d)	$J_{1,6} = 9.7$; $J_{1,4} = 2.1$
H-2	1.80 (d)	$J_{2,5} = 4.3$
H-3	1.79 (s)	
H-4	2.18 (m)	
H-5	2.66 (d)	$J_{2,5} = 4.3$
H-6 to H-8	4.83—6.03 (m)	

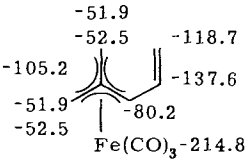


Fig. 1. Chemical shifts are in ppm relative to TMS = 0.

Received: May 8, 1972 [Z 653 IE]
German version: Angew. Chem. *84*, 684 (1972)

[*] Dr. W. E. Billups, Lee-Phone Lin, and Dr. O. A. Gansow
Department of Chemistry
Rice University
Houston, Texas 77001 (USA)

[1] This work was supported by the Robert A. Welch Foundation and the Petroleum Research Fund administered by the American Chemical Society.

[2] a) *S. Sarel, R. Ben-Shoshan*, and *B. Kirson*, J. Amer. Chem. Soc. *87*, 2517 (1965); b) *R. Ben-Shoshan* and *S. Sarel*, Chem. Commun. *1969*, 883; c) *C. H. Depuy, V. M. Kobal*, and *D. H. Gibson*, J. Organometal. Chem. *13*, 266 (1968); d) *R. Noyori, T. Nishimura*, and *H. Takya*, Chem. Commun. *1969*, 89; e) *R. Aumann*, Angew. Chem. *83*, 175, 176, 177 (1971); Angew. Chem. internat. Edit. *10*, 188, 189, 190 (1971); f) *R. M. Moriarty, C. L. Yeh*, and *K. C. Ramey*, J. Amer. Chem. Soc. *93*, 6709 (1971).

[3] *T. C. Shields, W. E. Billups*, and *A. R. Lepley*, J. Amer. Chem. Soc. *90*, 4749 (1968).

[4] *G. F. Emerson, K. Ehrlich, W. P. Giering*, and *P. C. Lauterbur*, J. Amer. Chem. Soc. *88*, 3172 (1966).

Three Isomerization Routes Originating from Different Electronic States of a Linearly-Conjugated Cyclohexadienone[1][***]

By *Gerhard Quinkert, Bernd Bronstert*, and *Klaus R. Schmieder*[*]

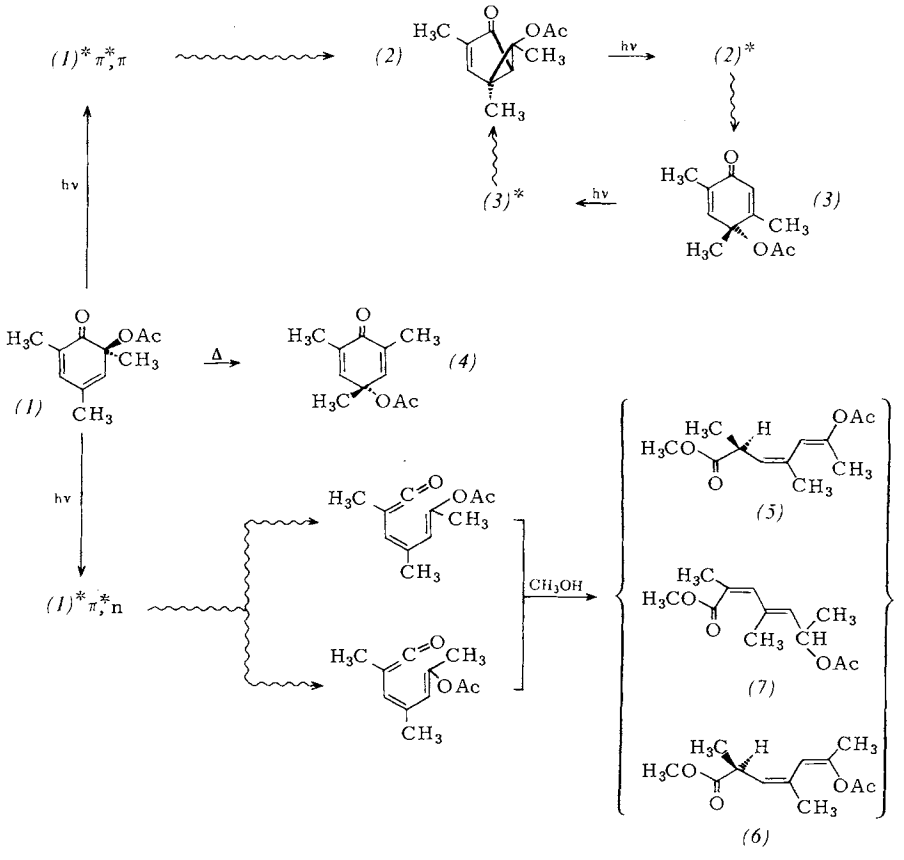
Comparative chemistry is directed towards the elucidation of the reaction paths starting from different electronic states of a compound[2]. The chiral but racemic 6-acetoxy-

[*] Prof. Dr. G. Quinkert, Dr. B. Bronstert [**], and Dipl.-Chem. K. R. Schmieder
Institut für Organische Chemie der Universität
6 Frankfurt, Robert-Mayer-Str. 7—9 (Germany)

[**] Now: Badische Anilin- & Soda-Fabrik AG, 67 Ludwigshafen (Germany)

[***] The work was supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. K. R. Sch. thanks Schering AG for a grant.

2,4,6-trimethylcyclohexa-2,4-dien-1-one *(1)*[3] provides an example in which the routes originating from the electronic ground state, from the π^*,n or from the π^*,π excited states, respectively, lead to different products (see reaction scheme).



If solutions of *(1)* in polar solvents are heated they yield mainly the cross-conjugated cyclohexadienone *(4)* together with minor amounts of phenols (see Table 1). The constitution of the symmetrical isomerization product follows from its spectroscopic properties (see Table 2) and from the observation that, on treatment with zinc in boiling acetic acid, mesitol is produced.

Table 1. Composition of the products isolated after heating of *(1)*. 5.15×10^{-2} M solutions were kept at the temperature stated for 24 h with exclusion of light.

Solvent	Temp. (°C)	Compounds isolated (%) *(1)*	*(4)*	Phenols [a]
Methanol	65	60	30	10
Trifluoroethanol	70	40	50	10
+ cyclohexylamine [b]	70	40	50	10
Xylene	140	60	35	5
Cyclohexane	80	100	—	—
Carbon tetrachloride	77	100	—	—

[a] Mainly mesitol.
[b] 0.769 M.

Irradiation of *(1)* in 2,2,2-trifluoroethanol at room temperature with 365 or 313 nm light furnishes, besides a small amount of phenols[4], the isomeric ketones *(2)* and *(3)* in a *spectroscopically complex photoreaction* (non-linear ED diagram[5]); the relative yields of the ketones depend on the wavelength and on the irradiation time used. According to spectroscopic monitoring, the complex process is composed of two partial photoreactions (linear EDQ diagram[5] for the irradiation of *(1)* and linear ED diagram[5] for the separate photoisomerization of *(2)* to *(3)*; see reaction scheme).

Photoisomerization of *(3)* to *(2)* can be effected by 254 nm light, considerable amounts of phenols[7] being formed during this process. The constitution of the unsymmetrical cross-conjugated cyclohexadienone *(3)* is supported by spectroscopic data (see Table 2) and by the formation of 2,4,5-trimethylphenol on reaction with zinc in boiling acetic acid; for the constitution and stereochemistry[8] of the bicyclo[3.1.0]hexenone *(2)*, see the spectroscopic data in Table 2.

Irradiation of *(1)* in methanol[9] at room temperature with 365 or 313 nm light affords the stereoisomeric methyl esters *(5)* (93%) and *(6)* (2%) in a *spectroscopically simple photoreaction* (linear ED diagram[5]); in addition to traces of phenols (<1%), the constitutionally isomeric methyl ester *(7)* (5%) is also produced. The constitution and stereochemistry of all three esters are confirmed by their spectroscopic data (see Table 2). The carboxylic acid derivatives arise from respective 1,2- or 1,6-addition of the nucleophilic solvent to the corresponding dienylketenes (see reaction scheme); low temperature UV- and IR-spectroscopic evidence for the existence of the transient[10], *seco*-isomeric with *(1)*, has already been presented earlier[11]

The thermal isomerization of *(1)* to *(4)* can be interpreted as a sigmatropic rearrangement of the order [3,3][12] occurring on the lowest energy surface. Since the light-induced isomerization of *(1)* either to *(2)* or to the dienylketene precursors of *(5)* and *(6)* does not give *(4)*[13], one can safely argue that the photoisomerizations do not originate from the electronic ground state of the reactant. Which of the two photoisomerizations actually takes place is

Table 2. Physical data for the isomers obtained from *(1)* and their transformation products [a].

(2) (racem.)	M. p. 58—59 °C UV: λ_{max} (ε) = 225.5 (6050), 259 (2600), 333 nm (250) IR: ν_{max} = 1745 (s), 1690 cm^{-1} (s) NMR: τ = 8.63 (s) [3], 8.55 (s) [3], 8.3 (d; *J* = 1 Hz) [3], 8.05 (ψd) [1], 7.97 (s) [3], 3.0 ppm (m) [1]
(3) (racem.)	M. p. 68—69 °C UV: λ_{max} (ε) = 243.5 (13500), 327 (60), 355 nm (26) IR: ν_{max} = 1742 (s), 1673 (s), 1655 (m), 1630 cm^{-1} (s) NMR: τ = 8.49 (s) [3], 8.07 (ψs) [3], 8.05 (ψs) [3], 7.91 (s) [3], 3.92 (m) [1], 3.40 ppm (m) [1]
(4)	M. p. 55—56 °C UV: λ_{max} (ε) = 234 (11500), 330 (60), 342 (S) nm (30) IR: ν_{max} = 1742 (s), 1676 (s), 1660 (m), 1645 (s) cm^{-1} NMR: τ = 8.48 (s) [3], 8.11 (ψs) [6], 7.97 (s) [3], 3.33 ppm (ψs) [2]
(5) (racem.)	UV: λ_{max} (ε) = 229 nm (6900) IR: ν_{max} = 1755 (s), 1735 cm^{-1} (s) NMR: τ = 8.80 (d; *J* = 7 Hz) [3], 8.25 (m) [3], 8.15 (ψd; *J* = 0.9 Hz) [3], 8.10 (s) [3], 6.70 (m) [1], 6.55 (s) [3], 4.60 (m) [1], 4.31 (m) [1]
(6) (racem.)	UV: λ_{max} (ε) = 234 nm (11000) IR: ν_{max} = 1755 (s), 1735 cm^{-1} (s) NMR: τ = 8.83 (d; *J* = 7 Hz) [3], 8.40 (ψd; *J* = 1.3 Hz) [3], 8.29 (s) [3], 8.01 (ψd; *J* = 1.1 Hz) [3], 6.70 (m) [1], 6.66 (s) [3], 4.50 (m) [1], 4.35 (m) [1]
(7) (racem.)	UV: λ_{max} (ε) = 238 nm (4950) IR: ν_{max} = 1735 cm^{-1} (s) NMR: τ = 8.81 (d; *J* = 6 Hz) [3], 8.31 (s) [3], 8.23 (m) [3], 8.16 (ψd; *J* = 1.5 Hz) [3], 6.66 (s) [3], 4.75 (m) [1], 4.42 (m) [1], 3.57 (m) [1]

[a] Satisfactory analytical data have been secured for all compounds.
The UV spectra were measured in methanol; S = shoulder.
The IR spectra of the crystalline ketones were determined in KBr, those of the liquid methyl esters as films; s = strong, m = medium.
The NMR spectra of the ketones and methyl esters were measured in $CDCl_3$ and C_6D_6, respectively; s = singlet, ψs = pseudosinglet, d = doublet, ψd = pseudodoublet, m = multiplet.

controlled by solvent effects that also influence the relative positions of the π*, π and π*, n transitions in the absorption spectrum (see Fig.) not, however, by the wavelength of the absorbed light (365 or 313 nm). This indicates that the initially excited states are not necessarily the reactive ones. In the present example the rule is obviously obeyed that in the condensed phase the reaction starts on the lowest rung of a given multiplicity ladder. We attribute π*, n and π*, π character to the reactive excited states of the *cyclo/seco* isomerization[12] and the intramolecular $[_\sigma 2 + _\pi 2]$ cycloaddition[14] respectively.

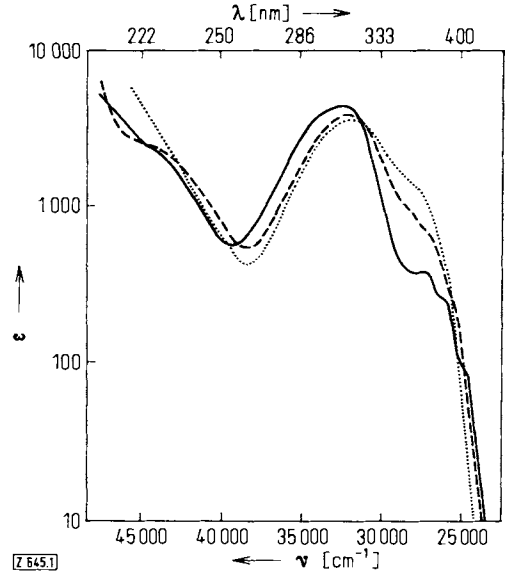


Fig. 1. Electronic absorption spectra of *(1)* in methylcyclohexane (——), ethanol (– – – –), and trifluoroethanol (·····) at room temperature.

Received: April 14, 1972 [Z 645 IE]
German version: Angew. Chem. *84*, 638 (1972)

[1] 14th Communication on Light-induced Reactions.—13th Communication: *G. Quinkert, T. Tabata, E. A. J. Hickmann*, and *W. Dobrat*, Angew. Chem. *83*, 212 (1971); Angew. Chem. internat. Edit. *10*, 199 (1971).

[2] *G. Quinkert*, Angew. Chem. *84*, in press (1972); Angew. Chem. internat. Edit. *11*, in press (1972).

[3] *F. Wessely* and *F. Sinwel*, Monatsh. Chem. *81*, 1055 (1950).

[4] 2,4,5-Trimethylphenol [from *(3)*] as well as mesitol and mesitol 3-acetate [from *(1)*; see Ref. [6]] were obtained. The total yield of phenols for complete reaction of *(1)* amounted to *ca.* 1% with 365 nm light and to *ca.* 15% with 313 nm light.

[5] For definition, construction and evaluation of diagrams of extinction differences (ED diagrams) and of diagrams of quotients of extinction differences (EDQ diagrams) see *H. Mauser*, Z. Naturforsch. *23b*, 1025 (1968). For the use of these diagrams in photochemical studies of linearly-conjugated cyclohexadienones see Ref. [2].

[6] *D. H. R. Barton* and *G. Quinkert*, J. Chem. Soc. (London) *1960*, 1.

[7] Mainly 2,4,5-trimethylphenol.

[8] We favor the *endo* orientation of the methyl group at C-6 for the single stereoisomer isolated.

[9] On irradiation of *(1)* in methanol at −8 °C *J. E. Baldwin* and *M. C. McDaniel* [J. Amer. Chem. Soc. *90*, 6118 (1968)] found a single methyl ester (λ_{max} = 220 nm) to which they ascribe the 3*Z*, 5*E* structure *(5)*.

[10] In distinction from a previous case [*G. Quinkert, B. Bronstert, P. Michaelis*, and *U. Krüger*, Angew. Chem. *82*, 221 (1970); Angew. Chem. internat. Edit. *9*, 240 (1970)], it was impossible here to detect the two stereoisomeric dienylketenes NMR spectroscopically. The lower kinetic stability of the intermediate (τ = 13 min at −75 °C) and the very different behavior of its two components (see reaction scheme) make a direct analysis of the complexity difficult.

[11] *G. Quinkert*, Photochem. Photobiol. *7*, 783 (1968).

[12] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[13] *(4)* fails to occur in the irradiation product of *(1)* in 2,2,2-trifluoroethanol only if *(1)* has reacted completely or if the residue of *(1)* cannot thermoisomerize during the working up procedure.

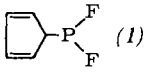
[14] *J. Griffiths* and *H. Hart*, J. Amer. Chem. Soc. *90*, 5296 (1968).

1-Cyclopentadienyldifluorophosphane: A New Fluxional Molecule

By *John E. Bentham, Evelyn A. V. Ebsworth, Hans Moretto,* and *David W. H. Rankin*[*]

Cyclopentadienyl derivatives of silicon[1], germanium[1], and tin[1] have been shown by NMR spectroscopy to behave as fluxional molecules. We have prepared cyclopentadienyldifluorophosphane, whose ^{19}F-NMR spectrum demonstrates this behavior simply and clearly.

When potassium cyclopentadienide is allowed to react for 1 h with an excess of bromodifluorophosphane at −78 °C in the absence of solvent, a mixture of products is obtained, from which pure cyclopentadienyldifluorophosphane can be isolated in 25% yield by fractional distillation (−12 °C/8 torr). The compound has been characterized by its molecular weight, by its mass and infrared spectra, and by vapor pressure measurements: the m.p. is −71 °C, the extrapolated b.p. is 88 °C, and the infrared spectrum is typical of a σ-bound C_5H_5 derivative.



(1)

At low temperatures in a mixture of $CFCl_3$ and $(CH_3)_4Si$ (1:1) as solvent the ^{19}F-NMR spectrum shows the pattern expected for 1-cyclopentadienyldifluorophosphane; there is a wide doublet due to PF coupling [^1J(PF) = 1170 Hz], at $\delta_F = 76.8$ ppm, and each component of the doublet shows a further doublet splitting due to coupling with the single proton bound to the saturated carbon atom [^2J(HF) = 11.5 Hz]. Further splittings were not resolved at temperatures down to −85 °C. At temperatures above −30 °C the wide doublet splitting remains, but the narrower splitting collapses, and at temperatures above 25 °C a sextet pattern develops in its place; at 50 °C the resonance consists of a wide doublet of well-resolved sextets. This shows that at temperatures above 25 °C the fluorine nuclei are coupled equally to all 5 ring protons [^2J(HF) = 2.5 Hz], and therefore that the molecule is fluxional. There is no change in ^1J(PF) over this temperature range, which emphasizes that the fluxional process is intramolecular.

The ^{1}H resonance spectrum also reflects this behavior. At 50 °C the spectrum consists of a single very broad line near 3.2 ppm. At −10 °C this splits into a strong and complex resonance with two peaks near 3.1 and 3.6 ppm and a weaker triplet resonance (J = 11 Hz) near 6.1 ppm, due to the proton bound to the saturated carbon atom. At −85 °C the complex resonance consists of two strong and complex lines at 3.07 and 3.57 ppm, and the triplet at 6.06 ppm shows further splittings. It appears that ^2J(HP) is small, at least at low temperatures.

Received: May 8, 1972 [Z 652 IE]
German version: Angew. Chem. *84*, 683 (1972)

[1] *A. Davison* and *P. Rakita*, Inorg. Chem. *9*, 289 (1970).

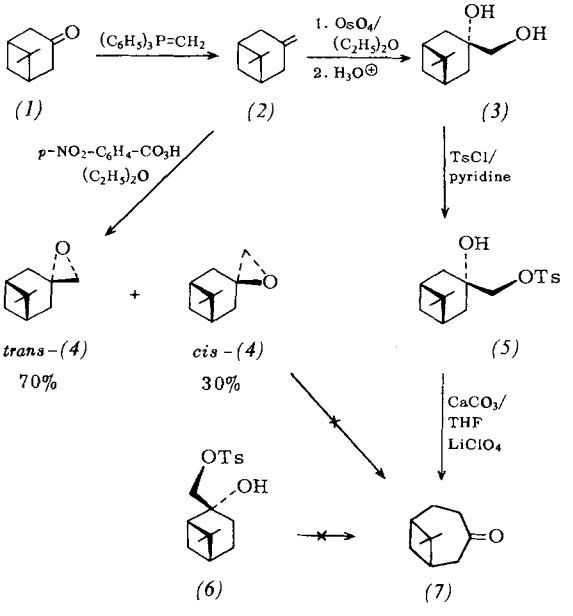
[*] Dr. J. E. Bentham, Prof. Dr. E. A. V. Ebsworth, Dr. H. Moretto, and Dr. D. W. H. Rankin
University of Edinburgh
Department of Chemistry
King's Buildings
West Mains Road, Edinburgh EH9 3JJ (Scotland)

Synthesis of 7,7-Dimethylbicyclo[4.1.1]octan-3-one by Pinacolic Rearrangement[**]

By *William Tubiana* and *Bernard Waegell*[*]

Access to ketones of the bicyclo[4.1.1]octane series is difficult[1]. We have found that the pinacolic rearrangement of the monotosylate *(5)* provides an entry into this series by way of a ring expansion reaction.

A Wittig reaction of isonopinone *(1)*[3] gave the methylene derivative *(2)* which could be converted, *via* the diol *(3)*[4], into the monotosylate *(5)*[4]. Compound *(5)* was then transformed into 7,7-dimethylbicyclo[4.1.1]octan-3-one *(7)* by *Corey*'s procedure for pinacolic rearrangement[5] [*(2)* → *(3)* → *(5)* → *(7)*, see experimental procedure].



Epoxide *(4)* is not an intermediate in this reaction because the mixture of isomers obtained from *(2)* was found to give *(1)* and the corresponding aldehyde under the conditions of pinacolic rearrangement. The monotosylate *(6)* isomeric with *(5)*[6] does not rearrange to the ketone under the above conditions[5].

[*] Dr. W. Tubiana and Prof. Dr. B. Waegell
Laboratoire de Stéréochimie associé au CNRS
Université de Provence, Centre de St. Charles
F-13 Marseille 3[0] (France)

[**] We thank Dr. *Teisseire* for providing us with α-pinene, and the Roure Bertrand et J. Dupont for a research scholarship *(W. T.)*.

Experimental:

Alkene *(2)* (1 g, 7.3 mmol) is added to a solution of osmium tetroxide (2 g, 7.7 mmol) in dry ether (50 ml). After four hours' stirring (magnetic stirrer) at room temperature the reaction solution is mixed with a solution of sodium chlorate (3 g) in dioxane (20 ml), water (10 ml), and a few drops of acetic acid, and heated gently until decoloration. The pH is adjusted to 10 by addition of sodium hydroxide. The organic products are extracted with ether, and the extract is washed with water, dried over magnesium sulfate, and the solvent evaporated. Purification of the residue (620 mg) by GLC (S.E.30 3%, 3.0 m, 160 °C) yields a white crystalline product (400 mg, 50%). IR (CCl_4): 3400, 1050 cm^{-1}. NMR (CCl_4): $\tau = 7.25$ (2H/complex), 6.60 ppm (2H/s). $m/e = 152$ $(M-18)^+$.

Diol *(3)* (500 mg, 2.9 mmol) is dissolved in dry pyridine (20 ml). A stoichiometric amount of *p*-toluenesulfonyl chloride is added portionwise and the mixture then stirred overnight at room temperature. Water (20 ml) is added and the tosylate extracted in the usual manner with ether. Yield 70%. IR (CCl_4): 1600, 1180—1170, 3600, and 3400 cm^{-1}. NMR (CCl_4): $\tau = 2.5$ (4H/m); 6.10 (2H/s), 6.7 (1H/broad), and 7.6 (3H/s).

(5) (1.32 g, 4.0 mmol) is stirred in dry tetrahydrofuran in presence of calcium carbonate (400 mg, 4.0 mmol) and a catalytic amount of lithium perchlorate for 72 hours at 60 °C. The solution is washed with water, dried over magnesium sulfate, and evaporated. The residue (300 mg) is transferred to an alumina column (Merck, activity grade II-III) and eluted with pentane. The procedure yields 200 mg (50%) of *(7)*, m.p. (semicarbazone = 142 to 143 °C, IR (CCl_4): 1715 cm^{-1}; NMR (CCl_4): $\tau = 2.2$ (5 H/broad) and 3.5 ppm (4 H/m); $m/e = 152$ (M^+).

Received: May 16, 1972 [Z 654a IE]
German version: Angew. Chem. *84*, 642 (1972)

[1] *A. N. Vereschagin, S. G. Vul'fson, N. I. Gubkina,* and *B. A. Arbuzov,* Izv. Akad. Nauk SSSR, Ser. Khim. *1970*, 2467; *J. Hatem* and *B. Waegell,* Tetrahedron Lett. *1971*, 2069; *D. Joulain* and *F. Rouessac,* C. R. Acad. Sci. Paris *273*, 561 (1971).

[2] *C. D. Gutsche* and *R. Redmore:* Carbocyclic Ring Expansion Reactions. Academic Press, New York 1968.

[3] *Y. Chretien-Bessiere,* C. R. Acad. Sci. Paris *255*, 943 (1962); *A. J. Baretta, C. W. Jefford,* and *B. Waegell,* Bull. Soc. Chim. Fr. *1970*, 3985.

[4] *Y. Bessiere-Chretien* and *B. Maklati,* Bull. Soc. Chim. Fr. *1971*, 2591.

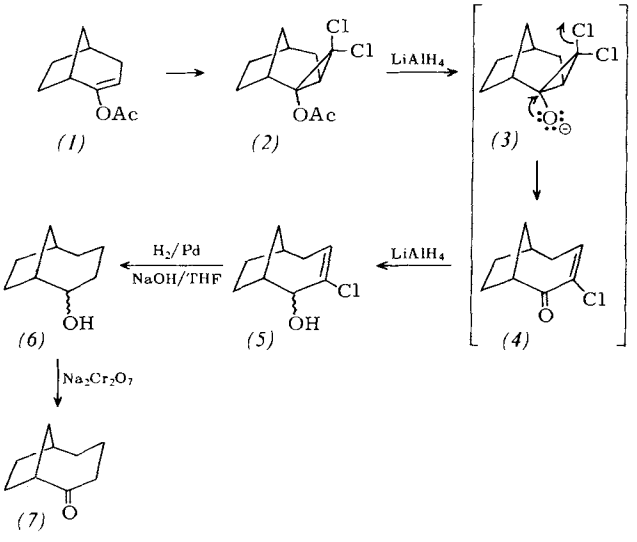
[5] *E. J. Corey,* J. Amer. Chem. Soc. *83*, 1251 (1961); *86*, 478 (1964).

[6] *J. M. Coxon, E. Dansted, M. P. Hartshorn,* and *K. E. Richards,* Tetrahedron *24*, 1193 (1968).

Reductive Fragmentation of 3,3-Dihalotricyclo[4.2.1.0^{2,4}]non-2-yl Acetates: a New Route to the Bicyclo[4.2.1]nonane Series[1]

By *Wolfgang Kraus, Walter Rothenwöhrer, Horst Sadlo,* and *Gerhard Klein*[*]

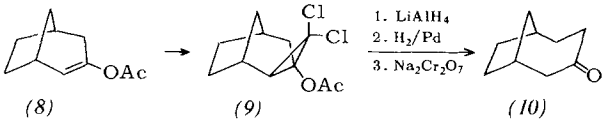
Bicyclo[3.2.1]oct-2-en-2-yl acetate *(1)*, b.p. 86 °C/10 torr, which can be obtained in 87% yield from bicyclo[3.2.1]octan-2-one by means of isopropenyl acetate, does not react with dihalocarbenes if these are produced by potassium *tert*-butoxide from trihalomethanes or from sodium trihaloacetates[2]. However, treatment of *(1)* by *Mąkosza*'s procedure[3], namely, with chloroform and 50% aqueous sodium hydroxide, and catalytic amounts of benzyltriethylammonium chloride, affords 3,3-dichloro-*exo*-tricyclo[4.2.1.0^{2,4}]non-2-yl acetate *(2)*, b.p. 96 °C/0.5 torr, in 67% yield.



(1) *(2)* *(3)* *(4)* *(5)* *(6)* *(7)*

With $LiAlH_4$ in ether[4], *(2)* yields a mixture (91% yield) of the *exo-endo*-isomeric allylic alcohols *(5)* *via* the alkoxy anion *(3)* and the ketone *(4)*, by reductive fragmentation. Hydrogenation of *(5)* over palladized charcoal in tetrahydrofuran and aqueous sodium hydroxide gives the saturated alcohols *(6)* (93% yield), which can be oxidized to pure bicyclo[4.2.1]nonan-2-one *(7)*, m.p. 92—93 °C (92% yield). This ketone thus becomes accessible by a simple route, whereas previously it could be prepared in a pure state only relatively tediously by cyclization of *cis*-4-(3-cyanocyclopentyl)butyronitrile[5-7] or 5-(tosyloxymethyl)cyclooctanone[10].

Bicyclo[3.2.1]oct-2-en-3-yl acetate *(8)*, b.p. 84 °C/10 torr, accessible in 93% yield from bicyclo[3.2.1]octan-3-one and isopropenyl acetate, affords bicyclo[4.2.1]nonan-3-one *(10)* (62% yield; m.p. 117—118 °C) analogously by reductive fragmentation by way of 3,3-dichloro-*exo*-tricyclo[4.2.1.0^{2,4}]non-3-yl acetate *(9)* (58% yield) with subsequent hydrogenation and oxidation.



(8) *(9)* *(10)*

The IR spectra of *(7)* and *(10)* are identical with those of authentic samples[2, 5, 11].

Received: May 19, 1972 [Z 654b IE]
German version: Angew. Chem. *84*, 643 (1972)

[*] Priv.-Doz. Dr. W. Kraus, Dr. W. Rothenwöhrer, Dipl.-Chem. H. Sadlo, and Dipl.-Chem. G. Klein
Chemisches Institut der Universität
74 Tübingen, Wilhelmstrasse 33 (Germany)

[1] Part of a lecture given at Heidelberg in April, 1972. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[2] *W. Rothenwöhrer,* Dissertation, Universität Tübingen 1967.

[3] *M. Mąkosza* and *M. Wawrzyniewicz,* Tetrahedron Lett. *1969*, 4659.

[4] *R. C. DeSelms,* Tetrahedron Lett. *1966*, 1965.

[5] *M. Hartmann,* Z. Chem. *4*, 457 (1964).

[6] *M. Hartmann*, Liebigs Ann. Chem. *724*, 103 (1969).

[7] Ring expansion of bicyclo[3.2.1]octan-2-one by diazomethane [8] affords bicyclo[4.2.1]nonan-2-one only as a difficultly separable mixture with bicyclo[4.2.1]nonan-3-one and higher homologs [2, 9].

[8] *E. Müller, M. Bauer*, and *W. Rundel*, Liebigs Ann. Chem. *654*, 92 (1962).

[9] Cf. *N. A. Belikowa, M. Ordubadi, L. A. Koslowa*, and *A. F. Plate*, Zh. Org. Khim. *7*, 1880 (1971); *G. Fachinetti, F. Pietra*, and *A. Marsili*, Tetrahedron Lett. *1971*, 393.

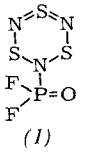
[10] *K. H. Baggaley, J. R. Dixon, J. M. Evans*, and *S. H. Graham*, Tetrahedron *23*, 299 (1967).

[11] *M. Hanack, W. Kraus, W. Rothenwöhrer, W. Kaiser*, and *G. Wentrup*, Liebigs Ann. Chem. *703*, 44 (1967).

4-(Difluorooxophosphoranyl)-1λ⁴,3,5,2,4,6-trithiatriazine

By *Herbert W. Roesky* and *Ludwig F. Grimm*[*]

Reaction of *N,N'*-bis(trimethylsilyl)sulfur diimide[1] with the anhydride of difluorophosphoric acid occurs exothermally with cleavage of trimethylsilyl difluorophosphate. Sublimation of the residue under vacuum (oil pump) affords a yellow compound, m.p. 68 °C, which according to elemental analysis and IR, ^{31}P-NMR, ^{19}F-NMR and mass spectra, probably has the cyclic structure *(1)*. Investigation of the reaction mechanism is in progress.



(1)

The mass spectrum shows, alongside the molecular ion at *m/e* 223, fragment ions at *m/e* 177 ($OPF_2N_2S_2$), 131 (OPF_2NS), 92(N_2S_2), 85 (OPF_2), 78 (NS_2), 69 (PF_2), 66 (OPF), 64 (S_2), 50 (PF), 47 (OP), 46 (NS), and 32 (S). The mass spectrum of tetrasulfur tetranitride, S_4N_4, shows similar fragments; thus, *e.g.*, the fragmentation of S_4N_4 also involves initial cleavage of an SN unit from the ring.

IR spectrum (NaCl and KBr region): 1325 (s), 1303-1265 (s), 1153 (vs), 1015 (w), 985 (w), 960 (w), 917 (vs), 890 (vs), 735 (vs), 718 (s), 700 (m), 645 (m), 580 (m), 536 (vs), 450 (s), 447 (m), 425 (vs) cm^{-1}. The absorptions between 1325 and 960 cm^{-1} are tentatively assigned to the (P=O), (S=N), and (S—N) vibrations and those at 917 and 890 cm^{-1} to the asymmetric and symmetric (P—F) stretching vibrations.

The ^{19}F- and ^{31}P-NMR spectra show that the fluorine atoms are magnetically non-equivalent. A characteristic ABX spectrum, $J_{AB}/J_{BX} \approx 1$, is obtained. The ^{31}P-NMR spectrum contains two doublets of equal intensity, $\delta_P = 9.8$ ppm (against 85% H_3PO_4, external), $J_{P-F} = 1010$, $J_{P-F'} = 1016$ Hz; the most accurate value that has been measured is $J_{AB} + J_{BX} = 2026.3$ Hz. ^{19}F-NMR: $\delta_F = 8.85$, $\delta_{F'} = 13.9$ ppm (against CF_3COOH, external), $J_{F-F'} = 102$ Hz; measured in CH_2Cl_2.

Experimental:

$[F_2(O)P]_2O$ (0.25 mol) is added dropwise with stirring to $[(CH_3)_3SiN]_2S$ (0.125 mol), the temperature of the reaction mixture not being allowed to increase beyond 40 °C. After addition of $[F_2(O)P]_2O$ is complete, components of the reaction mixture which are volatile under oil-pump vacuum are sucked from a sublimation apparatus into a condensation trap. Sublimation of the residue remaining in the apparatus at 30—40 °C/0.01 torr affords 7g of crude product (74%), from which pure *(1)* can be obtained in 57% yield (6 g) on resublimation.

Received: February 8, 1972 [Z 655a IE]
German version: Angew. Chem. *84*, 684 (1972)

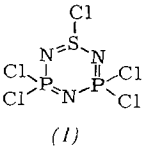
[1] *U. Wannagat* and *H. Kuckertz*, Angew. Chem. *74*, 117 (1962); Angew. Chem. internat. Edit. *1*, 113 (1962); *O. J. Scherer* and *R. Wies*, Z. Naturforsch. *25b*, 1486 (1970).

[*] Prof. Dr. H. W. Roesky and Dr. L. F. Grimm
Anorganisch-Chemisches Institut I der Universität
6 Frankfurt 1, Robert-Mayer-Strasse 7–9 (Germany)

1,3,3,5,5-Pentachloro-1λ⁴,2,4,6,3λ⁵,5λ⁵-thiatriazadiphosphorine

By *Herbert W. Roesky*[*]

Although "trichlorocyclotrithiazene" (1,3,5-trichloro-1λ⁴,3λ⁴,5λ⁴,2,4,6-trithiatriazine, $S_3N_3Cl_3$)[1] and hexachlorocyclotriphosphazene" (2,2,4,4,6,6-hexachloro-1,3,5,2λ⁵,-4λ⁵,6λ⁵-triazatriphosphorine, $P_3N_3Cl_6$)[2] were known before the turn of the century, no reports have appeared in the literature regarding a "mixed derivative" of these two compounds. It has now been shown that $S(N{=}S{=}O)_2$, prepared from thionyl chloride and ammonia[3], reacts with PCl_5 to give "cyclothiaphosphazene" (1,3,3,5,5-pentachloro-1λ⁴,2,4,6,3λ⁵,5λ⁵-thiatriazadiphosphorine) *(1)*.



(1)

Small amounts of $P_3N_3Cl_6$ and $O{=}PCl_2{-}N{=}PCl_3$ are also formed in the reaction. *(1)* can be isolated from the reaction mixture by distillation at reduced pressure.

The phosphorus atoms in *(1)* are magnetically equivalent; the ^{31}P-NMR spectrum shows a singlet at −24.5 ppm (in 40% CH_2Cl_2, external standard 85% H_3PO_4). By way of comparison, chemical shifts of about −20 ppm were found for $P_3N_3Cl_6$[4].

The structure of *(1)* follows from its mass spectrum, which, alongside the molecular ion at *m/e* 311, shows the following, in part characteristic fragments: 276 (M − Cl), 241 (M − Cl_2), 216 (PCl_2NPCl_2), 206 (M − Cl_3), 181 (Cl_2PNPCl), 160 ($P_2N_2Cl_2$), 146 (ClPNPCl), 111 (ClP_2N), 101 (PCl_2), 91 (PN_2S), 90 (P_2N_2), 80 (NPCl), 77 (PNS), 76 (P_2N), 66 (PCl), 46 (NS), 45 (PN). The isotopic ratio is not given here; the peaks with the highest relative intensity correspond to (M − Cl), (NS), and (PCl_2).

At room temperature *(1)* is a colorless, readily hydrolyzable liquid, b.p. 68—70 °C/0.01 torr (decomp.) whose composition could be confirmed by complete elemental analysis.

The IR spectrum (capillary film between KBr plates) contains broad absorption bands in the region of the N=P- and S=N-ring vibrations. Strong bands also appear in the

[*] Prof. Dr. H. W. Roesky
Anorganisch-Chemisches Institut I der Universität
6 Frankfurt 1, Robert-Meyer-Strasse 7–9 (Germany)

region of the S—Cl and P—Cl stretching vibrations. Because of coupling and the small mass differences, an assignment of the vibrations is, as yet, impossible: 1330 (m), 1255 (w), 1205 (vs), 1110 (vs), 1065 (w), 1015 (s), 980 (vs), 855 (s), 785 (w), 730 (s), 660 (s), 600 (vs), 525 (vs), 460 (s), 432 (s) cm^{-1}.

Experimental:

A mixture of $S(NSO)_2$ (19 g) and PCl_5 (46.7 g) in carbon tetrachloride (100 ml) is heated at 35—38 °C for 2—3 h, stirred for 12 h at room temperature, and filtered. Finally, the solvent and the volatile products are removed by evaporation under vacuum (oil pump) and the residue is purified by distillation at a bath temperature of 45—47 °C. Yield of *(1)*: 4.1 g. About four days are required for the distillation; the reaction product soon becomes viscous if a higher temperature is used for the separation.

Received: March 20, 1972 [Z 655 b IE]
German version: Angew. Chem. *84*, 685 (1972)

[1] *W. Muthmann* and *E. Seitter*, Ber. Deut. Chem. Ges. B. *30*, 627 (1897).

[2] *H. Rose*, Ann. Chem. Pharm. *11*, 129 (1834); *J. v. Liebig* and *F. Wöhler*, ibid. *11*, 139 (1834).

[3] *M. Goehring* and *J. Heinke*, Z. Anorg. Allg. Chem. *273*, 297 (1963).

[4] *M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark*, and *J. R. van Wazer*, Top. Phosphorus Chem. *5*, 392 (1967).

Dimethylphosphane(phenylmethoxy)methylene-pentacarbonylchromium(0) – A Route from Carbene- to Ylide Complexes[1]

By *Fritz R. Kreissl, Cornelius G. Kreiter*, and *Ernst Otto Fischer*[*]

Alkoxycarbenepentacarbonylchromium(0) complexes react with ammonia, primary and secondary amines, and with thiols or selenols with cleavage of alcohol to give the corresponding amino-[2], thio-[3], and seleno-carbene complexes[4]. Tertiary phosphanes, on the other hand, readily substitute a carbonyl or the carbene ligand of the above mentioned complexes at elevated temperatures[5].

By way of contrast, dimethylphosphane *(1)* merely adds to phenylmethoxycarbenepentacarbonylchromium(0) *(2)* in pentane at −50 °C without cleavage of either methanol or a ligand.

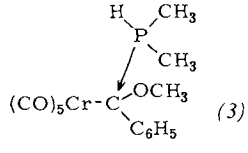
$$\underset{(1)}{HP(CH_3)_2} + \underset{(2)}{(CO)_5Cr{-}C(OCH_3)C_6H_5} \xrightarrow[-50\,^\circ C]{\text{pentane}} \underset{(3)}{CrC_{15}H_{15}O_6P}$$

The addition product *(3)* precipitates as a pale yellow, diamagnetic complex. Analytical data and the mass spectrum prove that *(3)* has the empirical formula $CrC_{15}H_{15}O_6P$. The mass spectrum contains, in addition to the molecular ion at $m/e = 374$, the expected fragmentation pattern for the $(CO)_5Cr$ residue, $[Cr(CO)_nC_{10}H_{15}OP]^+$ with $n = 4.3$, ..., and the peaks of the starting components *(1)* and *(2)* at $m/e = 62$ and 312.

The structure of *(3)* follows from the ^{1}H-NMR spectrum in [D$_6$]-acetone at −10 °C; a total of four signals occur at $\tau = 2.68$ (M, 5), 6.57 (S, 3), 7.55 (M, 3), and 8.12 (M, 3)[6]. The first two signals are assigned to a phenyl group and a methoxy group, the latter two to *P*-methyl groups. A *P*-H signal was not observed[7]; the presence of the *P*-H atom, however, is revealed by the splitting of the *P*-methyl signals.

The fact that two separate signals occur for the two *P*-methyl groups characterizes them as being magnetically non-equivalent. Their signals are split by coupling both with the P atom and as well as with the *P*-H atom. Hence, four peaks are to be expected for each *P*-methyl group. In the spectrum, there now appear double triplets and not the expected double doublets. The additional peaks are attributed to a slow H/D exchange of the *P*-H atom with the solvent; their intensity increases rapidly on addition of only a small amount of [D$_4$]-methanol to the sample. Compared to the original signal peaks they are noticeably broadened by coupling with the *P*-D atom.

The absolute values of the coupling constants of the two *P*-methyl signals at $\tau = 7.55$ and 8.12, $^3J_{HPCH}$ and $^2J_{PCH}$ differ very little from each other, being 5.0 and 13.7 and 5.5 and 12.2. Hz. The values are indicative of a quadrivalent phosphorus atom[8]. The signs of the coupling constants were not determined.



(3)

The ^{1}H-NMR spectrum of *(3)* is consistent with a bonding of *(1)* to *(2)*, provided one assumes that the lone pair on the phosphorus interacts with the "vacant" p orbital of the strongly positive carbene carbon[9]. The nonequivalence of the *P*-methyl groups is caused by the asymmetric carbon atom[10]. Highly informative is the position of the OCH_3 signal, which, compared to that of *(2)* (*cis*: $\tau = 5.76$, *trans*: $\tau = 4.93$)[11] is shifted to very much higher field strength and thus lies in the region of normal OCH_3 signals.

Addition of *(1)* to *(2)* obviously leads to formation of a phosphorus ylide complex from a carbene complex, namely to formation of dimethylphosphane(phenylmethoxy)methylenepentacarbonylchromium(0) *(3)*. Directly synthesized

[*] Dipl.-Chem. F. R. Kreissl, Priv.-Doz. Dr. C. G. Kreiter, and Prof. Dr. E. O. Fischer
Anorganisch-chemisches Laboratorium der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[1] Part 47 of the series: Transition Metal-Carbene Complexes.-Part 46: *E. O. Fischer* and *S. Fontana*, J. Organometal. Chem. in press.

[2] *U. Klabunde* and *E. O. Fischer*, J. Amer. Chem. Soc. *89*, 7141 (1967).

[3] *E. O. Fischer, M. Leupold, C. G. Kreiter*, and *J. Müller*, Chem. Ber. *105*, 150 (1972).

[4] *G. Kreis*, Diplomarbeit, Technische Universität München 1970.

[5] *H. Werner* and *H. Rascher*, Inorg. Chim. Acta, *2*, 181 (1968).

[6] (Multiplicity, intensity), M = multiplet, S = singlet.

[7] In the IR spectrum (KBr pellet), on the other hand, the P—H vibration appears at 2445 cm^{-1}.

[8] *H. Dreeskamp, H. Elser*, and *C. Schumann*, Ber. Bunsenges. Phys. Chem. *70*, 751 (1966); *H. Elser* and *H. Dreeskamp*, ibid. *73*, 619 (1969).

[9] *C. G. Kreiter* and *V. Formáček*, Angew. Chem. *84*, 155 (1972); Angew. Chem. internat. Edit. *11*, 141 (1972).

[10] *M. van Gorkom* and *G. E. Hall*, Quart. Rev. Chem. Soc. *22*, 14 (1968).

[11] *E. O. Fischer, C. G. Kreiter, H. J. Kollmeier, J. Müller*, and *R. D. Fischer*, J. Organometal. Chem. *28*, 237 (1971).

[12] Cf. *e.g. P. A. Arnup* and *M. C. Baird*, Inorg. Nucl. Chem. Lett. *5*, 65 (1969); *C. Krüger, B. L. Barnett*, and *Y.-H. Tsay*, Angew. Chem. *83* 915 (1971); Angew. Chem. internat. Edit. *10*, 841 (1971).

[13] *H. Werner, E. O. Fischer, B. Heckl*, and *C. G. Kreiter*, J. Organometal. Chem. *28*, 367 (1971).

transition metal complexes of other phosphorus ylides have already been reported[12]; however, *(3)* is of additional significance as a model compound for the primary step of the aminolysis of alkoxycarbene complexes[13].

Experimental:

All reactions must be carried out in an inert atmosphere (N_2) and in N_2-saturated, anhydrous solvents. A solution of dimethylphosphane (1.0 g, 16 mmol) in pentane (10 ml) is slowly added dropwise at −60 °C to a solution of phenylmethoxycarbenepentacarbonylchromium(0) (0.73 g, 2.4 mmol) in a 100 ml flask fitted with dropping funnel, magnetic stirrer, and tube for nitrogen supply. The mixture rapidly changes color from red to yellow and a precipitate is formed. The contents of the flask are stirred for 2 h at −50 °C and then filtered at this temperature through a G3 frit. The yellow residue is washed five times with 10 ml portions of pentane (−50 °C) and finally dried for 10 h at −30 °C under vacuum. Yield *ca.* 0.75 g [84% based on *(2)*].

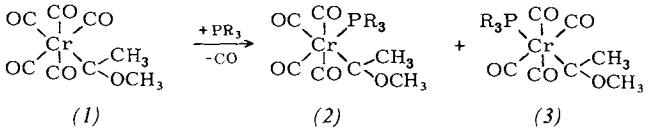
Received: March 15, 1972 [Z 635 IE]
German version: Angew. Chem. *84*, 679 (1972)

Demonstration of Isomers and Intramolecular Isomerization of Carbene Complexes of Chromium[1]

By *Ernst Otto Fischer, Helmut Fischer,* and *Helmut Werner*[*]

Reaction of pentacarbonyl(methoxyorganylcarbene)chromium(0) complexes $Cr(CO)_5C(OCH_3)R'$ *(1)* with $P(C_6H_5)_3$ occurs with replacement of one CO group and formation of *cis*-$Cr(CO)_4P(C_6H_5)_3C(OCH_3)R'$[2].

We have now found[3] that by interaction of trialkylphosphanes with *(1)*, $R' = CH_3$, in solvents such as hexane, benzene and tetrahydrofuran at *ca.* 60 °C one obtains mixtures of *cis*- and *trans*-$Cr(CO)_4PR_3C(OCH_3)CH_3$ [*(2)* and *(3)*, respectively].



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

(a), R = C_2H_5 *(d)*, R = C_6H_{11}
(b), R = i-C_3H_7 *(e)*, R = n-C_8H_{17}
(c), R = n-C_4H_9

The pairs of isomers *(2)* and *(3)* can be separated by column chromatography on silica gel. They form orange-red, diamagnetic crystals that are insoluble in water but very readily soluble in organic solvents and are only slightly sensitive to oxidizing agents.

Two isomers are also obtained if trialkylarsanes or trialkylstibanes are used instead of trialkylphosphanes[4].

When *(2)* or *(3)* are heated in hexane, benzene, toluene or methylcyclohexane at *ca.* 60 °C isomerization occurs and proceeds to establishment of an equilibrium:

$$(2) \underset{k_2}{\overset{k_1}{\rightleftharpoons}} (3)$$

[*] Prof. Dr. E. O. Fischer and Dipl.-Chem. H. Fischer
Anorganisch-chemisches Laboratorium der Technischen Universität
8 München 2, Arcisstr. 21 (Germany)
Prof. Dr. H. Werner
Anorganisch-chemisches Institut der Universität
CH-8001 Zürich, Rämistr. 76 (Switzerland)

The rate of isomerization can be determined by measurement of infrared spectra [*e.g.* ν(CO) of *(2a)*: 2008, 1919, 1911, 1896 cm^{-1}; *(3a)*: 1900, 1880 cm^{-1}; in hexane] or ^{1}H-NMR spectra [*e.g.* τ values of *(2a)*: CH_3 7.40 (D), OCH_3 6.16 (S); *(3a)*: CH_3 7.12 (S). OCH_3 5.66 (S) in [D_8]-toluene]. The rate constants for isomerization of *(2a)* are collected in Table 1.

Table 1. Rate constants for the isomerization of *cis*-$Cr(CO)_4P(C_2H_5)_3C(OCH_3)CH_3$ *(2a)* in methylcyclohexane and toluene.

[*(2a)*] [mmol/liter]	Temp. [°C]	$k_1 \times 10^3$ [s^{-1}]	$k_2 \times 10^3$ [s^{-1}]
In Methylcyclohexane			
0.0134	46	0.57	0.59
0.0134	52	1.29	1.20
00075	62	3.21	3.18
0.0134	62	2.83	3.00
0.0227	62	3.17	3.27
0.0134[a]	62	3.41	2.84
0.0134[b]	62	3.08	2.70
0.0134	71	5.84	7.55
In Toluene			
0.041	41	0.42	0.83
0.041	46	0.68	1.33
0.041	52	1.52	2.60
0.041	62	4.41	7.17
0.0227	62	4.29	6.89
0.0114	62	3.76	6.14
0.041[a]	62	3.75	6.93
0.041[b]	62	3.80	5.70
0.041	71	10.50	15.85

[a] Solvent saturated with CO.
[b] Five-fold molar excess of free $P(n\text{-}C_4H_9)_3$.

The results show that conversion of the geometrical isomers occurs according to a first-order rate law:

$$d[(3)]/dt = k_1[(2)] - k_2[(3)]$$

The activation parameters for isomerization of *(2a)* to *(3a)* and of *(3a)* to *(2a)* in methylcyclohexane and toluene can be seen in Table 2.

Table 2. Activation parameters for the isomerization of *(2a)* and *(3a)* at 65 °C.

Solvent	Direction of reaction	$\Delta H^{\neq}$ [kcal/mol]	$\Delta S^{\neq}$ [cal mol^{-1} deg^{-1}]
Methylcyclohexane	*(2a)*→*(3a)*	21.2 ± 0.5	−6.5 ± 1.5
Methylcyclohexane	*(3a)*→*(2a)*	22.5 ± 0.5	−3.5 ± 1.5
Toluene	*(2a)*→*(3a)*	24.3 ± 0.5	+2.8 ± 1.5
Toluene	*(3a)*→*(2a)*	22.2 ± 0.5	−2.5 ± 1.5

According to these findings the following mechanisms must be considered for the isomerization:

(a) Dissociation of a Cr—CO bond and readdition of the CO ligand.

(b) Dissociation of the Cr—PR_3 bond and readdition of the PR_3 ligand.

(c) Dissociation of the Cr—$C(OCH_3)CH_3$ bond and readdition of the carbene ligand.

(d) Intramolecular rearrangement without bond fission.

Isomerization by (a) or (b) should be slowed down by addition of free CO or free PR_3, respectively. As Table 1 shows, this is apparently not the case. If the isomerization of *(2a)* is followed by ^{1}H-NMR spectroscopy in $[D_8]$-toluene in presence of a five-fold molar excess of $P(C_6H_{11})_3$, it is found that the intensity of the CH_3 and OCH_3 signals of *(2a)* decrease and those of *(3a)* increase to almost identical extents. Signals that would indicate formation of *(2d)* or *(3d)* are not detectable[5]. The small difference between the sums of the corresponding peaks of *(2a)* and *(3a)* increases slowly during the reaction, but this is to be ascribed to decomposition with formation of $Cr(CO)_4P(C_6H_{11})_3P(C_2H_5)_3$[6]. The rate of decomposition is, however, distinctly smaller than that of the isomerization. Thus not only mechanism (a) and (b) but very likely also mechanism (c) are excluded as possible routes for the isomerization, so that only the *intramolecular rearrangement* (hitherto observed only for octahedral *chelate* complexes) should occur. Whether the mechanisms previously discussed in the literature[7] prove right for this rearrangement cannot be decided on the basis of the present results; clarification is being sought in current investigations.

Received: May 12, 1972 [Z 651 IE]
German version: Angew. Chem. *84*, 682 (1972)

[1] Part 49 of the Series: Transition-metal-Carbene Complexes.—Part 48: *E. O. Fischer, F. R. Kreissl, C. G. Kreiter,* and *E. W. Meinecke,* Chem. Ber. in the press. Also Part 13 of the Series: Kinetic Investigations of the Reaction of Metal Complexes.—Part 12: *H. Werner, E. O. Fischer, B. Heckl,* and *C. G. Kreiter,* J. Organometal. Chem. *28*, 367 (1971).

[2] *U. Klabunde,* Dissertation, Northwestern University, Evanston, Illinois, USA, 1967; *E. O. Fischer* and *U. Klabunde,* unpublished work.

[3] For the first results see: *S. Fontana,* Dissertation, Technische Universität München 1971.

[4] *E. O. Fischer* and *K. Richter,* unpublished work.

[5] When $P(C_2H_5)_3$ reacts with *(2d)*, an isomeric mixture of *(2a)* and *(3a)* is formed. From qualitative investigations it is to be assumed that this phosphane exchange does not follow a first-order rate law, since the rate of formation of the complexes *(2a)* and *(3a)* is dependent on the concentration of $P(C_2H_5)_3$.

[6] *H. Werner* and *H. Rascher,* Inorg. Chim. Acta *2*, 181 (1968).

[7] *J. C. Bailar Jr.,* J. Inorg. Nucl. Chem. *8*, 165 (1958); *P. C. Ray* and *N. K. Dutt,* J. Indian Chem. Soc. *18*, 289 (1941); *20*, 81 (1943); *C. S. Springer, Jr.* and *R. E. Sievers,* Inorg. Chem. *6*, 852 (1967).

CONFERENCE REPORTS

Enzymic Synthesis of Homogeneous Stereoregular Polymers

By *Beate Pfannemüller*[*]

The lecture concerned the use of enzymes for specific synthesis of models of carbohydrate polymers.

Enzymic synthesis affords strictly stereoregular polymers. The molecular weight and the molecular weight distribution of native biopolymers are, however, determined by *in vivo* conditions; it is thus not possible to change these two parameters which are significant for the physical properties of the products.

As an example, it was shown for the *in vitro* synthesis of amylose by phosphorylase, that, provided certain conditions are maintained, enzymic synthesis may be directed towards production of monodisperse polymers with any desired degree of polymerization. When maltotetraose or higher maltooligomers are used as a primer the kinetics of phosphorolytic synthesis of amylose are comparable to those of anionic polymerization: in both cases the mechanism of initiation and propagation is the same; chain termination does not occur; the degree of polymerization is determined by the number of initiator molecules and the degree of conversion of monomer. Since the enzymic products exhibit a Poisson distribution it follows that the enzyme dissociates from the growing chain after each step (multi-chain reaction). When maltotriose is used as a primer a characteristically unsymmetrical molecular weight distribution is obtained since in this case the initiation step is rate-determining.

Since the enzyme is specific only for the sugar residues immediately adjacent to the initiation point phosphorolytic synthesis can also be used for preparation of branched polymers with a "comb" or "star" structure. The degree of branching can be controlled at will.

Some of the various applications of the substances were illustrated:

1. Study of the mode of action of exo-, endo-, and debranching enzymes.

2. Study of the influence of chain length on the conformation and solubility of amylose in water and on the properties of the amylose-iodine complexes (ORD and CD investigations).

3. Electron-microscopic study of the supermolecular structure of substances when complexed with iodine.

Lecture at Darmstadt, April 28, 1972 [VB 339 IE]
German version: Angew. Chem. *84*, 644 (1972)

[*] Dr. B. Pfannemüller
Institut für makromolekulare Chemie der Universität
78 Freiburg, Stefan-Meier-Strasse 31 (Germany)

High-Pressure Properties and Their Dependence on Molecular Structure

By *Eduard Kuss*[*]

Density is the most important factor in the evaluation of measurements and the interpretation of other physical properties at high pressure, since the relative distance between the molecules and the intermolecular forces that depend thereon determine the properties of the material.

[*] Prof. Dr. E. Kuss
Institut für Erdölforschung
3 Hannover, Am kleinen Felde 30 (Germany)

In the equation of state for compressed *gases* the second virial coefficient B is found from the potential energy U as a function of r, the distance between the molecules. The higher virial coefficients C, D, E ... are given by the simultaneous interaction of 3,4,5 ... molecules. In considering more than two molecules the mathematical difficulties become so great that the sixth virial coefficient, for instance, cannot be calculated for $U(r)$ but only for hard spheres without attractive forces.

For compressed *liquids* an exact theoretical treatment meets with further difficulties and, as yet, is not possible since:

a) such high densities require a knowledge of the seventh and eighth virial coefficients;

b) the spatial partition of molecules is not random and the partition function must also be taken into account;

c) even in simple cases and for the lower virial coefficients only a potential with spherical symmetry can be used. At high densities, however, the geometrical form of the molecule plays an important role and it is therefore necessary to take into account a very complicated non-spherical potential.

To investigate this influence of molecular structure the pVT-data of homologous series and isomers were measured with a special high-pressure piezometer. The compressibility and also the constant B of *Tait's* equation of state depend markedly on the chain length of the molecule, but are relatively little influenced by the side-chain groups in the molecule[1].

In contrast to this the viscosity-pressure coefficient, as measured by high-pressure capillary and falling ball viscometers, depends largely on the number and the positions of side-chain groups in the molecule and only rarely on chain length[2]. To characterize the behavior a "degree of molecular branching" was defined, whose numerical value is a direct measure of the positions of side-chain groups. Substances could be synthesized whose viscosity was 6 powers of ten greater at 2000 at than at atmospheric pressure[3].

Finally the electric double refraction, which is very sensitive to small changes of molecular structure, was discussed. In a strong electric field not only polar but also apolar molecules are turned in the direction of field because of their anisotropy of polarizability. The double refraction caused thereby leads to a difference in the ninth decimal of the refractive indices for the two light components, polarized parallel and perpendicular to the direction of the field. The pressure dependence of the Kerr constant, together with the *Langevin-Born* orientation theory, permits conclusions concerning the hindrance to rotation of the apolar molecule and the anisotropy of the internal field due to the structure of liquids. Here benzene behaves highly anomalously[4].

Lecture at Hamburg, Germany, February 11, 1972 [VB 341 IE]
German version: Angew. Chem. *84*, 686 (1972)

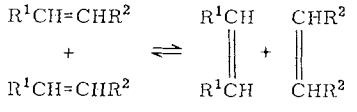
[1] *E. Kuss* and *M. Taslimi*, Chem.-Ing.-Techn. *42*, 1073 (1970).
[2] *E. Kuss* and *P. Pollmann*, Z. Phys. Chem. N. F. *68*, 205 (1969).
[3] *E. Kuss*, Chem.-Ing.-Techn. *37*, 465 (1965).
[4] *E. Kuss* and *H. H. Heydemann*, Z. Phys. Chem. N. F. *43*, 97 (1964).

REVIEW ABSTRACTS

The deformation of polyethylene is dealt with by *R. S. Stein*. Polyethylene is a typical semicrystalline polymer whose idealized form consists of perfect crystallites embedded in a rubbery phase. The mechanical properties of the polymer depend not only upon the crystallite content but also upon details of chain topology and morphology and defects of the crystallites. No complete theory of the deformation processes is yet available. The processes are dependent upon the rate of extension because realignment of the crystallites requires finite time. Changes during extension can be followed, *e.g.* by microscopy and by light-scattering and X-ray diffraction experiments. [Deformation Mechanisms of Polyethylene. Accounts Chem. Res. *5*, 121—127 (1972); 37 references]

[Rd 513 IE –L]

Metathetic reactions of olefins are reviewed by *N. Calderon*. Such reactions comprise catalytically-induced bond rearrangements as shown in the following scheme:



Experiments with 2-pentene and 6-dodecene led to the expected statistical distribution and prove that the rearrangements occur by transalkylidenation. The catalytic formation of macrocycles from olefins and catalytic *cis-trans* isomerizations are also metathetic reactions. [Olefin Metathesis. Accounts Chem. Res. *5*, 127—132 (1972); 41 references]

[Rd 514 IE –L]

Synthetic Peptides. Vol. 1. By *G. R. Pettit.* Van Nostrand Reinhold Co., New York–London 1971. 1st Edit., xii, 467 pp., numerous tables, £ 10.00.

One of the chief problems for workers in the field of synthetic chemistry is to find out as quickly as possible whether the substance in question has already been prepared, and if not, the way in which substances of similar structure can be obtained. This is particularly troublesome in the case of bio-oligomers, and therefore peptides. Specialized handbooks in which substances that have already been characterized are brought together are thus extremely useful.

The present book, which covers the period 1960—1969, links up with earlier reviews of similar nature (*e. g. Goodman* and *Kenner* 1957, *Greenstein* and *Winitz* 1961). The great upsurge in peptide synthesis has resulted in the fact that practically the entire volume consists of tables on amino-acid derivatives and di- to polypeptides. Physical constants (m. p., [α]) and synthetic routes are included. In some cases the tabulated data have been critically selected. For the derivatives this evaluation agrees with the experience of other peptide chemists, except that the *o*-nitrobenzenesulfenyl protective group may not have been ranked highly enough. Not all compounds of a given type are included in the tables, but random sampling in the reviewer's laboratory showed that only a few compounds have been overlooked.

The number of printing errors *etc.* is not outside the limits expected for a work as ambitious as these tables. The only thing that may bother the reader is the inconsistent use of abbreviations; in many cases these differ from the ones given in the introduction. Some compounds are not in the proper order (*e. g.* pp. 366, 425).

This book will be a useful aid to all chemists concerned with peptide synthesis.

Karel Bláha [NB 39 IE]

Regeln und Steuern. Eine Einführung für Chemiker und Ingenieure (Regulation and Control. An Introduction for Chemists and Engineers). By *A. Schöne.* Verlag Chemie GmbH, Weinheim/Bergstrasse. 1971, 1st Edit. viii, 207 pp., 136 figures, 8 tables, bound DM 33.—.

The high degree of automation of chemical production plants inevitably confronts chemists and engineers involved in process development and operation with problems of control engineering. The purpose of the present book is to provide this group of persons with an account of the fundamentals of control engineering and to explain the regulatory function of control circuits frequently encountered in practice. The author therefore places the main emphasis on the process, and in particular the dynamic behavior of processes, and has consciously renounced any attempt to present a complete account of the theory of control or measuring techniques which usually occupy a large part of monographs on control engineering. The many standard terms of control engineering are not presented *en bloc* in an introductory section, as is usually the case, but introduced almost in passing in the individual chapters, a feature which will certainly facilitate their assimilation. Fundamentals are explained with the aid of simple and illustrative examples presented as block circuit diagrams; the occasional analytical treatment of these examples contributes to an improved understanding without making too severe demands on the mathematical knowledge of the reader.

A brief introduction to the typical dynamic behavior of processes and the basic dynamic models derived therefrom is followed by four chapters on the mode of action of a regulator and the regulatory processes employed in practice, ranging from the simple control loop to the control of multi-loop systems with many variables. A short chapter is devoted to the functioning of analog computing modules and their practical use in switching operations.

The most important chapter, and also a particularly valuable aspect of the book, is doubtless the following one on dynamic behavior and control systems of process plant. Current knowledge of the dynamics of the most important groups of equipment in chemical production plant—heat exchangers, distillation columns, and reactors—is surveyed, and proven circuitry is demonstrated, and, insofar as is possible, critically discussed. The experienced control engineer will also find this chapter stimulating, due in part to the numerous literature references which will be a great help to further study.

In view of the present-day significance of fully automated control of batch processes in chemical process engineering, the next chapter on control could have been more detailed. The book closes with a chapter on process computers, in which a terse review of the mode of action and process periphery of computers precedes accounts of direct digital control (DDC) and process optimization.

The book is a highly successful, practically oriented introduction to control engineering that can be warmly recommended to production chemists and engineers, as well as to control experts.

Theo Ankel [NB 42 IE]

Essential Fiber Chemistry. By *M. E. Carter.* Marcel Dekker Inc., New York 1971. 1st Edit., vii, 216 pp., numerous figures, bound $ 19.50.

No such book has hitherto been available. Its appearance is most welcome, particularly in view of its numerous virtues, and will certainly satisfy a need of all those having an interest in fiber chemistry. The book presents a didactically exemplary introduction to the chemistry and physics of natural and synthetic fibrous materials. The description of fundamental principles of chemical and physical structure and their relation to the most important properties of fibers is completely devoid of such ballast as the various techniques available for working the fibers. Interesting indications of new developments and fiber modification, particularly with regard to dyeability, flame resistance, and temperature resistance, round off the survey of an interesting area of modern organic and macromolecular chemistry.

In spite of a certain degree of criticism with regard to unnecessarily extensive tables of patents, the preference for American literature, and the absence of any assessment of the technical and economical viability of certain processes, the book can be warmly recommended to textile chemists and all those who were unable to devote sufficient attention to this field as students.

Giselher Valk [NB 43 IE]

Mass Spectrometry of Heterocyclic Compounds. By *Q. N. Porter* and *J. Baldas*. John Wiley and Sons, London–New York 1971. 1st Edit., xvii, 564 pp., numerous figures, bound £ 11.75.

The importance that mass spectrometry has acquired in organic chemistry in recent years has led to such a spate of primary literature, distributed through a wide range of journals under a variety of titles, that an overall view of the field is becoming increasingly elusive. The related difficulty of becoming acquainted with even a restricted range of material or of merely keeping abreast of recent developments often has the result that the possibilities of mass spectrometric analysis are not fully exploited. Good secondary literature has therefore become a *conditio sine qua non*.

With this in mind the authors of the present work have turned their attention to an area of study that was in desperate need of a critical assessment and survey, *i.e.* mass spectrometry of heterocyclic compounds. The effect of the ring system on the general fragmentation behavior in various environments is discussed on the basis of ring size and the nature and the number of hetero atoms and illustrated by numerous examples of spectra. Although the subject matter is extremely heterogeneous, in spite of being limited to saturated and unsaturated N, O, and S heterocycles, the description of the individual structural types is both detailed and, particularly, not uncritical, thus obviating the need to refer back to the original literature in many cases. It would have been better, however, if the relative intensities of the fragments had been listed more consistently.

Generally speaking, the relevant literature has been covered in considerable detail (apart from papers in the Russian language) although examples from the field of natural products (particularly alkaloids) are included only when they are characteristic of the behavior of a particular fundamental skeleton in a specific environment. Unfortunately, and this remark concerns more the publisher than the authors, more than three years seem to have passed between completion of the manuscript (the literature is evaluated up to 1967) and appearance of the book, and research has by no means stood still during this time; the brief addenda at the end of each chapter, which provide a survey of the most important publications up to 1970, are rather inadequate.

Nevertheless, the present book is not only a great help to the mass spectroscopist as far as information content and a solid basis for further literature searches are concerned, but it also provides the organic chemist with an overall picture of where he can profitably apply mass spectrometry in the wide field of heterocyclic chemistry. It is to be hoped that supplementary volumes surveying the latest developments will appear at regular intervals.

Herbert Budzikiewicz [NB 44 IE]

Quantitative Management in R & D. By *C. J. Beattie* and *R. D. Reader*. Chapman and Hall Ltd., London 1971. 1st Edit., x, 347 pp., numerous figures, bound £ 5.00.

The use of quantitative methods to increase the profitability of research and development has been attracting increasing interest in recent years even though the objective value of such methods is still disputed. Although the knowledge hitherto collected has long been the subject of numerous seminars organized by consultant companies the publication of the present book is to be welcomed. The authors have presented the current situation in an extremely understandable and purposely simplified manner in order to assist the reader in familiarizing himself with the subject matter. Anybody who wishes to delve deeper into the methods described can refer to the highly informative appendix and to the exceptionally detailed bibliography at the end of each chapter.

The book opens with a brief introduction (5 pages) to the essential phases of a research project followed by a chapter on the generation of useful ideas (12 pages) which describes special methods such as "brainstorming" and also more conventional practices such as the cooperation between colleagues from different disciplines.

There follows a chapter on the planning of research projects (30 pages) which is concerned with the preparation required for the evaluation of a project. The most important diagrammatic planning techniques are briefly considered. The chapter on project evaluation itself (38 pages) discusses in how far the intuitive assessment of suggestions can be supported by analyses of the expected costs on the one hand and the expected economic advantage on the other.

This kind of numerical assessment is a prerequisite for choice of research projects as considered in the next chapter (48 pages). The methods described range from simple classification on the basis of a more or less suitable parameter to relatively complicated processes requiring access to a computer.

Further chapters essentially provide practical instructions for the application of such systems of choice (together 40 pages) and for the execution and control of research projects (13 pages). Particular emphasis is placed on the writing of suitable reports on the results of studies (34 pages).

The appendix contains detailed information about methods of technological forecasting (20 pages), diagrammed planning techniques (55 pages), discounted cash flow calculations (9 pages), and uncertainty analyses (21 pages). An index makes for easy reference to the book.

Peter Haug [NB 45 IE]

The Avenue of Years—A Memoir of Sir James Irvine. By *Mabel V. Irvine*. William Blackwood, Edinburgh and London 1970. 1st Edit., iv, 268 pp., 9 figures, bound £ 1.80.

Sir James Colquhoun Irvine (1877—1952) was Professor of Chemistry at St. Andrews, Scotland, from 1909 to 1920, and was then Principal and Vice Chancellor of this university from 1921 to 1952. He is one of the leading figures of Scottish university history and was well known far beyond the boundaries of his country. As a chemist he was active in the field of carbohydrate chemistry and among other achievements he introduced the methylation of hydroxyl groups as an aid in the structural elucidation of carbohydrates.

Irvine's wife, who survived her husband by 15 years, authored the present biography which remained uncompleted and does not extend beyond 1944. The book is not an historical work, and makes no pretence to be one, but rather a very personal series of recollections. The authoress describes family life, social obligations, the atmosphere of the small Scottish university town steeped in tradition, *Irvine*'s administrative activities, and his numerous journeys abroad in his capacity as Principal.

Unfortunately the reader learns next to nothing about *Irvine*'s research as a carbohydrate chemist, which was

held in such high esteem by *Emil Fischer* that he suggested an agreement regarding research programs. The missing information can be obtained from an obituary by *John Read* in J. Chem. Soc. *1954*, 476. However, it is even difficult to gain a true picture of *Irvine*'s personality since the authoress tends to idealize her husband in a rather uncritical manner, which disqualifies the book as source material for future historical studies.

The book cannot therefore really be recommended to the chemist who is interested in the history of his subject unless he would enjoy reading a biographical report described by the authoress as "an old-fashioned chronicle of an era that is past."

Jost Weyer [NB 46 IE]

Solid Acids and Bases. By *K. Tanabe*. Academic Press, New York–London 1970. 1st Edit., viii, 175 pp., numerous tables and figures, bound $ 11.50.

The author of the present work is not content to "put new wine in old vessels" since the topicality of his subject can readily be assessed even from a glance at the bibliography which contains mainly references from the last ten years (up to 1970). Why is it that acid-base catalysis, well known for a long time in the homogeneous phase, should again arouse such great interest?

The main reason lies in the discovery of numerous refined methods (color indicators, spectroscopic measurements, adsorption from the gas phase or from solution, titrations with substances showing acidic or basic reactions, *etc.*) for determination of acidity and basicity (Hammett function) and the concentration of functional groups on solid surfaces. Two chapters are concerned with these methods and the important question of distinguishing between Brønsted and Lewis acids is also discussed.

In two other chapters the author undertakes a characterization and systematic treatment of solids. At the beginning of his book he divides a large number of solids into solid acids and bases and uses the largest chapter (chapter 4) for a treatment of the structure and the acid and basic properties of the sites present on the surfaces of solids (metal oxides and sulfides, mixtures of metal oxides, zeolites, metal sulfates and phosphates). The connection between catalytic activity and selectivity and the nature of the surface is shown for reactions of widely differing kinds (decomposition reactions, cracking, isomerization, polymerization, *etc.*) on catalysts having acidic, basic, or bifunctional character.

Both the scarcity of literature on this scientifically and industrially important subject and the presentation of the book with its clear tables and illustrations make the work a valuable aid for all who are concerned with heterogeneous catalysis or wish to enter the field.

Willi Herzog [NB 47 IE]

Allgemeine Organische Chemie (General Organic Chemistry). By *K. Heyns*. Akademische Verlagsgesellschaft, Frankfurt 1970. 1st Edit., x, 348 pp., bound DM 19.60.

The series of study texts including the present work presents lecture manuscripts of proven value in somewhat modified form. An experimental presentation which relies heavily on the illustrative power of the experiments themselves can only be incompletely replaced by a manuscript, however good it is. The above text by *Heyns* has been thoroughly prepared and betrays many years of lecturing experience. Its information content and size approach those of a textbook. The many references to experiments in the text are no doubt intended as suggestions for experiments during a practical course rather than as a replacement for experimental demonstration.

The present study text is intended for students of chemistry, medicine, pharmacy, and biology from the second semester onwards. The amount of material included is probably rather overpowering for biologists and medical students. For such an audience it would certainly have been better to emphasize the more important points by use of different types. For students of pharmacy and chemistry, on the other hand, this text is highly recommended as supplementary material to lectures and as an aid in preparation for examinations.

Harald Suhr [NB 48 IE]

Chemical Analysis in Extractive Metallurgy. By *R. Young*. Charles Griffin and Co., London 1971. 1st Edit., vii, 427 pp., bound £ 7.—.

The book deals primarily with the analysis of 42 technically significant elements, primarily metals, and is intended mainly as a list of procedures for analysts working in the field of nonferrous metals. According to the concept of the author it should be "less comprehensive and more selective than the excellent multi-volume treatises on analytical chemistry, be more attuned to the routine industrial tempo than is desirable in a university textbook, and to contain more discussion of theory and interferences than is found in the valuable analytical manuals of companies and trade associations."

The individual chapters usually open with rather general statements about separation procedures, which are followed by more or less detailed instructions for gravimetric, titrimetric, and, in some cases, also photometric methods. Instrumental methods dominating the present industrial scene are dismissed with brief comments that frequently are devoid of real information content.

Overall the book fails to fulfil the stated aim of the author. Only a few analytical procedures are described so precisely that successful repitition is assured; essential details are frequently missing. Trivial and elementary analytical information also occupy considerable space. A general preference for time-consuming gravimetric methods grossly contradicts the author's intention to consider mainly fast methods.

The book which contains 1200 references, exclusively to English-language literature, can therefore only be regarded as a relatively comprehensive survey but not as a really useful tool for the analyst working in this field.

Günther Kraft [NB 50 IE]

Practical Catalytic Hydrogenation. Techniques and Applications. By *M. Freifelder*. John Wiley and Sons Ltd., New York 1971. 1st Edit., xxii, 663 pp., numerous figures, bound £ 11.75.

Catalytic hydrogenation can certainly be regarded as a particularly effective and reliable method throughout the whole field of organic chemistry whose successful application to particular problems nevertheless requires adherence

to specific conditions and catalysts recorded in a large body of rather widely distributed empirical data.

The present book has been born out of the personal participation of the author in over 7500 catalytic reduction reactions and provides a wealth of suggestions for use in practice when a suitable method has to be sought and executed for a particular case.

The index covers barely three pages and provides but little information about individually treated compounds. More ready access to the subject matter is afforded by a detailed list of contents (14 pages) where the various sections and classes of compounds are easily found along with the representative examples treated in the text. The initial sections are concerned with the catalysts and the general reaction conditions and are followed by broadly subdivided sections on functional groups and finally by reductive amination, alkylations, debenzylation, dehalogenation, hydrogenolysis of compounds containing O and N, *etc.* A section on gas phase hydrogenation would have been welcome.

Directly applicable working prescriptions are not given so recourse to the original publications is necessary. More than 2000 literature references are given (unfortunately not in alphabetical order) at the end of each of the 35 chapters. It is therefore almost impossible to follow the work of a particular author, especially since there is no author index at the end of the book.

The work draws on a rich mine of experience and offers much well-founded and valuable information to all concerned with catalytic hydrogenation and the reduction of organic compounds.

Kurt Heyns [NB 49 IE]

Flavor Research Principles and Techniques. By *R. Teranishi, I. Hornstein, P. Issenberg*, and *E. Wick*. Marcel Dekker Inc., New York 1971. 1st Edit., ix, 315 pp., numerous figures, bound $ 19.50.

Flavor research with physical and chemical methods is a young branch of science caught up in rapid development about which there is little in the way of comprehensive surveys. The authors' attempt to provide such a survey in the present book can be described as very successful.

Complete descriptions of all principles and techniques are not given. Instead the authors have been able to present all the essentials in a terse, precise manner and to illustrate them with the aid of individual well-chosen examples. They restrict themselves largely to volatile flavors. The greatest space is devoted to analytical techniques (221 pages): isolation of flavor concentrates, separation by gas chromatography, identification by NMR, IR, and Raman spectroscopy, and above all by mass spectrometry which, as the method of choice, is deservedly treated particularly thoroughly, especially in combination with gas chromatography. These methodological chapters are set off against general considerations of odor and taste perception, the connections between odor and chemical constitution, and those between sensory and instrumental analysis. Perhaps the purely sensory method could have been described in a little more detail.

The book is of a relatively high standard. The problems and the pros and cons of the various methods are discussed very critically. The literature coverage is by no means complete but all important publications, especially the more recent ones up to 1969, seem to be included. The monograph is warmly recommended to all interested persons, particularly to those wishing to gain an overall picture.

H. G. Maier [NB 52 IE]

Einführung in die Immunchemie und Immunologie (Introduction to Immunochemistry and Immunology). By *E. A. Kabat*. Translated by *K. Jann* and *E. Rüde*. Heidelberger Taschenbücher Vol. 79. Springer-Verlag, Berlin–Heidelberg–New York 1971. 1st Edit., 322 pp., paperback, DM 18.80.

The present book is more than just an introduction to immunochemistry and immunology. In accord with the English title "Structural Concepts in Immunology and Immunochemistry" it attempts not only to describe immunological phenomena but also to interpret them on a molecular level. Since fundamentals are also described the work can be regarded as a successful synthesis of classical and modern immunology.

An introduction to serological specificity is followed by a detailed chapter on antigens which places particular emphasis on the characterization of antigenic determinants. The resulting possibility of elucidating the structure of antigens with the aid of antibodies is illustrated by practical examples. Quantitative and qualitative serological methods of detection are also considered in this context. On the other hand, a complete chapter is devoted to the characterization of the site of antibody binding by antigens. Considerable attention is also paid to the heterogeneity of antibodies and the resulting purification problems. The account of studies on the primary structure of antibodies is afforded much space with regard to both the binding site and the mechanism of antibody formation. There follow concluding chapters on complements, allergy, and immunotolerance.

Summing up, this book is written in a very understandable and clear manner and can be heartily recommended to anyone interested in immunology.

Norbert Hilschmann [NB 53 IE]

Spektroskopische Methoden in der organischen Chemie (Spectroscopic Methods in Organic Chemistry). By *D. Williams* and *J. Flemming*. Translated by *B. Zeeh*. Georg Thieme Verlag, Stuttgart 1971. 2nd Edit., ix, 346 pp.,145 figures, 42 tables, bound DM 12.80.

The book is divided into six chapters: A short summary of the physical methods currently in use for structural elucidation of chemical compounds is followed by accounts of the four established spectroscopic methods ultraviolet, infrared, nuclear magnetic resonance, and mass spectroscopy, in that order. A final chapter is devoted to examples designed to give practice in the combination of the methods discussed.

The present 2nd German edition differs from the 1st edition in the following points only: The section on NMR now contains a survey of recently developed special techniques; the chapter on mass spectrometry has been rearranged or slightly expanded in a number of places; and the number of exercises has been increased from 15 to 71.

Without delving too deeply into the physical fundamentals the book provides a simple and lucid description of those

physical phenomena which can be utilized in analytical chemistry. The relationship between measured physical values and structural units is demonstrated with the aid of selected examples and in tabular form. This limitation to the purely analytical aspects makes the book an ideal introduction to these techniques for chemistry students. Owing to the good selection of examples and tables the work will also prove useful to the preparative chemist who wishes to use the methods described for product characterization.

J. B. Pawliczek [NB 55 IE]

Struktur und Funktion der Proteine (Structure and Function of Proteins). By *R. Dickerson* and *I. Geis*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 1st ed., vii, 120 pp., 134 figures, 10 tables, bound DM 32.—.

The text of this book by *R. Dickerson* presents the quintessence of the enormous growth that has become possible in science over the past 14 years through the X-ray analysis of the structures of proteins. The book begins with a description of simple bonding, and the approach of the crystallographer who can "see" many of these things in his X-ray structure analysis, is immediately evident in the interpretaion here. *Via* the description of fibrous structural proteins, in which even weighty subject matter is incorporated with playful ease into a readable and fascinating account, the book passes to the crowning achievements of X-ray structure analysis, *i. e.* the description of the enzymes whose tertiary and quaternary structures are now known, and of their mode of action. It ends with a chapter on more complicated interactions of proteins, on antibodies and the complement system.

Electron micrographs of current interest in this field are reproduced in this part in a very striking and understandable manner.

The book can be recommended for students, but there is no doubt that specialists in the field of protein chemistry will also be able to learn from it. The description of the interaction of many proteins in the serum complement system is itself a masterpiece of a feuilletonistically interesting and at the same time extremely accurate account of a very complicated situation.

The second author is *I. Geis*, and it is clearly only through the cooperation of these two specialists that the excellent presentation by which this book is characterized has been possible. The hand of this master artist of molecular biology, whose unmistakable brilliance must now be known to every biologist and biochemist, can be discerned on every page of the book, in cleverly selected drawings, in structural formulas that give a clear picture of spatial relationships, in skillfully shaded diagrams, and in careful but extremely striking arrangements of drawings and photographs.

Hugo Fasold [NB 58 IE]

Physikalische Chemie in Experimenten – Ein Praktikum (Physical Chemistry in Experiments—A Practical Handbook). By *H.-D. Försterling* and *H. Kuhn*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 1st ed., ix, 505 pp., 348 figures, 23 tables, bound DM 38.80.

Owing to the rapid development of instrument techniques, which is having a particularly pronounced effect on physico-chemical investigation methods, the older German-language standard works on physico-chemical practical work are now quite out of date. The appearance of a book that takes into account the use of modern instruments is therefore very welcome.

The book is divided into the following sections: the working principles (with a short description of the most important instruments and an introduction to the evaluation of experiments), the main part, which contains about 80 experiments, and an appendix on physical quantities and units as well as some special experimental techniques. A list of references and an index complete the book.

In reading the book, one finds a number of well-known experiments, but these are largely carried out with modern instruments. However, there are also many extremely instructive new experiments, particularly from the fields of spectroscopy, photochemistry, and quantum chemistry. The related fields of macromolecular chemistry and biochemistry are also represented by a number of very fascinating experiments. In this connection, as one of many, mention should be made of a model experiment on the evolution of self-organizing systems, which is to be carried out with a digital computer, and which is very impressive in its didactic conception. Provision is also made in some experiments for the use of analog computers, which the student can construct for himself with the aid of detailed instructions.

Many passages in the theoretical explanations that accompany the experiments show that the authors place particular value on an intuitive presentation. As can be seen from the preface, this effort has led to the avoidance of the use of the chemical potential in thermodynamic calculations. However, the reviewer is doubtful whether the use of cyclic processes promotes intuitiveness.

The layout and printing are good. However, it is to be feared that the binding will be unable to withstand for long the treatment received by practical handbooks. The inevitable printing errors of a first edition are not excessive in number.

The reviewer, whose long experience has made him well aware of the special problems of a practical handbook of physical chemistry, can wholeheartedly recommend this book to students, assistants, and laboratory supervisors. The book should be particularly valuable in re-equipping a physico-chemical laboratory.

W. Eichenauer [NB 59 IE]

Dictionary of Science and Technology—German–English. By *A. F. Dorian*. Elsevier, Amsterdam 1971. 1st Edit., viii, 879 pp., bound Dfl. 95.00.

Since the beginning of the 1950's there has been a succession of specialist dictionaries for various subjects and languages. This situation reflects not only the demand that exists but also the frequent inadequacy of the existing dictionaries. The specialist generally has no need of a dictionary in his own narrow field since he will be keeping abreast of latest developments in foreign journals and can assimilate new terms as they occur without any special effort. Difficulties arise in neighboring fields. In place of a collection of small dictionaries for each individual subject, *Dorian* now offers the whole vocabulary of science and technology in one volume extending into the boundary fields of economics and law insofar as they are of interest to the scientist and technologist.

As the author states in the preface it is no simple task to cover all these topics with the same degree of thoroughness.

He has nevertheless succeeded well in doing so. Although it would be illusory to expect absolute completeness, cases in which one has to approach an expert are rare.

The German–English volume is now available. It will clearly be of most use to English-speaking scientists in evaluating German specialist literature. Anyone whose mother tongue is German will need this volume less, except when he requires an English term to refer to an English-language encyclopedia or when attempting to write an English summary. A difficulty encountered in such cases should be mentioned. For instance, the word "Kristallebene" is rendered as "crystal face, crystal plane" and the word "Kristallfläche" likewise as "crystal face, crystal plane". A crystallographer naturally knows which expression to use: but he does not have to look it up anyway. It would be more helpful to the nonspecialist for whom the dictionary is intended if the less common terms were to be given in parentheses.

However, we can well be grateful for what is probably one of the best dictionaries of its kind available. It is hoped that the present volume will prove as useful as the previously published English–German volume[*].

H. K. Kugler [NB 57 IE]

[*] Cf. Angew. Chem. internat. Edit. *8*, 154 (1969).

The Organic Compounds of Germanium. By *M. Lesbre, P. Mazerolles* and *J. Satge*. From the series "The Chemistry of Organometallic Compounds". John Wiley and Sons, London–New York 1971. 1st Edit., xii, 701 pp., bound £ 16.00.

The present book continues the series of monographs on organometallic compounds which has so far dealt with the metallocenes of the iron group and the organometallic compounds of lead and tin. It is not the first comprehensive work on this branch of organometallic chemistry, which only attracted sporadic interest for many a year; a similar book by *Mironov* and *Gar* was published in Russian in 1967 and a monograph by *Glockling* appeared in 1969. Nevertheless, its publication just a few years after the above two books is most welcome since it represents the first monograph to give a really complete account of all the work so far performed in the field of organogermanium chemistry. A total of 2127 literature references, including patents, covers all the relevant literature up to 1968.

The book is clearly arranged and deals with the synthesis, properties, and reactions of all organogermanium compounds. A chapter on general aspects of organogermanium chemistry is followed by accounts of compounds with germanium-carbon bonds, cyclic organogermanium compounds, derivatives with bonds between germanium and hydrogen, halogen, oxygen, sulfur, selenium, tellurium, nitrogen, and phosphorus, as well as polygermanes and compounds having germanium-metal bonds.

Each one of these chapters contains tables of the compounds so far found in these classes with structural formulas, molecular formulas, and the most important physical constants. These tables appear absolutely complete to the reviewer. Modern physical and spectroscopic aspects, as well as mechanistic ones, have been included and are critically discussed by the authors who have all been active in this field for some time. Particular mention should be made of the fact that the authors have repeatedly compared the properties and the reactions of the organogermanium compounds with those of analogous silicon and tin derivatives and have thus been able to demonstrate with the aid of numerous examples the often astonishing independence of germanium chemistry. A bibliography is appended to each subsection, thus enhancing the overall clarity of the work and facilitating rapid reference to the original literature.

The book is a valuable reference work which surpasses and effectively replaces existing surveys and monographs on organogermanium chemistry. It provides the reader with a comprehensive overview of this branch of organometallic chemistry which has become more and more important in recent years. It only remains to hope that a work of this kind is frequently revised and brought up to date so that it does not lose its value as a reference book all too quickly.

Herbert Schumann [NB 56 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without the permission in writing of the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 4036/4037, Telex 465516 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N.Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P.O. Box 129/149 Germany, Telephone Weinheim (06201) 4031, Telex 465516 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 8
August 1972
Pages 653–738

International Edition in English

Decomposition of Organometallic Complexes in the Mass Spectrometer

By Jörn Müller[*]

The reliable interpretation of mass spectra for the determination of molecular constitutions requires systematic studies on the fragmentation behavior of classes of compounds, since the large number of kinetic and energy parameters that determine the decomposition of excited polyatomic ions makes *ab-initio* predictions of spectra almost impossible. In this progress report, a number of general rules for the decomposition of organometallic complexes upon electron impact are discussed; a classification into decomposition types is also presented, and is illustrated by selected examples.

1. Introduction

Mass spectroscopy, together with NMR and IR spectroscopy, is nowadays one of the most important standard methods of investigation in the field of molecular chemistry[1]. Its application to problems of structure and bonding in the organometallic complexes of transition elements started with systematic investigations around 1964, and has so far embraced the following aspects[2]:

1. analysis, *i.e.* the accurate determination of relative masses of molecules (molecular weights) and chemical molecular formulas, determination of constitutions;

2. measurement of ionization energies and metal-ligand bond energies;

3. study of ion-molecule reactions.

In the most common analytical application of the mass spectrometer, the ionization of the vaporized substance is brought about by bombardment with 50—100 V electrons. The energies thus transferred to the molecules, which vary within wide limits, lead to numerous differently populated excited states of the resulting molecular ions, from which various decomposition processes can take place. The molecular weight of the compound in the gaseous state is found directly from the group of parent ion peaks recorded in the spectrum after mass separation. The precise molecular formula of the substance can also be found by accurate determination of the mass of the molecular ion by means of a double-focusing instrument. The transition metals mostly have characteristic isotope distribution patterns; from the appearance of a group of molecular ion or fragment ion peaks in the mass spectrum, it is then possible to deduce whether one or more of the atoms in question are present in a complex. The fragment ions resulting from the decomposition of the parent ion and the decomposition scheme constructed on the basis of the "metastable bands"[1] observed provide fundamental information about the constitution of a compound.

Numerous attempts have been made to devise a general theory of mass spectra that would allow the prediction of the nature and abundance of fragment ions of a molecule. The "statistical" or "quasiequilibrium the-

[*] Doz. Dr. J. Müller
Anorganisch-chemisches Laboratorium der Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

ory"[3-6], which has been developed furthest, allows the calculation of the relative intensities of fragments of small molecules, but it is necessary to know the appearance potentials of these ions and to have relatively reliable estimates of the energies transferred in the ionization process and of the frequency factors of decomposition processes. The quantitative description of the decomposition of larger molecules fails because of the complexity of the problem. The mass spectroscopist therefore still has to derive empirical rules for the degradation of ionized and energetically excited molecules in the mass spectrometer. The mechanistic interpretation of decomposition reactions is complicated by the fact that ions in the spectrometer are primarily identifiable only by their masses; the elucidation of ionic structures, on the other hand, requires very complicated processes such as comparisons of the decomposition characteristics of ions, labeling with isotopes, measurement of appearance potentials, investigations of the shapes and intensity ratios of "metastable bands", and the study of ion-molecule reactions. The reader of mass spectroscopic literature should always bear in mind that most of the suggested ion structures are fictitious, and are merely based on plausibility considerations regarding the most stable form of an ion or the most suitable form for a decomposition process. Nevertheless, the heuristic value of such representations is undeniable, so long as speculation remains within acceptable limits.

On the basis of the now fairly extensive body of mass-spectroscopic data, an attempt is made in the following discussion to develop a general picture of the laws determining the fragmentation of organic complexes of transition metals and to present a series of characteristic decomposition reactions.

2. Experimental Problems

If the mass spectrum of a substance is to be recorded, the substance must be volatilizable, *i.e.* when heated in a high vacuum it must be capable of reaching a vapor pressure of about 10^{-6} to 10^{-4} torr without decomposing completely. Salt-like complexes or complexes that are thermally unstable and at the same time difficult to volatilize are at best identifiable from their pyrolysis products.

Thermal decomposition phenomena frequently complicate the mass-spectroscopic investigation of organometallic complexes[7] and not uncommonly lead to incorrect interpretations regarding the constitution or the purity of a compound. For example, ferrocene appears as a thermolysis product in the mass spectra of cyclopentadienylcarbonyliron derivatives[8,9], $(CO)_5MnCl$ similarly gives $Mn_2(CO)_{10}$[10], and many pentacarbonylchromium or tetracarbonyliron compounds decompose with formation of $Cr(CO)_6$ or $Fe(CO)_5$, to give only a few examples. The decomposition of the complexes is accelerated by the metal walls of the inlet systems and of the ion source; the fine metal deposits left behind by the compounds degraded in the instrument prove to have a particularly strong catalytic action[7,10]. These handicaps can be greatly mitigated by evaporation of the sample in the immediate vicinity of the ionization chamber of the ion source, which should be kept at the lowest possible temperature, and in the investigation of very volatile complexes by the use of glass inlet systems; however, they cannot be completely eliminated. The deposition of metal, which occurs in particular in the region of the hot cathode, may necessitate more frequent cleaning of the source.

The molecular weight determined from the mass spectrum, particularly in the case of polynuclear complexes, may differ from the molecular weight in the solid or dissolved state if the evaporation is accompanied by dissociation. This type of behavior is exhibited *e.g.* by dimeric cyclopentadienyltricarbonylchromium, which, as is shown *inter alia* by the mass spectrum, exists exclusively as the monomer in the gaseous state because of a weak Cr—Cr bond[11].

Cases that must be distinguished from the irreversible thermolyses or reversible dissociations that precede the ionization are those in which only fragment ions appear in the mass spectrum, while the molecular ion is absent. The decomposition here is initiated entirely by the vertical ionization, and requires no additional excitation. For example, the heaviest ion in the mass spectra of the following compounds is the fragment containing one CO group less than the molecular ion: $RSn[Co(CO)_4]_3$ ($R = CH{=}CH_2$, Cl, Br, I)[12], $(CO)_4FeL$ (L = maleic anhydride, dimethyl maleate)[13], $C_5H_5(CO)_2Fe{-}COC_6H_5$, and $C_5H_5(CO)_3Mo{-}CH_2CO_2C_2H_5$[9].

3. Ionization and Charge Localization

A qualitative approach that is very useful for the interpretation of the mass-spectroscopic decomposition of organic compounds is the primary excitation theory[14]. This is based on the idea that during the interaction of the bombarding electron and the molecule, certain centers of the latter, particularly π bonds, p electrons on hetero atoms, and bonds that are easily broken, are readily excited and hence preferentially emit an electron. The excitation processes start at the center of excitation and charge, and lead preferentially to the formation of the stablest possible ionic and neutral cleavage products.

This concept can be applied directly to the fragmentation of organometallic complex ions. The central metal can generally be regarded as the site of the highest positive charge density. Energy-level diagrams show that the highest occupied MOs (*e.g.* t_{2g} for $Cr(CO)_6$, e'' for $Fe(CO)_5$, a'_{1g} for $Cr(C_6H_6)_2$, or e_{2g} for $Fe(C_5H_5)_2$), from which an electron is primarily removed on ionization, are nonbonding or only weakly bonding or antibonding, and largely possess the character of metal d electrons, if such exist in the compound. This is confirmed experimentally by photoelectron spectra[15-18] and by the ionization energies found by mass spectroscopy for organometallic complexes. It can be seen from Table 1 that the ionization potentials (IP) of representative complexes are much

closer to the IP value of the free metal atom than to that of the free ligand.

Table 1. Ionization potentials [eV] of some organometallic complexes as found by electron bombardment.

Complex	IP	IP of the free metal atom	IP of the free ligand
$Cr(CO)_6$	8.20 [18]	6.76	14.01
$Cr(C_6H_6)_2$	5.91 [19]	6.76	9.25
$Cr(C_5H_5)_2$	6.26 [20]	6.76	8.69 [21]
$Fe(CO)_5$	8.14 [22]	7.87	14.01
$Fe(C_5H_5)_2$	7.15 [20]	7.87	8.69 [21]
$Ni(CO)_4$	8.64 [24]	7.63	14.01
$Ni(C_5H_5)_2$	7.16 [20]	7.63	8.69 [21]

Two important consequences arise from these considerations:

1. The decomposition of organometallic complexes is largely controlled by the central metal; the decomposition of complexed ligands follows mechanisms different from those of the fragmentation of the free organic molecules.

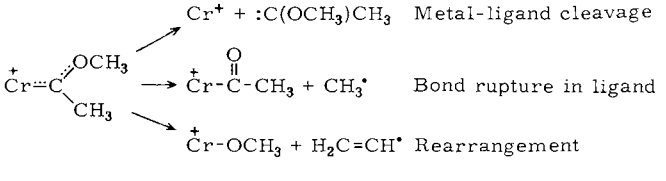
2. On decomposition of a complex ion, the positive charge usually remains on the fragment containing the metal.

Ions with multiple positive charges occur relatively often in the mass spectra of organometallic complexes. The tendency for this to happen increases considerably from complexes of the first transition period to those of the third, and thus corresponds to the general trend of metals in the stabilization of higher oxidation states. Moreover, ions carrying a double positive charge are found in a higher intensity for polynuclear than for mononuclear compounds. The fragmentation of ions with multiple positive charges has not been very extensively investigated, and will not be discussed here. It will merely be pointed out that differences in the decomposition characteristics have been found in some cases between singly and doubly charged ions.

4. Decomposition Reactions of Organometallic Ions

The decomposition processes of complex ions can be divided into three groups: the cleavage of metal-ligand bonds, simple cleavage of bonds within the complex ligands, and fragmentation reactions with rearrangement. Owing to the difficulties in the elucidation of the structures of ions, it is not generally possible to determine whether decomposition reactions of the first two types are accompanied by rearrangements.

In many cases, competition between all three principal degradation types is possible, starting from one and the same ion, as is shown by the following example[23]:



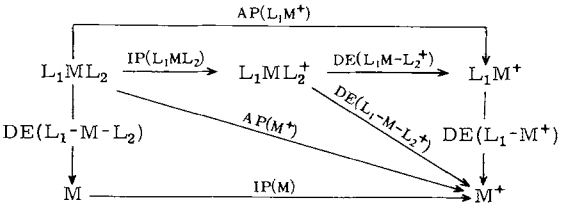
4.1. Cleavage of Metal-Ligand Bonds

This degradation type, which is both the simplest and the most common, is found both for parent ions and for fragment ions. There is a high probability of elimination of the ligand if the ligand molecules or radicals are themselves sufficiently stable to allow their removal as neutral particles, if they contain no easily degradable functional substituents, and if the metal-ligand bond is not too strong in relation to the bonds between the atoms of the ligand. Eliminations of ligands are characterized by their successive course, though exceptional cases of the simultaneous removal of two ligands have also been observed. The order of the degradation processes is determined by the relative metal-ligand bond strengths in the ions, which may well differ from those in the neutral compounds. The end product of fragmentations by this scheme, which are accompanied in most cases by the corresponding "metastable bands", is the free metal ion.

The simple decomposition route presented here allows a rapid identification purely on the basis of the mass spectrum in the case of complexes with simple ligands such as CO, NO, ethylene, acetylene, cyclopentadienyl, and benzene, and is therefore of great practical significance. Another consequence of the cleavage of the metal-ligand bonds is the possibility of obtaining information about metal-ligand bond strengths by measurement of the appearance potentials (AP)[1] of fragment ions. Consider the decomposition of a complex L_1ML_2 (M = metal atom, L = ligand) in the mass spectrometer:

$$L_1ML_2 \xrightarrow{+e;\,-2e} L_1ML_2^+ \xrightarrow{-L_2} L_1M^+ \xrightarrow{-L_1} M^+$$

If the appearance potentials of the ions $L_1ML_2^+$ [$= IP(L_1ML_2)$], L_1M^+, and M^+ are known, it is possible to construct an energy cycle:



Four different bond dissociation energies (DE) are found:

$$DE(L_1M{-}L_2^+) = AP(L_1M^+) - IP(L_1ML_2)$$
$$DE(L_1{-}M^+) = AP(M^+) - AP(L_1M^+)$$
$$DE(L_1{-}M{-}L_2^+) = AP(M^+) - IP(L_1ML_2)$$
$$DE(L_1{-}M{-}L_2) = AP(M^+) - IP(M)$$

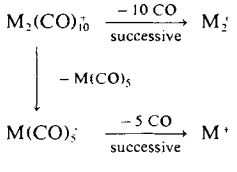
Since the fragment ions may be formed with excess kinetic or electronic excitation energy, the calculated DE values are upper limits for the true values. It is recommended that such calculations be carried out only if the fragmentation path is known as definitely as in the example given.

4.1.1. Complexes with Like Ligands

The principle of the metal-ligand cleavage can be best demonstrated for the simplest compounds of this type, the carbonylmetal and bis(π-aromatic) metal complexes.

In accordance with the rules discussed earlier, the mass spectra of the binary mononuclear carbonyl complexes $M(CO)_n$, *e.g.* $V(CO)_6$, $Cr(CO)_6$, $Fe(CO)_5$, and $Ni(CO)_4$, always contain the complete series of ions $M(CO)^+_{n-x}$ ($x = 0 - n$) formed by successive removal of the CO groups[22,24-30]. It follows from the appearance potentials of the fragment ions that the dissociation energies required for the removal of the CO ligands increase with increasing x; during the stepwise decomposition of a carbonylmetal ion, therefore, the M—CO bond becomes stronger. An increase in stability is also found on transition from the carbonyl complexes of the first to those of the third transition period, this increase being manifested *e.g.* in the series $Cr(CO)_6$—$Mo(CO)_6$—$W(CO)_6$ in an increase both in the appearance potentials of analogous fragment ions and in the relative intensities of the CO-richer fragments[22,25].

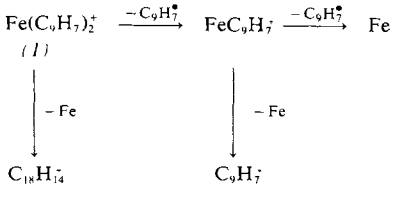
In polynuclear binary carbonyl complexes $M_m(CO)_n$, the cleavage of the metal-metal bonds competes with the elimination of CO[31-35]. The tendency toward the breakdown of the metal cluster decreases markedly from metals of the first to those of the third transition series. The decacarbonyl compounds of manganese and rhenium, for example, exhibit the following somewhat simplified fragmentation scheme:



At 55 eV the intensity ratio $\Sigma M(CO)_x^+ / \Sigma M_2(CO)_x^+$ is 0.2 for M = Mn, but only 0.05 for M = Re[33]. The increase in the stability of the metal-metal bonds with increasing number of metal atoms in the cluster is also reflected in the fragmentation behavior. Thus the mass spectrum of $Co_2(CO)_8$ contains the series of ions $Co_2(CO)^+_{0-8}$ and $Co(CO)^+_{0-4}$ in comparable intensities[31], whereas in the decomposition of $Co_4(CO)_{12}$, all twelve CO ligands are preferentially eliminated before the stepwise breakdown of the Co_4^+ cluster begins[34]. Even trinuclear ions $Co_3(CO)^+_{1-6}$ appear with only a low intensity, while these ions are completely lacking in the spectrum of the analogous iridium compound. Finally, an extreme example is the decomposition of $Ru_6C(CO)_{17}$[36]; the stepwise loss of all seventeen CO molecules leads to the ion Ru_6C^+, which does not undergo any further fragmentation.

Binary cyclopentadienylmetal[20,37,38] and dibenzenemetal complexes[19,39-41] also decompose in the same way as the binary carbonylmetal complexes, with stepwise loss of the ligands, but partial fragmentation of the π-bonded aromatic groups may also occur to a considerable extent here (cf. Section 4.3.1.). Characteristic differences exist between carbonyl and pure bis(aromatic) complexes in the variation of the energy requirements during the fragmentation; the latter, unlike the carbonyl complexes, require much more energy for the removal of the first ligand than for that of the second. The molecular ions of bis(aromatic) complexes therefore appear in a much higher intensity than those of the carbonyl compounds. On the other hand, the parent ions are less abundant in the spectra of the tris- and tetrakis(cyclopentadienyl) complexes; the intensity ratios in this case reflect the relative stabilities of the various oxidation states of the metals (the removal of a C_5H_5 radical is associated with a decrease in the formal oxidation number). Corresponding to the preference for the oxidation numbers +3 in the lanthanoids and +4 in uranium and thorium, the ions $(C_5H_5)_2$Lanthanoid$^+$, $(C_5H_5)_3U^+$ and $(C_5H_5)_3Th^+$ appear with the greatest intensity at 50 eV. The relatively high intensity of $C_5H_5Yb^+$ in the spectrum of $(C_5H_5)_3Yb$ is explained by the fact that the oxidation number +2 is easily attainable by ytterbium[38].

The ionization potentials of highly condensed aromatic hydrocarbons are often lower than those of transition metals. In such cases the positive charge may remain on the aromatic group on cleavage of the metal-ligand bond, as is illustrated by the fragmentation of bis(indenyl)iron *(1)*[42].



4.1.2. Complexes with Unlike Ligands

In the majority of known organometallic compounds, several different ligands are bonded to the central atom. The sequence of the metal-ligand cleavages is important in the decomposition of these complexes upon electron impact. The ligands can be roughly divided into two groups, according to their ease of removal:

Group 1 (easily removed ligands): CO, NO, N_2, H, PF_3, CH_3, CF_3, PH_3, AsH_3, ethylene, acetylene.

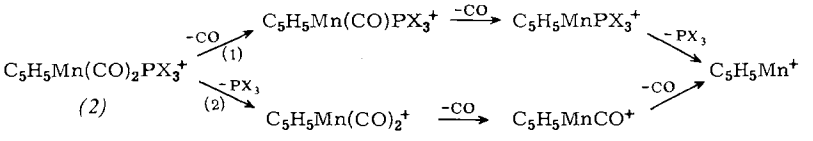
Group 2 (ligands that are difficult to remove): F, phenyl, allyl, phosphanes, phosphites, amines, isocyanides, carbenes, thioethers, sulfoxides, cyclic oligoolefins, aromatic hydrocarbons.

Gradations occur within these groups, but no rigorously valid elimination series can be constructed, since the central metal affects the ease of elimination of ligands, and ligand interactions may also affect the sequence.

The donor strength/acceptor strength ratio of the ligand is of considerable importance to the ease of cleavage of metal-ligand bonds. Thus the ease of removal of some of the ligands of the first group (CO, NO, N_2, PF_3) is due to their pronounced acceptor character. In

the complex ions, the back-bonding, *i.e.* the transfer of d-electron density into empty acceptor orbitals of the ligand, is greatly weakened by the positive charge located predominantly on the central metal atom. This is in agreement with the small number of cationic carbonylmetal complexes known and with the fact that carbonyl complexes have been found to be most suitable for the study of negative ions in the mass spectrometer[31,43-45]. The second group, on the other hand, contains mainly donor ligands; donor bonds are stabilized by the positive charge on the central metal atom.

The donor/acceptor ratio of ligands and hence also their ease of removal can be varied within wide limits by the choice of the substituents on the complexed ligand center. This can be illustrated by the decomposition of cyclopentadienyldicarbonyl-manganesephosphane complexes *(2)* containing various groups X[18,46,47]; among others, two decomposition paths starting with the molecular ion are observed.



(2)

In path (1), the removal of the two CO molecules may also be coupled. The competition of paths (1) and (2) can be expressed in a simplified form by a ratio Q of the ion intensities I:

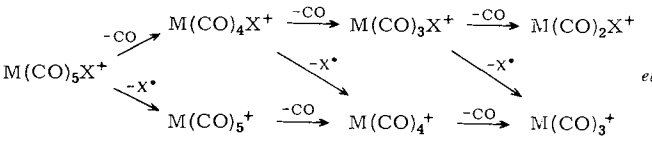
$$Q = \frac{I[C_5H_5Mn(CO)_2^+] + I[C_5H_5MnCO^+]}{I[C_5H_5Mn(CO)PX_3^+] + I[C_5H_5MnPX_3^+]}$$

A measure of the donor/acceptor ratio of the PX_3 ligands is provided by the ionization potentials of the complexes, which generally increase as the ratio of donor strength to acceptor strength decreases, and hence as the d-electron density produced on the central metal atom by the metal-ligand interaction decreases[18,23,39,46-51]. A comparison of the ionization potentials and of the Q values in Table 2 confirms the close relationship between the donor/acceptor ratio and the ease of removal of ligands. If the donor properties of PX_3 predominate (corresponding to lower IP values), the alternative decomposition path (2) is no longer followed and Q disappears. Similar relations have been found for other types of complexes[13,51].

Table 2. Ionization potentials [eV] and Q values of $C_5H_5Mn(CO)_2PX_3$ complexes (IP of $C_5H_5Mn(CO)_3 = 8.12$ eV).

(2), X =	IP	Q
F	8.24	5.57
Cl	8.12	0.69
Br	8.01	0.63
C_6H_5O	7.40	0.02
H	7.28	0.05
i-C_3H_7O	7.17	0
C_6H_5	6.93	0
i-C_3H_7	6.90	0

In addition to the donor/acceptor strength, the number of bonds to be broken also determines the ease of removal of a ligand. Let us consider the decomposition

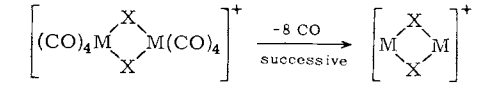


etc. (3)

M = Mn, Re; X = Cl, Br, I[32, 34, 52, 53], H[54, 55]

of carbonyl halides and carbonyl hydrides. If halogen or hydrido ligands are bonded terminally to the central metal, they are eliminated as easily as CO [eq. (3)].

In halogen-bridged carbonyl complexes, on the other hand, the cleavage of the metal-halogen bond occurs only after the complete loss of all the CO groups [eq. (4)][32,34,52]. The complex $(CO)_5Re{-}Re(CO)_4{-}H{-}Re(CO)_5$, with a linear Re—H—Re grouping, loses up to fourteen CO molecules, while a competing elimination of hydrogen begins at the earliest from the fragment $HRe_3(CO)_2^+$[56].



(4)

M = Mn, Re; X = Cl, Br, I

The following elimination sequence for π ligands also shows the influence of the number of bonds to be broken:

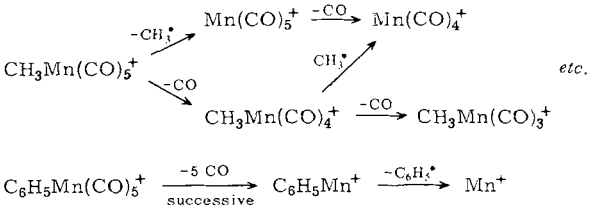
ethylene, acetylene, cyclic monoolefins > diolefins > aromatic hydrocarbons.

Among the aromatic systems, the cyclopentadienyl ring is the most difficult to eliminate.

The number of electrons transferred in the cleavage of a metal-ligand bond may also determine the ease of removal. The fragmentation of nitrosyl-carbonyl complexes shows clearly that CO is more easily eliminated than NO, whose removal involves a three-electron step, whereas the loss of CO is only a two-electron process.

Some examples of decomposition schemes in which the above-mentioned relationships regarding elimination sequences are evident are given below (partial fragmentations of the complexed ligands are not taken into account).

Methyl- and phenylpentacarbonylmanganese[57]:



Bis(cyclopentadienyl)hydridotechnetium[20]:

$$(C_5H_5)_2TcH^{\cdot} \xrightarrow{-H^{\bullet}} (C_5H_5)_2Tc^{\cdot} \xrightarrow{-C_5H_5^{\bullet}}$$

$$C_5H_5Tc^{\cdot} \xrightarrow{-C_5H_5^{\bullet}} Tc^{\cdot}$$

Cyclopentadienylnitrosylcarbonylchromium-L complexes with L = monoolefin, acetylene[58], methylmethoxycarbene[59]:

$$C_5H_5Cr(NO)(CO)L \xrightarrow{-CO} C_5H_5Cr(NO)L^{\cdot} \xrightarrow{-NO}$$

$$C_5H_5CrL^{\cdot} \xrightarrow{-L} C_5H_5Cr^{\cdot} \xrightarrow{-C_5H_5^{\bullet}} Cr^{\cdot}$$

Cycloheptatrienylcycloheptadienechromium[60]:

$$C_5H_5CrC_7H_{10} \xrightarrow{-C_7H_{10}} C_7H_7Cr^{\cdot} \xrightarrow{-C_7H_7^{\bullet}} Cr^{\cdot}$$

Cyclopentadienylbenzenemetal complexes[19]:

$$C_5H_5MC_6H_6^{\cdot} \xrightarrow{-C_6H_6} C_5H_5M^{\cdot} \xrightarrow{-C_5H_5^{\bullet}} M^{\cdot}$$

M = Cr, Mn

Cyclopentadienylcycloheptatrienylmetal complexes[19,61,62]:

$$C_5H_5MC_7H_7 \xrightarrow{-C_7H_7^{\bullet}} C_5H_5M^{+} \xrightarrow{-C_5H_5^{\bullet}} M^{+} \qquad (5)$$

M = Ti, V, Cr

The effects governing the elimination of the terminally bonded halogens chlorine, bromine, and iodine are difficult to incorporate into a scheme, since these can compete in their ease of removal both with ligands such as CO and NO and with allyl and even cyclopentadienyl ligands, as is shown by the decomposition of cyclopentadienylcarbonylmetal halides[63] [eq. (6)].

$$\begin{array}{ccccc} C_5H_5Fe(CO)_2Br^{+} & \xrightarrow{-2\,CO} & C_5H_5FeBr^{+} & \xrightarrow{-C_5H_5^{\bullet}} & FeBr^{+} \\ \downarrow{\scriptstyle -Br^{\bullet}} & & \downarrow{\scriptstyle -Br^{\bullet}} & & \downarrow{\scriptstyle -Br^{\bullet}} \\ C_5H_5Fe(CO)_2^{+} & \xrightarrow{-2\,CO} & C_5H_5Fe^{+} & \xrightarrow{-C_5H_5^{\bullet}} & Fe^{+} \end{array} \qquad (6)$$

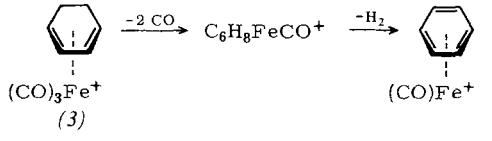
However, the marked increase in the strength of the metal-halogen bond from iodine to fluorine can be detected mass-spectroscopically; in the decomposition of the cyclopentadienylmetal fluorides investigated so far, only the loss of the C_5H_5 ligands is observed[38].

4.2. Simple Bond Cleavages in Complexed Ligands

4.2.1. Removal of Hydrogen

The removal of H atoms and H_2 molecules occurs mainly in the decomposition of π-bonded cyclic olefins. The driving force of such processes is the formation of new double bonds and their coordination to the central metal if this no longer has the inert gas configuration in a complex ion after the occurrence of a few decomposition steps. The elimination of hydrogen is facilitated in particular if it involves the formation of 6π-electron systems.

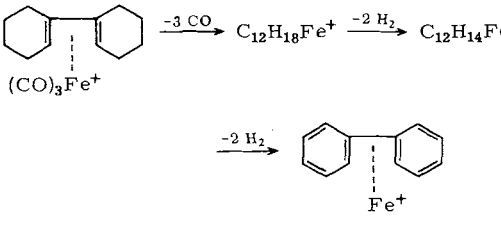
Whereas no appreciable elimination of hydrogen is observed in the decomposition of 1,3-dienetricarbonyliron complexes with open-chain dienes, the loss of H_2 occurs in the case of 1,3-cyclohexadienetricarbonyliron *(3)* before all three CO ligands have been removed[64-66] [eq. (7)]. The base peak in the spectrum of free 1,3-cyclohexadiene, on the other hand, is due to the $C_6H_7^{+}$ ion.



(7)

(3)

Cyclopentadienyl-1,3-cyclohexadienecobalt, $C_5H_5CoC_6H_8$, similarly forms the fragment $C_5H_5CoC_6H_6^{+}$, from which all further decomposition processes proceed, whereas cyclopentadienyl-1,3-butadienecobalt exhibits no elimination of H_2[67]. Cyclohexene ligands can also be aromatized[65] [eq. (8)].



(8)

The relatively high stability of cationic cyclopentadienyl complexes greatly favors the elimination of H from cyclopentadiene compounds. The base peak in the mass spectrum of cyclopentadienylcyclopentadienerhodium, $C_5H_5RhC_5H_6$, is due to the fragment $(C_5H_5)_2Rh^{+}$ [68].

Free cycloheptatriene loses an H atom on electron impact to form the very stable tropylium ion, whereas this tendency is not necessarily shown by π-bonded

cycloheptatriene. Cyclopentadienylcycloheptatrienechromium, $C_5H_5CrC_7H_8$, gives the ion $C_5H_5CrC_7H_7^+$ in a very high intensity; the fragments $C_7H_7VC_7H_8^+$ and $(C_7H_7)_2V^+$ similarly appear in the spectrum of bis(cycloheptatriene)vanadium, $(C_7H_8)_2V$[68]. On the other hand, the intensity ratio of the ions rC_7H_7 and $CrC_7H_8^+$ in the spectrum of $(CO)_3CrC_7H_8$ is only 1:58[69].

In this connection, let us consider briefly the question of the benzylium-tropylium analogy. The ion $C_7H_7^+$, which is formed usually as a fairly intense fragment from toluene, cycloheptatriene, and benzyl and cycloheptatrienyl compounds, always exhibits the same fragmentation characteristics, irrespective of the starting compound; a rapid interconversion between the benzylium and the tropylium structure is postulated. This type of mutual rearrangement is suppressed by π-complex formation, *i.e.* in ions having the composition $MC_7H_7^+$ the benzyl or cycloheptatrienyl structure of the starting compound is retained, and different modes of decomposition are accordingly found[69].

4.2.2. Cleavage of the C—O Bond in Carbonylmetal Complexes

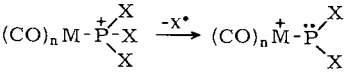
The mass spectra of carbonylmetal compounds also show ions of the type $M(CO)_xC^+$, which are formed by cleavage of the C—O bond of complexed carbon monoxide. The intensities of these fragments are determined by the ratio of the strengths of the M—C and of the C—O bonds in the ions that act as the precursors of the $M(CO)_xC^+$ fragments. Since the strength of the M—C bond increases with the number of CO ligands removed (cf. Section 4.1.1.), the C—O cleavage normally begins only after the loss of some CO molecules. Moreover, the intensities of $M(CO)_xC^+$ ions increase with increasing atomic numbers of the metal atom, since the stability of the metal-carbon bond also increases in this order.

4.2.3. Removal of Halogen Atoms and of R, OR, and NR_2 Radicals

In the partial fragmentation of complexed ligands, the elimination of stable neutral particles generally predominates; however, free radicals may also be eliminated under certain conditions. Free-radical eliminations, like all simple bond cleavages, are fast reactions (high frequency factor) even on the mass-spectroscopic time scale; there are therefore often no accompanying "metastable bands", or else these are only of low intensity. Of the organometallic complexes whose decomposition involves the loss of free radicals, four different types will be dealt with here.

1. Groups X (X = halogen, alkyl, aryl, alkoxyl, phenoxyl, dialkylaminyl) that are bonded to the central metal *via* a hetero atom such as N, P, As, O, or S may be eliminated as free radicals. Numerous processes of this type have been observed for PX_3 complexes[46,47,51,70–74] and their arsenic analogs[68,75,76]. The trifluorophosphanemetal compounds, which are similar in many respects to the carbonylmetal compounds, exhibit the cleavage of P—F bonds together with the successive elimination of PF_3. The mass spectrum of $Ni(PF_3)_4$ thus shows, *inter alia*, the series of ions $Ni(PF_3)_n^+$ ($n = 0–4$) and $Ni(PF_3)_mPF_2^+$ ($m = 0–3$), as well as the fragment $NiPF^+$[70].

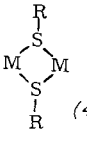
An unusual mode of decomposition is found for mixed carbonylmetal-PX_3 complexes with X = halogen, OR, and $N(CH_3)_2$; the elimination of an X radical from the molecular ion occurs here in competition with the elimination of CO. The reason for this may be assumed to be that the tetracoordinate phosphorus takes over positive charge density in the molecular ion, and this leads to weakening of the P—X bond and simultaneous stabilization of the M—CO bond (cf. Section 4.1.2) [eq. (9)].



(9)

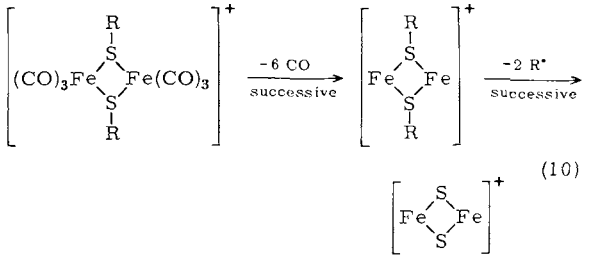
These processes evidently have a very low energy requirement, so that even thermal excitation of the molecules affects the relative intensities of $(CO)_nMP_2^+$ ions[46]. The spectrum of $(CO)_5WAs[N(CH_3)_2]_3$ even shows fragments having the composition $(CO)_nWAsN(CH_3)_2^+$ ($n = 0–2$) as well as ions formed by the stepwise elimination of CO and the series $(CO)_nWAs[N(CH_3)_2]_2^+$ ($n = 0–5$)[75].

A group of μ-mercapto compounds contain the structure *(4)*.



(4)

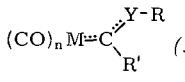
The four-membered M_2S_2 ring is found to be very stable, as can be deduced *e.g.* from the decomposition scheme of $(CO)_6Fe_2(SR)_2$ complexes[52,77] [eq. (10)].



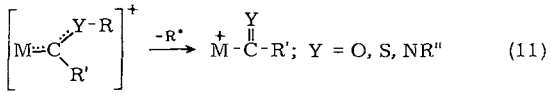
(10)

Similar decomposition modes are found for μ-alkoxo and μ-dialkylamino compounds[78,79]. If R is an alkyl residue, elimination of olefin with migration of hydrogen becomes increasingly prominent with increasing chain length of R (cf. Section 4.3.2).

2. In carbene complexes of the type *(5)*, the removal of an R radical from the CO-free fragment leads to an acylmetal fragment, the oxidation number of the central metal being increased by one unit[23] [eq. (11)].

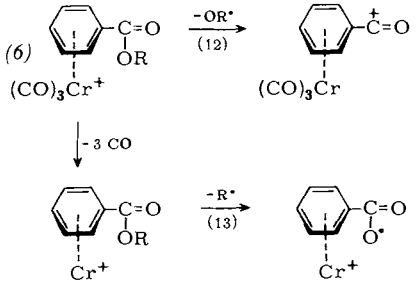


(5)



(11)

3. The decomposition of ester functions in π complexes with aromatic or olefinic ligands is also characterized by free-radical eliminations, and differs markedly in this respect from the fragmentation of the free esters. If the complex also contains CO ligands, the elimination of an OR radical from the molecular ion is also observed, while the CO-free fragment in some cases loses an R radical instead[68,69,80]. This is illustrated by part of the decomposition scheme of benzoic acid ester tricarbonylchromium complexes *(6)*[80].



The decomposition processes (12) and (13) are independent of the chain length of R. The reaction (12) leads to an ion in which the π-bonded ligand can take over the positive charge, with relative stabilization of the metal-CO bond.

4. As was mentioned in Section 4.2.1, π-bonded cyclic olefins lose hydrogen to form π-bonded aromatic groups. It can be seen from the mode of decomposition of cycloheptatrienetricarbonylchromium complexes and cyclopentadienemetal complexes substituted on the methylene group of the ring ligand in the *exo* or *endo* position with respect to the metal that the *exo* substituent is preferentially eliminated as a free radical[68,69,81]. This provides one of the rare possibilities of distinguishing conclusively between stereoisomers by mass spectroscopy. The comparison of the mass spectra of such an *exo-endo* isomer pair in Figure 1 shows that the substituent on the π-bonded ring is removed from the molecular ion M^+ only in the *exo* case (the elimination of *exo*-H atoms is of minor importance in this class of compounds).

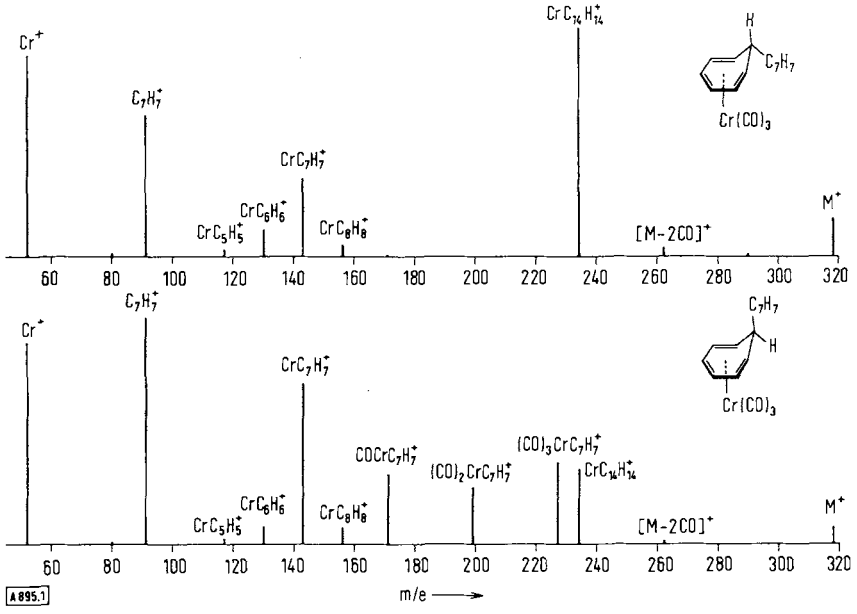


Fig. 1. Mass spectra of *exo*- and *endo*-7,7′-bi(1,3,5-cycloheptatrienyl)tricarbonylchromium (50 eV; the spectra are normalized with respect to the isotope distribution of the ions).

4.3. Rearrangements

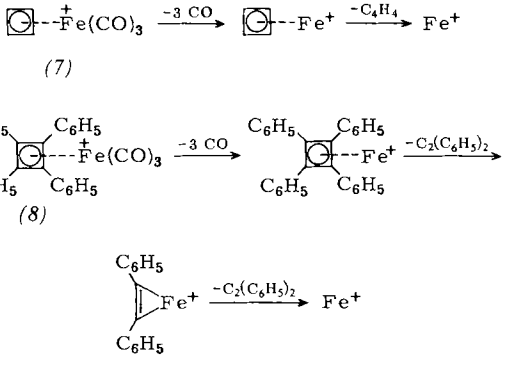
The decomposition of molecules upon electron impact is frequently accompanied by rearrangements. Whereas rearrangements involving the migration of hydrogen predominate in the mass spectroscopy of organic compounds, the range of atoms and groups that can migrate in the decomposition of organometallic complexes is much wider. The important role of the central metal in such processes is attributable to its character as a preferential carrier of the positive charge and to its tendency to enter into coordinate bonding with newly formed ligand centers that are capable of complex formation. Rearrangements generally proceed *via* sterically demanding transition states; they therefore have low kinetic frequency factors, and as slow reactions they are consequently accompanied in most cases by "metastable bands". In this review, only a few characteristic

types will be selected from the many known rearrangements of organometallic complexes upon electron impact.

4.3.1. Ring Cleavage Processes

Decomposition reactions with ring cleavage of cyclic ligands cannot always be definitely described as rearrangements, since there is often doubt regarding the constitution of the product ions. For the sake of simplicity, however, they will be treated together under this heading.

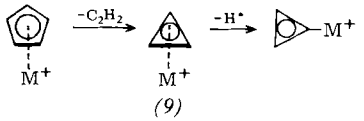
A typical ring cleavage reaction of π-bonded aromatic groups or cyclic olefins proceeds with loss of C_2 units, which are preferentially removed as acetylene in the case of aromatic complexes, but may also be removed as ethylene in the case of complexes with cycloolefins containing methylene groups in the ring (a further mode of ring decomposition with loss of C_3H_3 radicals is of limited importance). This type of partial ligand decomposition becomes increasingly important with increasing covalent character and increasing stability of the metal-ligand bond. Ferrocene and dibenzenechromium mainly undergo metal-ligand cleavage, whereas by far the predominant process in the decomposition of osmocene and dibenzenetungsten is the partial fragmentation of the ligands with stepwise elimination of acetylene, so that the mass spectra of these thermodynamically more stable homologous complexes provide practically no information about the structure. Owing to the predominance of the elimination of C_2H_2, for example, the isomeric compounds $C_5H_5WC_7H_7$ and $W(C_6H_6)_2$, unlike the corresponding chromium complexes, are practically indistinguishable by mass spectrometry[68,82]. Another example of the relationship between stability and partial fragmentation is provided by a comparison of the decomposition of the cyclobutadiene complexes *(7)* and *(8)*; the ring-metal bond is much stronger in *(8)* than in *(7)*[83].



(7)

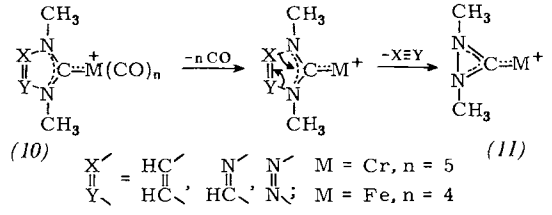
(8)

Cyclopentadienylmetal ions are converted by elimination of C_2H_2 into fragments that probably contain a cyclopropenylium structure *(9)*; loss of hydrogen may also occur, as is generally observed in the partial decomposition of hydrocarbon ligands.



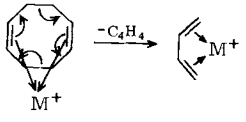
(9)

The partial ligand decomposition of π-pyrrolyl complexes proceeds similarly to the fragmentation of the corresponding π-cyclopentadienyl complexes, with loss of HCN, C_2H_2, and $C_2H_2N^{\bullet}$[61,84]. A related mode of decomposition is found for complexes with heterocyclic carbene ligands *(10)*; the fragment having the probable structure *(11)* undergoes a further ring cleavage reaction with loss of CH_3NC[85].



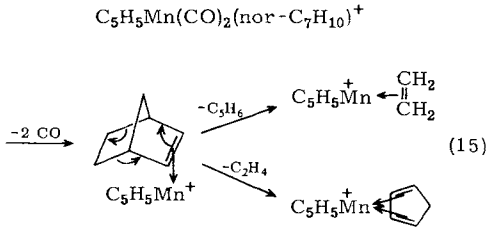
(10) *(11)*

The number of possible decomposition modes increases with the ring size of cyclic ligands. Even complexes with π-bonded eight-membered ring systems give highly branched fragmentation schemes[61,67,86–89]; the allylic cleavage of 1,5-cyclooctadiene complexes [eq. (14)] should also be mentioned here.



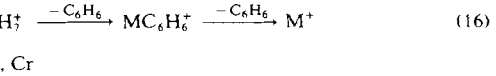
(14)

An interesting case is the decomposition of norbornene and norbornadiene complexes. Either of the fragments formed from the bicyclic ligands by retro-Diels-Alder degradation can remain on the central metal [eq. (15)]; the analogous norbornadiene complex similarly gives the fragments $C_5H_5MnC_5H_6^+$ and $C_5H_5MnC_2H_2^+$[47].



(15)

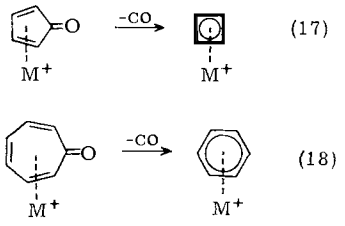
Mutual ring contraction-ring expansion processes of two π-bonded cyclic ligands have been observed in various cases. Cyclopentadienylcycloheptatrienylmetal complexes, in addition to the usual decomposition with ring-metal cleavage [eq. (5)], also exhibit the successive loss of two C_6H_6 units[19,61,90–92] [eq. (16)]. An already rearranged dibenzenemetal ion may be involved as an intermediate. The formation of the ion $CrC_8H_8^+$ that appears in the spectra of Figure 1 is due to a related process (elimination of benzene from $CrC_{14}H_{14}^+$).



(16)

M = Ti, V, Cr

Among the ring cleavage processes involving exocyclic groups, special mention should be made of the decomposition reactions of π-bonded cyclopentadienones[93,94] and cycloheptatrienones[92]. The CO elimination with ring contraction shown in equations (17) and (18) is explained by the stability of the neutral particle re-



(17)

(18)

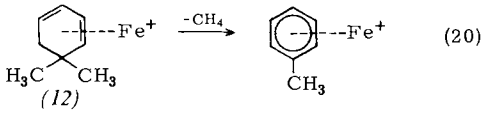
moved with simultaneous retention of the coordination number of the central metal ion.

4.3.2. Decomposition with Migration of Hydrogen

Rearrangements of organic or organometallic compounds that proceed with migration of hydrogen usually include the elimination of molecules, *e.g.* alkanes, alkenes, H_2O, H_2S, hydrogen halide, HCN, alcohols, thiols, aldehydes, azomethines, CO, or ketenes. The driving force for such processes lies in the stability of these neutral particles. On elimination of unsaturated systems, the hydrogen is transferred to the remaining ion containing the metal. Such partial fragmentations of complexed ligands frequently follow an entirely different course from the decomposition of the free organic molecules. This often led to the assumption that the central metal should be regarded as the actual hydrogen acceptor (formation of metal hydride ions)[52,71,95,96], though no conclusive proof for this could be given, except in cases where there was no ambiguity, as in equation (19).

$$MOC_nH_{2n-1}^+ \xrightarrow{-OC_nH_{2n}} MH^+ \qquad (19)$$

An example of the elimination of an alkane is given in equation (20). The aromatization of the π-bonded six-membered ring in *(12)*, unlike in *(3)*, cannot be achieved by H_2 elimination, but only by loss of methane[65].



(20)

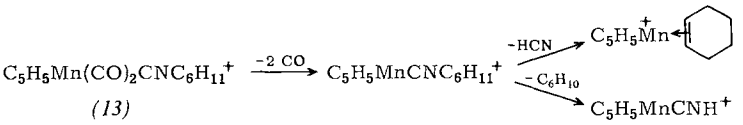
(12)

Alkylmetal ions, $MC_nH_{2n+1}^+$ with $n > 1$, decompose preferentially with elimination of olefin and formation of metal hydride fragments. In the decomposition of allyl complexes, the elimination of allene [eq. (21)][61] or propylene [eq. (22)][97] may occur in competition with the metal-ligand cleavage.

$$C_5H_5PdC_3H_5 \xrightarrow{-C_3H_4} C_5H_6Pd^+ \qquad (21)$$

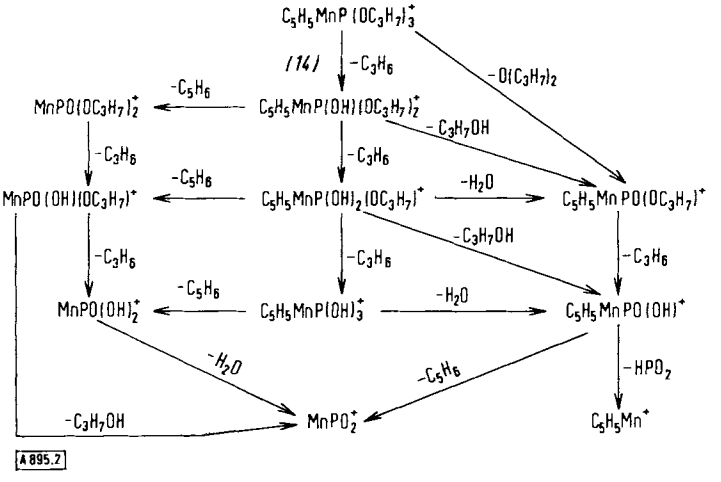
$$Pd(C_3H_5)_2^+ \xrightarrow{-C_3H_6} PdC_3H_4^+ \qquad (22)$$

The elimination of HCN (or CNH) with hydrogen transfer occurs preferentially in the case of isocyanide complexes[47,51]. The example of the decomposition of the cyclohexyl isocyanide compound *(13)* shows that the CNH fragment may also remain on the central metal[47].



(13)

Rearrangements with H migration are definitely to be expected in the decomposition of complex ions containing alkyl groups with chain lengths greater than C_2 bonded *via* O, S or N. It is of no importance, in principle, whether these hetero atoms are coordinated directly to the central metal [cf. eq. (19)] or occur in uncoordinated groups of ligands. The complete fragmentation scheme of the ion *(14)* (formed from cyclopentadienyldicarbonyl(triisopropyl phosphite)manga-



A 895.2

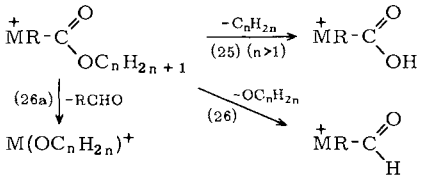
nese) gives an impression of the large number of possibilities that exist for H transfers[46]. Complexed phosphites can also decompose by elimination of aldehyde. This is true in particular of trimethyl phosphite ligands [eq. (23)], for which no elimination of olefin is possible[71,74]. Tris(dimethylamino)phosphane and tris(dimethylamino)arsane ligands decompose similarly with loss of *N*-methylazomethine [eq. (24)][71,73,75].

$$MP(OCH_3)_3^- \xrightarrow{-H_2C=O} MPH(OCH_3)_2^+ \qquad (23)$$

$$MP[N(CH_3)_2]_3^+ \xrightarrow{-H_3CN=CH_2} MPH[N(CH_3)_2]_2^+ \qquad (24)$$

Finally, mention will be made of a number of decompositions of π-bonded ligands with ester functions that are accompanied by hydrogen transfer, which have been very extensively studied[13,69,80,92,96,98,99]. Which of the processes (25) or (26) predominates depends on the central metal and on the π-bonded group R. Reaction (25) proceeds for the free esters with transfer of the H atom from the β position of the alkyl chain to the carbonyl oxygen (McLafferty rearrangement). How-

ever, investigations on deuterated π-benzoic acid ester tricarbonylchromium complexes showed that the H atom can be transferred from any position of the alkyl chain, an example of a change in the mechanism of the decomposition of an organic molecule by complexing, while the overall reaction remains similar[100]. Process (26) is not normally observed for the free ligand.



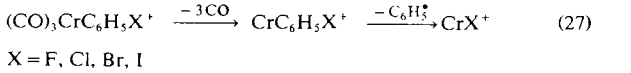
R = H_2C=CH, C_6H_5, C_5H_4, C_7H_6, C_7H_7

It is usually associated with a preceding, coupled, or subsequent removal of the carbonyl group with formation of the ion MRH^+. Processes corresponding to reactions (25) and (26) are also found in the partial fragmentation of π-bonded ligands with alkyl substituents.

4.3.3. Decomposition with Transfer of Nucleophilic Groups

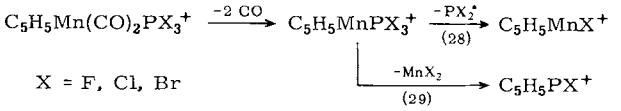
The electropositive character of the transition metals and the resulting substantial localization of the charge on the central atom in complex ions make this a preferred point of attack for nucleophilic atoms or groups if these are present in the complex as components of ligands and are not directly bonded to the central metal. Nucleophiles that may be capable of being transferred include electronegative substituents such as halogens, oxygen, and hydroxyl, alkoxy, cyano, or amino groups; the probability of migration increases with the electronegativity. Alkyl and aryl residues are transferred if certain structural features are also present in the ligand, particularly if these groups are bonded *via* a carbonyl function. The processes described here are frequently accompanied by drastic rearrangements of the remaining ligand fragments.

Among the atoms most easily transferred to the metal are the halogens. The spectra of halobenzenetricarbonylchromium compounds show chromium halide ions [eq. (27)], whose intensities increase markedly from the iodide to the fluoride, corresponding to the variation of the electronegativities[80].

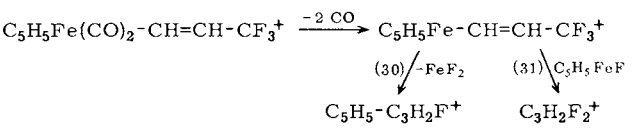


X = F, Cl, Br, I (27)

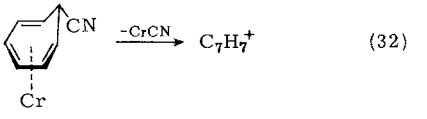
If the ligand contains several halogen atoms, metal dihalides are also formed during the decomposition of the complex; because of their high ionization energies, these are generally eliminated as neutral particles. Thus in the decomposition of trihalophosphane compounds, one [eq. (28)] or two [eq. (29)] halogen atoms can migrate[46].



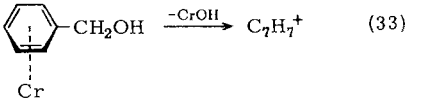
Such rearrangements are characteristic of the frequently described decomposition of complexes with halogenated organic ligands having a wide variety of structures[23,57,77,101–107]; two examples are given in equations (30) and (31).



The process (27) proceeds in the same manner when X = OH, NH_2, or OCH_3. Similarly, halogen can be replaced by OC_6H_5 in equations (28) and (29). Migrations of electronegative groups are particularly favored if very stable ions such as the tropylium ion can be formed at the same time [eq. (32)[69] and (33)[108]].

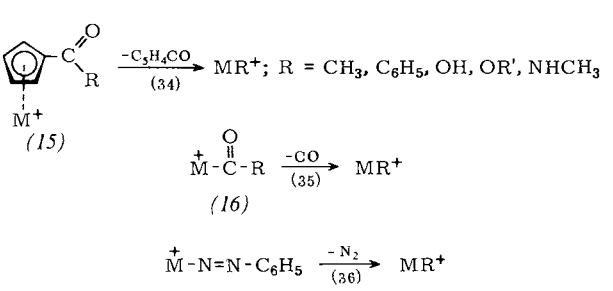


(32)



(33)

Complexes containing the structure *(15)* decompose *inter alia* in accordance with equation (34), as has been found above all for compounds with M = Fe and Mn[96,98,109]; alkyl and phenyl groups can also be transferred in decompositions of this type. Acylmetal ions *(16)* undergo fragmentation corresponding to the reversal of the formation of the neutral complexes (insertion of CO in metal-carbon σ bonds), again with formation of alkylmetal or arylmetal fragments [eq. (35)][9,23,57]; the latter are formed in a similar manner in the decomposition of arylazo complexes[110] [eq. (36)].

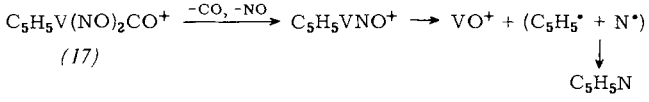


(15)

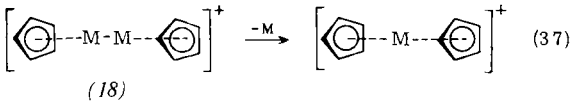
(16)

Very unusual fragmentation behavior is exhibited by complex ions that contain both nitrosyl and organic ligands and also have an even number of electrons. With migration of the O atom of an NO group to the central metal, the nitrogen is transferred to a free-radical ligand fragment[59]. The decomposition of *(17)* involves the formal elimination of a cyclopentadienyl radical and an N atom; an energetically plausible explanation is the combination of the two radicals to form the cyclopentadienylnitrene and the rearrangement of the latter to give the stable pyridine.

Finally, let us consider decompositions of polynuclear complexes, which can be provisionally assigned to the present rearrangement type with migration of nucleo-



philic groups to the central metal. The decomposition of polynuclear cyclopentadienylmetal carbonyl, nitrosyl, or halogeno complexes yields fragments *(18)*, which are stabilized by elimination of a metal atom and migration of a C_5H_5 ligand[32,63,111,112] [eq. (37)]. The decomposition of cyclopentadienylmetal thiolates yields the fragment *(19)*, which decomposes in a disproportionation reaction, again with formation of $M(C_5H_5)_2^+$ [78,79] [eq. (38)].



(18)



(19)

The number of examples of rearrangements in the decomposition of organometallic complexes in the mass spectrometer could be extended almost indefinitely; however, many of the rearrangement processes observed so far can be classified under the three main types proposed in this review.

Received: November 18, 1971 [A 895 IE]
German version: Angew. Chem. *84*, 725 (1972)
Translated by Express Translation Service, London

[1] A detailed introduction to the principles and applications of mass spectrometry is provided *e.g.* by: *J. H. Beynon:* Mass Spectrometry and its Applications to Organic Chemistry. Elsevier, Amsterdam 1960; *C. A. McDowell:* Mass Spectrometry. McGraw-Hill, New York 1963; *F. W. McLafferty:* Mass Spectrometry of Organic Ions. Academic Press, New York 1963; *C. Brunnée* and *H. Voshage:* Massenspektrometrie. Verlag Karl Thiemig KG, München 1964; *R. W. Kiser:* Introduction to Mass Spectrometry and its Applications. Prentice-Hall, Englewood Cliffs 1965; *R. I. Reed:* Mass Spectrometry. Academic Press, London 1965; *G. Spiteller:* Massenspektrometrische Strukturanalyse organischer Verbindungen. Verlag Chemie, Weinheim 1966; *H. Budzikiewicz, C. Djerassi* and *D. H. Williams:* Mass Spectrometry of Organic Compounds. Holden-Day, San Francisco 1967; *H. Kienitz:* Massenspektrometrie. Verlag Chemie, Weinheim 1968.

[2] The following reviews deal with mass spectra of organometallic compounds: *M. I. Bruce*, Advan. Organometal. Chem. *6*, 273 (1968); *D. B. Chambers, F. Glockling*, and *J. R. C. Light*, Quart. Rev. *22*, 317 (1968); *M. Cais* and *M. S. Lupin*, Advan. Organometal. Chem. *8*, 211 (1970); *R. B. King*, Fortschr. Chem. Forsch. *14*, 92 (1970).

[3] *H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig*, and *H. Eyring*, Proc. Nat. Acad. Sci. U.S. *38*, 667 (1952).

[4] *H. M. Rosenstock* and *M. Krauss* in *F. W. McLafferty:* Mass Spectrometry of Organic Ions. Academic Press, New York 1963, p. 2.

[5] *R. Taubert*, Z. Anal. Chem. *170*, 333 (1959).

[6] *M. L. Vestal*, J. Chem. Phys. *43*, 1356 (1965).

[7] *S. Pignataro* and *F. P. Lossing*, J. Organometal. Chem. *11*, 571 (1968).

[8] *R. B. King*, Inorg. Chem. *5*, 2227 (1966).

[9] *R. B. King*, J. Amer. Chem. Soc. *90*, 1417 (1968).

[10] *H. J. Svec* and *G. A. Junk*, Inorg. Chem. *7*, 1688 (1968).

[11] *R. B. King*, J. Amer. Chem. Soc. *88*, 2075 (1966).

[12] *D. J. Patmore* and *W. A. G. Graham*, Inorg. Chem. *5*, 2222 (1966).

[13] *E. Koerner von Gustorf, M. C. Henry*, and *D. J. McAdoo*, Liebigs Ann. Chem. *707*, 190 (1967).

[14] *G. Spiteller* and *M. Spiteller-Friedmann*, Liebigs Ann. Chem. *690*, 1 (1966).

[15] *D. W. Turner:* Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970, p. 361.

[16] *D. R. Lloyd* and *E. W. Schlag*, Inorg. Chem. *8*, 2544 (1969).

[17] *M. J. S. Dewar* and *S. D. Worley*, J. Chem. Phys. *50*, 654 (1969).

[18] *J. Müller, K. Fenderl*, and *B. Mertschenk*, Chem. Ber. *104*, 700 (1971).

[19] *J. Müller* and *P. Göser*, J. Organometal. Chem. *12*, 163 (1968).

[20] *J. Müller* and *L. D'Or*, J. Organometal. Chem. *10*, 313 (1967).

[21] *A. G. Harrison, L. R. Honnen, H. J. Dauben*, and *F. P. Lossing*, J. Amer. Chem. Soc. *82*, 5593 (1960).

[22] *A. Foffani, S. Pignataro, B. Cantone*, and *F. Grasso*, Z. Physik. Chem. (Frankfurt) *45*, 79 (1965).

[23] *J. Müller* and *J. A. Connor*, Chem. Ber. 102, 1148 (1969).

[24] *R. E. Winters* and *R. W. Kiser*, Inorg. Chem. *3*, 699 (1964).

[25] *R. E. Winters* and *R. W. Kiser*, Inorg. Chem. *4*, 157 (1965).

[26] *R. E. Winters* and *R. W. Kiser*, J. Chem. Phys. *44*, 1964 (1966).

[27] *R. E. Winters* and *J. H. Collins*, J. Phys. Chem. *70*, 2057 (1966).

[28] *B. Cantone, F. Grasso*, and *S. Pignataro*, J. Chem. Phys. *44*, 3115 (1966).

[29] *R. D. Bidinosti* and *N. S. McIntyre*, Can. J. Chem. *45*, 641 (1967).

[30] *G. A. Junk* and *H. J. Svec*, Z. Naturforsch. *23b*, 1 (1968).

[31] *R. E. Winters* and *R. W. Kiser*, J. Phys. Chem. *69*, 1618 (1965).

[32] *J. Lewis, A. R. Manning, J. R. Miller*, and *J. M. Wilson*, J. Chem. Soc. *A 1966*, 1663.

[33] *H. J. Svec* and *G. A. Junk*, J. Amer. Chem. Soc. *89*, 2836 (1967).

[34] *J. Lewis* and *B. F. G. Johnson*, Accounts Chem. Res. *1*, 246 (1968).

[35] *G. A. Junk* and *H. J. Svec*, J. Chem. Soc. *A 1970*, 2102.

[36] *B. F. G. Johnson, R. D. Johnston*, and *J. Lewis*, Chem. Commun. *1967*, 1057.

[37] *L. Friedman, A. P. Irsa*, and *G. Wilkinson*, J. Amer. Chem. Soc. *77*, 3689 (1955).

[38] *J. Müller*, Chem. Ber. *102*, 152 (1969).

[39] *G. E. Herberich* and *J. Müller*, J. Organometal. Chem. *16*, 111 (1969).

[40] *R. G. Denning* and *R. A. D. Wentworth*, J. Amer. Chem. Soc. *88*, 4619 (1966).

[41] *S. Pignataro* and *F. P. Lossing*, J. Organometal. Chem. *10*, 531 (1967).

[42] *R. B. King*, Can. J. Chem. *47*, 559 (1969).

[43] *R. E. Winters* and *R. W. Kiser*, J. Organometal. Chem. *4*, 190 (1965).

[44] *S. Pignataro, A. Foffani, F. Grasso*, and *B. Cantone*, Z. Physik. Chem. (Frankfurt) *47*, 106 (1965).

[45] *R. S. Sullivan, M. S. Lupin*, and *R. W. Kiser*, Chem. Commun. *1969*, 655.

[46] *J. Müller* and *K. Fenderl*, J. Organometal. Chem. *19*, 123 (1969).

[47] *J. Müller* and *M. Herberhold*, J. Organometal. Chem. *13*, 399 (1968).

[48] *J. Müller*, J. Organometal. Chem. *18*, 321 (1969).

[49] *A. Foffani, S. Pignataro, G. Distefano*, and *G. Innorta*, J. Organometal. Chem. *7*, 473 (1967).

[50] *G. Distefano, G. Innorta, S. Pignataro*, and *A. Foffani*, J. Organometal. Chem. *14*, 165 (1968).

[51] *S. Pignataro, A. Foffani, G. Innorta*, and *G. Distefano* in *E. Kendrick:* Advances in Mass Spectrometry, Vol. 4. Elsevier, Amsterdam 1968, p. 323.

[52] *K. Edgar, B. F. G. Johnson, J. Lewis, I. G. Williams*, and *J. M. Wilson*, J. Chem. Soc. *A 1967*, 379.

[53] *G. A. Junk, H. J. Svec*, and *R. J. Angelici*, J. Amer. Chem. Soc. *90*, 5758 (1968).

[54] *W. F. Edgell* and *W. M. Risen, Jr.*, J. Amer. Chem. Soc. *88*, 5451 (1966).

[55] *B. F. G. Johnson, J. Lewis*, and *P. W. Robinson*, J. Chem. Soc. *A 1970*, 1684.

[56] *J. M. Smith, K. Mehner*, and *H. D. Kaesz*, J. Amer. Chem. Soc. *89*, 1759 (1967).

[57] *M. J. Mays* and *R. N. F. Simpson*, J. Chem. Soc. *A 1967*, 1936.

[58] *M. Herberhold, H. Alt*, and *J. Müller*, unpublished.

[59] *J. Müller*, J. Organometal. Chem. *23*, C38 (1970).

[60] *E. O. Fischer, A. Reckziegel, J. Müller*, and *P. Göser*, J. Organometal. Chem. *11*, P13 (1968).

[61] *R. B. King*, Appl. Spectrosc. *23*, 148 (1969).

[62] *H. O. van Oven* and *H. J. de Liefde Meijer*, J. Organometal. Chem. *23*, 159 (1970).

[63] *E. Schumacher* and *R. Taubenest*, Helv. Chim. Acta *49*, 1447 (1966).

[64] *R. E. Winters* and *R. W. Kiser*, J. Phys. Chem. *69*, 3198 (1965).

[65] *W. G. Dauben* and *M. E. Lorber*, Org. Mass Spectrometry *3*, 211 (1970).

[66] *M. A. Haas* and *J. M. Wilson*, J. Chem. Soc. *B 1968*, 104.

[67] *K. Yasufuku* and *H. Yamazaki*, Org. Mass Spectrometry *3*, 23 (1970).

[68] *J. Müller*, unpublished.

[69] *J. Müller* and *K. Fenderl*, Chem. Ber. *103*, 3128 (1970).

[70] *R. W. Kiser, M. A. Krassoi*, and *R. J. Clark*, J. Amer. Chem. Soc. *89*, 3653 (1967).

[71] *P. S. Braterman*, J. Organometal. Chem. *11*, 198 (1968).

[72] *F. E. Saalfeld, M. V. McDowell, S. K. Gondal*, and *A. G. McDiarmid*, J. Amer. Chem. Soc. *90*, 3684 (1968).

[73] *R. B. King*, J. Amer. Chem. Soc. *90*, 1412 (1968).

[74] *V. Harder, J. Müller*, and *H. Werner*, Helv. Chim. Acta *54*, 1 (1971).

[75] *R. B. King* and *T. F. Korenowski*, Org. Mass Spectrometry *5*, *939 (1971)*.

[76] *J. Müller* and *K. Fenderl*, Angew. Chem. *83*, 445 (1971); Angew. Chem. internat. Edit. *10*, 418 (1971).

[77] *R. B. King*, J. Amer. Chem. Soc. *90*, 1429 (1968).

[78] *F. J. Preston* and *R. I. Reed*, Chem. Commun. *1966*, 51.

[79] *F. J. Preston* and *R. I. Reed*, Org. Mass Spectrometry *1*, 71 (1968).

[80] *J. Müller* and *P. Göser*, Chem. Ber. *102*, 3314 (1969).

[81] *K. Moseley* and *P. M. Maitlis*, Chem. Commun. *1969*, 616.

[82] *H. W. Wehner, E. O. Fischer*, and *J. Müller*, Chem. Ber. *103*, 2258 (1970).

[83] *R. B. King* and *A. Efraty*, Org. Mass Spectrometry *3*, 1233 (1970).

[84] *R. B. King* and *A. Efraty*, Org. Mass Spectrometry *3*, 1227 (1970).

[85] *J. Müller* and *K. Öfele*, unpublished.

[86] *R. B. King*, J. Organometal. Chem. *14*, P19 (1968).

[87] *I. M. T. Davidson, M. Jones*, and *R. D. Kemmitt*, J. Organometal. Chem. *17*, 169 (1969).

[88] *M. I. Bruce*, J. Mass Spectrometry Ion Physics *2*, 349 (1969).

[89] *J. Müller* and *P. Göser*, Angew. Chem. *79*, 380 (1967); Angew. Chem. internat. Edit. *6*, 364 (1967).

[90] *M. F. Rettig, C. D. Stout, A. Klug*, and *P. Farnham*, J. Amer. Chem. Soc. *92*, 5100 (1970).

[91] *H. O. van Oven* and *H. J. de Lifde Meijer*, J. Organometal. Chem. *23*, 159 (1970).

[92] *J. Müller* and *B. Mertschenk*, J. Organometal. Chem. *34*, C41 (1972).

[93] *M. I. Bruce*, J. Mass Spectrometry Ion Physics *1*, 335 (1968).

[94] *M. M. Bursey, F. E. Tibbetts*, and *W. F. Little*, J. Amer. Chem. Soc. *92*, 1087 (1970).

[95] *B. F. G. Johnson, J. Lewis, I. G. Williams*, and *J. M. Wilson*, J. Chem. Soc. *A 1967*, 338.

[96] *M. Cais, M. S. Lupin, N. Maoz*, and *J. Sharvit*, J. Chem. Soc. *A 1968*, 3086.

[97] *J. K. Becconsall, B. E. Job*, and *S. O'Brien*, J. Chem. Soc. *A 1967*, 423.

[98] *A. Mandelbaum* and *M. Cais*, Tetrahedron Lett. *1964*, 3847.

[99] *D. T. Roberts, Jr., W. F. Little*, and *M. M. Bursey*, J. Amer. Chem. Soc. *89*, 4917, 6156 (1967).

[100] *J. Müller* and *G. Krebs*, unpublished.

[101] *J. M. Miller*, J. Chem. Soc. *A 1967*, 828.

[102] *M. I. Bruce*, Org. Mass Spectrometry *1*, 503, 687 (1968); *2*, 63, 997 (1969).

[103] *M. I. Bruce* and *M. A. Thomas*, Org. Mass Spectrometry *1*, 835 (1968).

[104] *R. B. King*, J. Amer. Chem. Soc. *89*, 6368 (1967).

[105] *R. B. King*, Appl. Spectrosc. *23*, 137 (1969).

[106] *L. D. Smithson, A. K. Bhattacharya*, and *F. L. Hedberg*, Org. Mass Spectrometry *4*, 383 (1970).

[107] *E. O. Fischer, H.-J. Beck, C. G. Kreiter, J. Lynch, J. Müller*, and *E. Winkler*, Chem. Ber. *105*, 162 (1972).

[108] *J. Müller and B. Mertschenk*, unpublished.

[109] *N. Maoz, A. Mandelbaum*, and *M. Cais*, Tetrahedron Lett. *1965*, 2087.

[110] *R. B. King*, Org. Mass Spectrometry *2*, 387 (1969).

[111] *M. I. Bruce*, J. Mass Spectrometry Ion Physics *1*, 141 (1968).

[112] *R. B. King*, Org. Mass Spectrometry *2*, 657 (1969).

Metal Isotope Effect on Metal-Ligand Vibrations

By Kazuo Nakamoto[*]

Exploitation of the isotope effect using heavy metal isotopes now makes it possible to give clear-cut assignments of the metal-ligand vibrations in the IR and Raman spectra of complex compounds. The results previously obtained with this new method and their current limitations form the subject of this progress report.

1. Introduction

The metal-ligand vibrations of coordination compounds are most important since they provide direct information about the structure of the complex and the nature of the metal-ligand bond. These vibrations appear in the low-frequency region because of the relatively heavy mass of the metal atom and the weak nature of the metal-ligand bond. It is not an easy task to assign the metal-ligand vibrations unequivocally since the interpretation of low-frequency spectra is complicated by the appearance of ligand vibrations (some of which are activated by complex formation) and by the crystal field effect (lowering of symmetry, appearance of lattice modes, coupling of lattice with internal modes, *etc.*) in the solid state.

Thus far, the metal-ligand vibrations have been assigned by the use of one or more of the following methods:

1. A comparison of the spectra between a free ligand and its metal complex; the metal-ligand vibration should be absent in the spectrum of the free ligand. This method often fails to give a clear-cut assignment, since some ligand vibrations activated by complex formation may appear in the same region as the metal-ligand vibrations.

2. The metal-ligand vibration should be metal-sensitive and be shifted by changing the metal or its oxidation state. This method is applicable only when a series of metal complexes have exactly the same structure with different metals.

3. The metal-ligand stretching band should appear in the same frequency region if the metal is the same and the ligands are similar. For example, the Zn—N stretching frequencies of Zn^{II}-α-picoline complexes are similar to those of Zn^{II}-pyridine complexes. This method is applicable only when the metal-ligand vibration is known for one parent compound.

4. The metal-ligand vibration shows an isotopic shift if the ligand is isotopically substituted. For example, the Ni—N stretching band of $[Ni(NH_3)_6]Cl_2$ at 334 cm^{-1} is shifted to 318 cm^{-1} upon deuteration of the ammonia ligands[1]. The observed shift of 16 cm^{-1} is in good agreement with that predicted theoretically for the Ni—N stretching mode. Similar shifts are observed if the α-atom of the ligand (atom directly bonded to the metal) is isotopically substituted. For example, this method has been used to assign the metal-ligand vibrations of oxamido(^{14}N and ^{15}N)[2] and acetylacetonato-(^{16}O and ^{18}O) complexes[3]. It should be noted, however, that metal-ligand vibrations as well as ligand vibrations involving the motion of the α-atom are shifted by this method. Thus it may not provide a clear-cut assignment for the metal-ligand vibration.

5. The frequency of a metal-ligand vibration may be predictable if the metal-ligand stretching and other force constants are known *a priori*. At present, this method is not practical since not many force constants are known for coordination compounds.

It is obvious that none of these methods is perfect; furthermore, they encounter more and more difficulties as the structure of the complex (and hence the spectrum) becomes more complicated.

In order to solve this difficulty, we have recently developed a new method which utilizes the heavy metal isotopes[4]. The use of isotopes in vibrational spectroscopy is not new. The pairs of isotopes such as (H, D), (^6Li, ^7Li), (^{10}B, ^{11}B), (^{14}N, ^{15}N) and (^{16}O and ^{18}O) have long been used to assign the vibrations involving the motion of these atoms. However, the use of heavy metal isotopes had not been reported until our first communication appeared in 1969[4][*]. This is probably due to two reasons: (i) Pure metal isotopes were not commercially available, and (ii) the magnitude of such an isotopic shift was thought to be too small to be observed. The former obstacle has been eliminated since a number of metal isotopes can be purchased from Oak Ridge National Laboratory[**]. Table 1 lists some stable metal isotopes, their purity and current prices. Using these isotopes, it is possible to prepare a pair of metal complexes in which only the metals are isotopically substituted. Although metal isotopes are relatively expensive, this factor does not cause serious financial burden since most of the preparations can be carried out on a milligram scale and normally less than twenty milligrams of samples are sufficient to measure the entire spectrum. Furthermore, some of these metal isotopes can be easily recovered after the measurement. Table 1 also indicates that several natural abundant elements may be used as substitutes for pure metal isotopes such as ^{52}Cr, ^{56}Fe and ^{58}Ni since the concentrations of

[*] Prof. Dr. K. Nakamoto
The Todd Wehr Chemistry Building
Marquette University
Milwaukee, Wisconsin 53233 (USA)

[*] After our first communication appeared in 1969, *P. Tarte* and *J. Preudhomme* independently reported the application of the metal isotope technique to inorganic salts such as Ni_2GeO_4 and $CaMoO_4$ (C. R. Acad. Sci. Paris, *270*, 474 (1970); Spectrochim. Acta, *26A*, 2207 (1970)).

[**] Isotopes Development Center, Oak Ridge National Laboratory, P. O. Box X, Oak Ridge, Tennessee 37830 (USA).

these isotopes are exceptionally high in natural abundance.

As stated above, the magnitude of a metal isotope shift is expected to be small since relative mass difference between isotopes ($\Delta m/m$) is small and the metal-ligand bond is generally weak. However, it is beyond possible experimental errors in most compounds containing the metal isotopes listed in Table 1. For mass differences of 2 units or more, we have so far observed shifts ranging 10 to 1.5 cm^{-1} for the metal-ligand stretching modes. The instrumental resolution and reproducibility of typical far-infrared and Raman spectrophotometers is 0.5 cm^{-1} if proper conditions are used[*]. Therefore, a shift of more than 1 cm^{-1} can be observed without difficulty if a band is relatively sharp and not overlapped by other bands. Thus far, the heaviest isotopes we have studied are ^{116}Sn and ^{124}Sn. As will be shown later, the Sn—Cl and Sn—N stretching modes of $SnCl_4(py)_2$ are shifted by 5—4 cm^{-1} by such isotopic substitution. This method may be applicable to elements heavier than tin if a proper combination of metal isotopes and a ligand is found.

The ligand-metal-ligand bending modes are much less sensitive to the metal isotope substitution than the metal-ligand stretching modes. In fact, the observed shifts of the bending modes are less than 2.0 cm^{-1} in most cases. Thus, the metal isotope method is not so effective in assigning the metal-ligand bending modes.

It is well known that the Teller-Redlich product rule holds for the ratio of products of all the frequencies between two isotopic molecules. Consider an octahedral XY_6-type molecule where X is ^{58}Ni or ^{62}Ni and Y is an NH_3 ligand (point mass approximation). If the product rule is applied to the infrared active F_{1u} species which contains one stretching (ν_1) and one bending mode (ν_2), the result is

$$\frac{\nu_1'}{\nu_1}\frac{\nu_2'}{\nu_2} = \left\{\left(\frac{m_x'+6m_y}{m_x+6m_y}\right)\left(\frac{m_y}{m_y'}\right)\right\}^{1/2} = \left\{\left(\frac{164}{160}\right)\left(\frac{58}{62}\right)\right\}^{1/2} = 0.9793$$

This gives a general idea about the magnitude of the metal isotope shift. However, the product rule does not give information about the individual isotope shift. In order to predict individual isotope shifts for ν_1 and ν_2, normal coordinate analysis must be carried out on an XY_6-type molecule. Conversely, metal isotope data are highly useful in refining a set of force constants to be used for normal coordinate analysis. In some cases, vibrational coupling occurs between metal-ligand and ligand vibrations. If so, even ligand vibrations become slightly metal isotope sensitive. The degree of vibrational coupling can be estimated from the calculation of the L-matrix or the potential energy distribution. Thus, the metal isotope data are useful in confirming the presence of vibrational coupling predicted by normal coordinate analysis.

Table 1. Some stable isotopes available at Oak Ridge National Laboratory.

Element	Atomic Weight	Inventory Form	Isotope	Natural Abundance (%)	Purity (%)	Price ($/mg)
Chromium	51.996	Cr_2O_3	^{50}Cr	4.31	90—95	2.20
			^{52}Cr	83.76	> 99.9	0.90
			^{53}Cr	9.55	> 95	0.90
Iron	55.847	Fe_2O_3	^{54}Fe	5.82	> 90	1.50
			^{56}Fe	91.66	> 99.8	0.10
			^{57}Fe	2.19	> 90	3.80
Nickel	58.71	Ni	^{58}Ni	67.88	98—99	0.15
			^{60}Ni	26.23	86—99.8	0.20
			^{62}Ni	3.66	95—99	1.60
Copper	63.54	CuO	^{63}Cu	69.09	> 98	0.20
			^{65}Cu	30.91	> 90	0.35
Zinc	65.37	ZnO	^{64}Zn	48.89	> 99	0.35
			^{66}Zn	27.81	90—99	0.55
			^{68}Zn	18.57	95—99	0.80
Molybdenum	95.94	Mo	^{92}Mo	15.84	90—98	0.30
			^{95}Mo	15.72	85—99	0.30
			^{97}Mo	9.46	85—95	0.45
			^{98}Mo	23.78	90—99	0.85
			^{100}Mo	9.63	80—99	0.50
Zirconium	91.22	ZrO_2	^{90}Zr	51.46	90—99	0.25
			^{94}Zr	17.40	90—99	1.05
Palladium	106.4	Pd	^{104}Pd	10.97	70—85	4.25
			^{106}Pd	27.33	> 90	1.95
			^{108}Pd	26.71	> 93	1.60
			^{110}Pd	11.81	> 95	3.65
Tin	118.69	SnO_2	^{116}Sn	14.30	> 95	0.30
			^{118}Sn	24.03	90—99	0.15
			^{120}Sn	32.85	90—99	0.10
			^{124}Sn	5.94	80—96	0.50
Chlorine	34.453	NaCl	^{35}Cl	75.529	> 98	0.50
			^{37}Cl	24.471	> 95	1.75

[*] It is not necessary to measure the spectrum under high resolution unless two or more bands are closely located. In most cases, the spectra are run under normal resolution with a slow scanning speed and on an expanded scale to measure the peak position as accurately as possible. The peak frequency is calculated by taking an average value of multiple scans over the desired frequency range.

2. Phosphane Complexes[5,13,16]

Triethylphosphane complexes of the type, $M(PEt_3)_2X_2$, where M is Ni^{II} and Pd^{II} and X is a halogen, are known to be *trans*-planar. Thus, one M—X stretching and one M—P stretching vibration should be active in the infrared. Furthermore, both bands should be sensitive to metal isotope substitution. Figure 1 gives the actual tracing of the spectra of $^{58}Ni(PEt_3)_2X_2$ (X = Cl and Br) and their ^{62}Ni analogs[5]. Table 2 lists the observed frequencies, isotopic shifts and band assignments. The bands above 420 cm^{-1} are not listed since they are not sensitive to metal isotope substitution. It is seen that each complex exhibits two bands which give large isotopic shifts relative to others. The band at 403.3 cm^{-1} of $^{58}Ni(PEt_3)_2Cl_2$ is clearly due to the Ni—Cl stretching mode since this band is strong and not present in its bromo analog[6,7]. Then, the remaining band at 273.4 cm^{-1} must be assigned to the Ni—P stretching mode. This band persists in $^{58}Ni(PEt_3)_2Br_2$ at 265.0 cm^{-1}. Previously, the Ni—P stretching modes of the $Ni(PEt_3)_2X_2$ type complexes were assigned at 426—410 cm^{-1} [6,7]. These assignments must be revised in view of our new results.

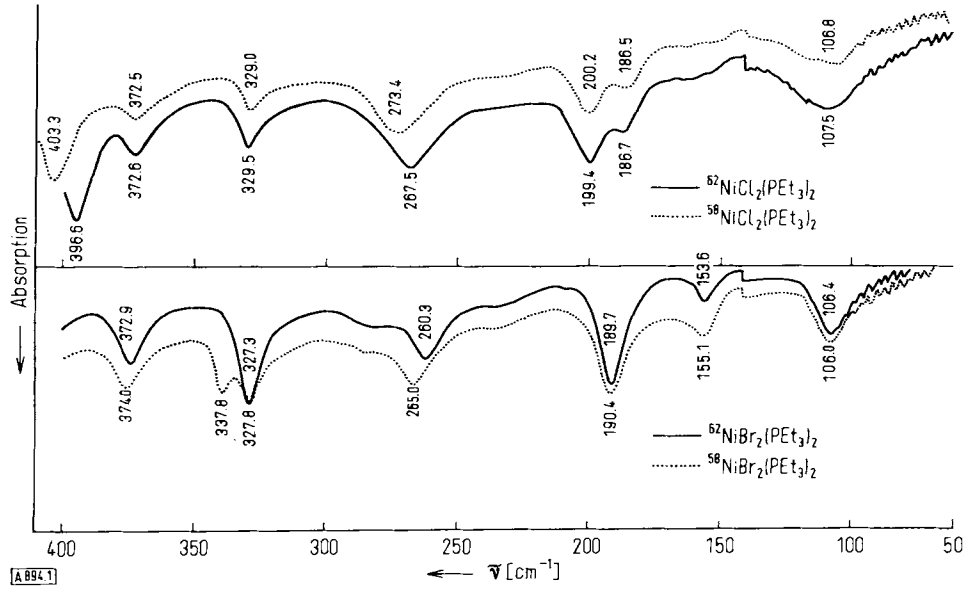


Fig. 1. Far infrared spectra of *trans*-$Ni(PEt_3)_2X_2$ (X = Cl and Br).

Table 2 also shows that two bands at 358.3 and 234.5 cm^{-1} of $^{104}Pd(PEt_3)_2Cl_2$ are sensitive to the ^{104}Pd-^{110}Pd substitution. The former can be assigned to the Pd—Cl stretching mode since it is in a frequency range expected for the Pd—Cl stretching mode (370—345 cm^{-1})[8]. Then, the band at 234.5 cm^{-1} must be assigned to the Pd—P stretching mode. Previous investigators[6,7,9] have assigned the Pd—P stretching bands of $Pd(PEt_3)_2X_2$ and $Pd_2(PEt_3)_2Cl_4$ type complexes at 450—380 cm^{-1}. The Pd—P stretching bands of analogous trimethylphosphane complexes have also been assigned at 380—340 cm^{-1} by many other investigators[7,10,11]. Our results show that these frequencies are too high for the Pd^{II}—P stretching modes of square-planar complexes.

The skeletal bending bands which appear below 200 cm^{-1} are much less sensitive to metal isotope substitution and more difficult to assign than the metal-ligand stretching modes. In Table 2, we have proposed band assignments which were predicted from an approximate normal coordinate analysis described later. The band at 183.8 cm^{-1} of $^{104}Pd(PEt_3)_2Cl_2$ gives an isotopic shift of 1.8 cm^{-1} which is rather large for a pure ligand vibra-

Table 2. Infrared frequencies of triethylphosphane complexes containing metal isotopes (cm^{-1}).

PEt_3	$^{58}Ni(PEt_3)_2Cl_2$		$^{58}Ni(PEt_3)_2Br_2$		$^{104}Pd(PEt_3)_2Cl_2$		Assignment[b]
$\tilde{\nu}$	$\tilde{\nu}$	$\Delta\tilde{\nu}$[a]	$\tilde{\nu}$	$\Delta\tilde{\nu}$[a]	$\tilde{\nu}$	$\Delta\tilde{\nu}$[a]	
408(m)	416.7(m)	(0.0)	413.6(m)	(1.2)	413.0	(−0.3)	δ(CCP)
—	403.3(vs)	(6.7)	337.8(m)	(10.5)[c]	358.3(vs)	(3.4)	ν_a(M—X)
365(m)	372.5(m)	(−0.1)	374.0(m)	(1.1)	375.7(sh)	(−0.3)	δ(CCP)
330(m)	329.0(m)	(−0.5)	327.8(s)	(0.5)[c]	330.8(m)	(0.0)	δ(CCP)
—	273.4(s)	(5.9)	265.0(m)	(4.7)	234.5(s)	(2.5)	ν_a(M—P)
245(m)	(hidden)		(hidden)		272.0(m,br)	(0.0)	δ(CCP)
	200.2(m)	(0.8)	190.4(s)	(0.7)	183.8(s)	(1.8)	δ(CPC)
	186.5(sh)	(−0.2)	155.1(m)	(1.5)	168.0(sh)	(−0.5)	δ(MX)
	161.5(vw)	(−0.5)	(hidden)		152.0(vw)	(1.0)	δ(MP)
	106.8(m,br)	(−0.7)	106.0(m)	(−0.4)	105.5(s,br)	(0.5)	?

[a] $\Delta\tilde{\nu}$ indicates metal isotope shift, $\tilde{\nu}(^{58}Ni) - \tilde{\nu}(^{62}Ni)$ or $\tilde{\nu}(^{104}Pd) - \tilde{\nu}(^{110}Pd)$.
[b] ν_a, asymmetric stretch, δ, bending. Ligand vibrations were assigned according to Ref. [12].
[c] In $^{62}Ni(PEt_3)_2Br_2$, these two bands are overlapped (see Figure 1). Therefore, $\Delta\tilde{\nu}$ values are only approximate.

tion. This may suggest the presence of vibrational coupling between this ligand vibration and the Pd—P stretching mode at 234.5 cm^{-1}.

$Ni(PPh_3)_2Cl_2$ is tetrahedral whereas $Pd(PPh_3)_2Cl_2$ is *trans*-planar. Thus, the former exhibits two Ni—Cl and two Ni—P stretching bands whereas the latter exhibits one Pd—Cl and one Pd—P stretching band. In fact, $^{58}Ni(PPh_3)_2Cl_2$ exhibits four bands at 341.2, 305.0, 189.6 and 164.0 cm^{-1} which are sensitive to the ^{58}Ni-^{62}Ni substitution. The former two bands are assigned to the Ni—Cl stretching modes since they are relatively strong and absent in the bromo analog. Then, the latter two bands must be assigned to the Ni—P stretching modes. In $^{104}Pd(PPh_3)_2Cl_2$, two bands at 360.3 and 191.2 cm^{-1} show large isotopic shifts (4.3 and 4.2 cm^{-1}, respectively) relative to others. The former band is in the region of terminal Pd—Cl stretching frequencies[8] and assigned safely to this mode. Then, the latter must be assigned to the Pd—P stretching mode. Again, previous workers[9] assigned the Pd—P stretching modes of $Pd_2(PPh_3)_2Cl_4$ at 450 and 428 cm^{-1}. These bands may be assignable to the vibrations of the triphenylphosphane ligand.

In order to calculate theoretical isotope shifts, we have carried out a normal coordinate analysis on a *trans*-planar MY_2X_2 model by assuming that the PEt_3 ligand is a single atom having the mass of PEt_3. Evidently, such an approximation provides only a rough measure of theoretical isotope shifts. Even so, the results of Table 3 are sufficient to show that the magnitudes of the observed shifts are at least reasonable.

Table 3. Comparison of theoretical and observed isotopic shifts for *trans*-$Ni(PEt_3)_2X_2$ (cm^{-1}).

$Ni(PEt_3)_2Cl_2$	Theoretical [a] ^{58}Ni	$\Delta\tilde{\nu}$	Observed ^{58}Ni	$\Delta\tilde{\nu}$
Ni—Cl Stretch	402.4	7.2	403.3	6.7
Ni—P Stretch	270.8	7.3	273.4	5.9
Ni—Cl Bend	189.5	0.0	186.5	−0.2
Ni—P Bend	168.2	1.7	161.5	−0.5
$Ni(PEt_3)_2Br_2$				
Ni—Br Stretch	340.9	8.6	337.8	10.5 [b]
Ni—P Stretch	265.9	7.5	265.0	4.7
Ni—Br Bend	141.0	0.1	155.1	1.5
Ni—P Bend	147.1	0.5	— [c]	

[a] The molecular parameters used for calculations were: Ni—Cl, 2.30 Å; Ni—Br, 2.40 Å; Ni—P, 2.25 Å. The four angles around the Ni atoms were assumed to be 90°. The Urey-Bradley force constants used were: K(stretching), 1.35 for Ni—Cl, 1.25 for Ni—Br and 0.75 for Ni—P; H(bending), 0.11 and F(repulsive), 0.13, all in units of mdyn/Å.
[b] See footnote [c] of Table 2.
[c] Hidden by the neighboring band.

Similar isotope studies have also been made on the $Ni(diphos)_2X_2$ type complexes where diphos is ethylene-bis(diphenylphosphane) and X is a halogen[13]. In this case, two Ni—X and two Ni—P stretching modes are infrared active since these compounds have a *cis*-planar NiP_2X_2 skeleton. Table 4 lists the four stretching frequencies determined by the Ni isotope method. It also compares the Ni—X and Ni—P stretching frequencies of *trans*-planar, *cis*-planar and tetrahedral $Ni(phosphane)_2X_2$ type complexes. It is seen that there are marked differences in Ni—X stretching frequencies between *cis* and *trans* complexes. The Ni—X stretching frequencies of the *cis*-complex are always lower than those of the corresponding *trans*-complex, since the Ni—X bond of the *cis* complex is *trans* to the phosphane ligand which exerts a strong *trans*-effect. Conversely, the Ni—P stretching frequencies of the *cis*-complex are always higher than that of the corresponding *trans*-complex since the Ni—P bond is *trans* to the halogen.

Table 4. Comparison of Ni—X and Ni—P stretching frequencies between various configurations (cm^{-1}).

	tr-$^{58}Ni(PR_2R')_2X_2$		*cis*-$^{58}Ni(diphos)X_2$		tet-$Ni(PPh_3)_2X_2$	
	ν(Ni—X)	ν(Ni—P)	ν(Ni—X)	ν(Ni—P)	ν(Ni—X)	ν(Ni—P)
X = Cl	401 [a]	252 [a]	341 [d]	379 [d]	341 [e]	190 [e]
			328	—	305	164
Br	338 [b]	265 [b]	290	365	265 [f]	193 [f]
			266	308	232	184
I	260 [c]	252 [c]	260	353	215 [f]	198 [f]
			212	278		182

[a] R = Ph, R' = Et; [b] R = R' = Et (Ref. [7]); [c] R = Me, R' = Ph (natural abundance Ni); [d] Form A (see Ref. [13]); [e] ^{58}Ni complex (see Ref. [5]); [f] see Ref. [14].

It is well known that complexes of the type, $Ni(PPh_2R)_2Br_2$ (R = alkyl) exist in two isomeric forms: tetrahedral (green) and *trans*-planar (brown) forms[15]. According to Table 4, the Ni—Br and Ni—P stretching frequencies of these two forms should be markedly different. This has also been confirmed by our Ni isotope experiments on both forms of $Ni(PPh_2Et)_2Br_2$[16]. In general, the tetrahedral form exhibits two Ni—Br stretching bands near 250 cm^{-1} whereas the *trans*-planar form exhibits one Ni—Br stretching near 330 cm^{-1} and one Ni—P stretching band near 260 cm^{-1}.

3. 8-Quinolinolato (Oxinato) Complexes[17]

Figure 2 shows the far-infrared spectra of potassium oxinate (abbreviated as KQ) and several anhydrous bis-(oxinato) complexes (MQ_2). These spectra are too complicated to allow empirical band assignments. It is possible, however, to assign the metal-ligand vibrations by using the metal isotope method and to elucidate the structure of these complexes based on observed numbers of metal-ligand vibrations. There are three probable structures for bis(oxinato) complexes: *trans*-planar (C_{2h}), *cis*-planar (C_{2v}) and tetrahedral (C_{2v})

structures. The number of infrared active metal-ligand stretching bands should be two for C_{2h} symmetry ($2B_u$) and four for C_{2v} symmetry ($2A_1 + 2B_1$ for *cis*-planar, and $2A_1 + B_1 + B_2$ for tetrahedral).

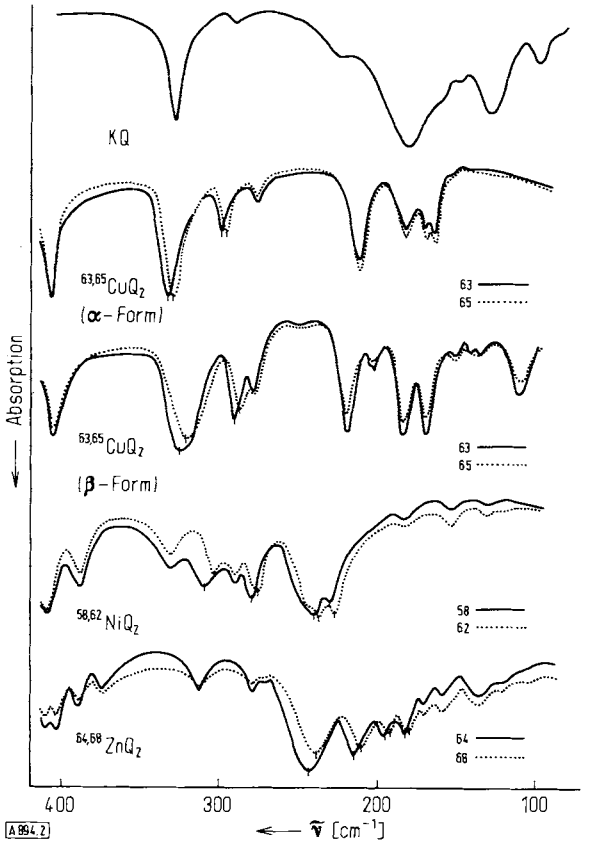


Fig. 2. Far-infrared spectra of KQ, CuQ_2, NiQ_2, and ZnQ_2 (Q = anion of 8-quinolinol).

Anhydrous copper oxinate (CuQ_2) has been isolated as two crystal forms, *i.e.*, α-form and β-form. As is seen in Fig. 2 and Table 5, both forms exhibit two bands (332.1 and 297.3 cm^{-1} for the α-form and 324.0 and 289.7 cm^{-1} for the β-form) which give relatively large isotopic shifts by the ^{63}Cu-^{65}Cu substitution. Thus the structures of both forms must be *trans*-planar (C_{2h}). The present results are in good agreement with those of previous X-ray studies[18–20].

In general, the metal-oxygen stretching band is stronger than the metal-nitrogen stretching band in the infrared. Therefore, the stronger bands (332.1 cm^{-1} (α) and 324.0 cm^{-1} (β)) with higher frequencies may be assigned to the Cu—O stretching modes, whereas the weaker ones (297.3 cm^{-1} (α) and 289.7 cm^{-1} (β)) with lower frequencies may be assigned to the Cu—N stretching modes.

Figure 2 and Table 5 show that four bands at 309.6, 280.8, 242.0 and 231.0 cm^{-1} of NiQ_2 show large isotopic shifts relative to other bands by the ^{58}Ni-^{62}Ni substitution. NiQ_2 is also known to have a magnetic moment of 3.24 μ_B[21]. Combining these results, it may be concluded that NiQ_2 is tetrahedral (C_{2v}). Generally, the asymmetric stretching mode appears at a higher frequency and is expected to give a larger isotopic shift by the ^{58}Ni-^{62}Ni substitution than the symmetric one. Considering this trend with their relative intensities and frequencies, we have assigned two bands at 309.6 and 280.8 cm^{-1} to the asymmetric (B_1) and symmetric (A_1) Ni—O stretching modes, respectively, and two bands at 242.0 and 231.0 cm^{-1} to the asymmetric (B_2) and symmetric (A_1) Ni—N stretching modes, respectively. It should be noted in Fig. 2 that the Ni—N stretching bands (242.0 and 231.0 cm^{-1}) are relatively strong since they are overlapped on the strong ligand band at around 230 cm^{-1}.

Table 5. Observed frequencies, isotopic shifts, and band assignments for MQ_2-type metal oxinates and potassium oxinate (cm^{-1}).

KQ	$^{63}CuQ_2$				$^{58}NiQ_2$		$^{64}ZnQ_2$		Assignment
	α	Δν̃[a]	β	Δν̃[a]		Δν̃[a]		Δν̃[a]	
642 (s)	645.7 (m)	0.0	646.0 (m)	0.0	649.8 (s)	0.2	650.5 (vs)	0.0	δ (ligand)
583 (s)	634.3 (s)	0.5	633.0 (s)	0.9	627.5 (m)	0.5	606.0 (vs)	0.0	δ (ligand)
					613.6 (sh)	0.3	591.0 (sh)	0.0	
					606.0 (sh)	0.0			
					598.0 (s)	0.0			
553 (m)	585.3 (m)	0.0	583.0 (m)	0.0	574.0 (m)	0.0	561.8 (m)	0.0	δ (ligand)
488 (m)	524.0 (vs)	0.0	522.5 (vs)	0.0	519.0 (sh)	0.6	503.5 (vs)	0.0	δ (C—O)[b]
481 (m)					506.3 (vs)	0.0			
—	406.0 (vs)	0.0	404.0 (s)	0.5	414.5 (s)	0.3	409.5 (s)	0.0	ring
				—	409.2 (s)	0.0	403.0 (s)	0.0	deformation
					388.5 (s)	0.5	389.0 (m)	0.0	
							374.0 (w)	0.0	
327 (m)	(overlapped)[b]		(overlapped)[b]		330.0 (m)	−0.6	312.5 (w)	0.0	ligand
288 (w)	274.5 (w)	0.0	277.0 (w)	0.0	290.0 (m)	0.4	279.5 (w)	0.0	ligand
—	*332.1 (s)*	*3.0*	*324 (vs)*	*3.5*	*309.6 (s)*	*6.0*	*243.0 (vs)*	*5.0*	ν_a(M—O)
—	—	—	—	—	*280.8 (s)*	*4.8*	*214.4 (s)*	*4.2*	ν_s(M—O)
224 (sh)	210.5 (s)	0.3	218.0 (s)	−0.4	246.0 (vs)	0.0	(overlapped)[b]		ligand
			202.4 (w)	0.0					
—	*297.3 (m)*	*2.8*	*289.7 (m)*	*3.2*	*242.0 (vs)*	*3.8*	*195.5 (m)*	*2.5*	ν_a(M—N)
—	—	—	—	—	*231.0 (s)*	*3.2*	*182.4 (m)*	*2.0*	ν_s(M—N)
180 (vs, vbr)	181.5 (m)	0.1	182.0 (m)	0.0	184.0 (w)	0.1	180.4 (m)	0.0	ligand
	168.4	0.6	168.2 (m)	0.0	—		170.0 (w)	0.2	ligand
159 (w)	163.2	0.4	—	—	—		158.5 (w)	0.0	ligand
149 (w)	153.0 (vw)	0.0	151.0 (vw)	0.0	153.8 (vw)	0.3	—	—	ligand
128 (m, br)	—	—	141 (vw)	−0.3	131. (w, br)	0	138 (w, br)	0	ligand
							131 (w, br)	0	
97 (m)	91 (w)	—	110 (m)	—	—		—		

[a] Δν indicates metal isotope effects; $\nu(^{63}Cu) - \nu(^{65}Cu)$, $\nu(^{58}Ni) - \nu(^{62}Ni)$ or $\nu(^{64}Zn) - \nu(^{68}Zn)$.
[b] Overlapped with ν(M—O).

In accordance with the expected tetrahedral structure, ZnQ_2 exhibits four bands which are sensitive to the ^{64}Zn-^{68}Zn substitution. Figure 2 also shows that the general pattern of the far-infrared spectrum of ZnQ_2 is similar to that of NiQ_2 but is rather different from that of CuQ_2 (*trans*-planar). From the intensity and frequency considerations, these four bands at 243.0, 214.4, 195.5 and 182.4 cm^{-1} may be assigned to the asymmetric Zn—O (B_1), symmetric Zn—O (A_1), asymmetric Zn—N (B_2) and symmetric Zn—N (A_1) stretching modes, respectively.

4. 2,4-Pentanedionato (Acetylacetonato) Complexes[22]

The band assignments of the Cr—O stretching modes of *tris*(acetylacetonato)chromium(III) have been a subject of controversy. Originally, *Nakamoto et al.*[23] assigned the bands at 459 and 307 cm^{-1} (calculated) to these modes based on normal coordinate analysis of the 1:1 (metal/ligand) model. *Gillard et al.*[24] extended the measurement down to 55 cm^{-1} and assigned two bands at 459 and 355 cm^{-1} to the Cr—O stretching modes. On the other hand, *Pinchas et al.*[3] assigned the 592 cm^{-1} band to the pure Cr—O stretching and the 456 cm^{-1} band to the C—CH_3 bending coupled with the Cr—O stretching mode since the former gave the largest isotopic shift (19 cm^{-1}) by ^{16}O-^{18}O substitution of the ligand. In order to solve this controversy, we have compared the infrared spectra of $^{50}Cr(acac)_3$ and its ^{53}Cr analog. As is seen in Fig. 3 and Table 6, the observed isotopic shift of the 592 cm^{-1} band (0.7 cm^{-1}) is much smaller than those of the 459 and 335 cm^{-1} bands (3.0 to 3.9 cm^{-1}). Thus, it is most reasonable to assign the latter two bands to the Cr—O stretching modes, and the former band at 592 cm^{-1} to a ring deformation in which the oxygen atom is displaced appreciably.

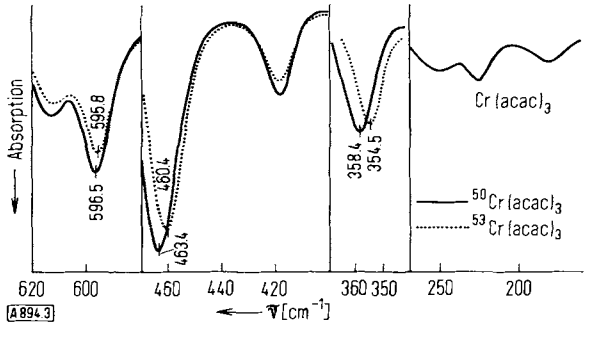


Fig. 3. Far-infrared spectra of $^{50}Cr(acac)_3$ and its ^{53}Cr analog.

Recently, *Mikami et al.*[25] carried out a rigorous normal coordinate analysis on $Fe(acac)_3$. In agreement with our metal isotope study, their results show that the 592 cm^{-1} band is due to an out-of-plane ring deformation and the bands at 459 and 355 cm^{-1} are due to the Cr—O stretching modes. As stated before, the band shifts due to isotopic substitution of the α-atom of the ligand must be interpreted with caution since the metal-ligand stretching as well as ligand vibrations involving the motion of the α-atom are shifted by such substitution.

5. Complexes of 2,2′-Bipyridyl and 1,10-Phenanthroline[26,27]

The assignments of the metal-ligand vibrations of *tris*-complexes of 2,2′-bipyridyl (bipy) and 1,10-phenanthroline (phen) have been controversial. Originally, *Inskeep*[28] assigned the M—N stretching bands of tris-(bipy) complexes of Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} in the 300—260 cm^{-1} region by assuming that the highest frequency band which is absent in the free ligand is the M—N stretching vibration. On the other hand, *Clark* and *Williams*[29] assigned these bands to ligand vibrations and concluded that no bands above 200 cm^{-1} can be assigned to the M—N stretching modes. In order to solve this controversy, we have carried out an extensive study on the far-infrared spectra of these and many other bipyridyl complexes by using the metal

Table 6. Observed frequencies, band assignments and isotopic shifts for $Cr(acac)_3$ (cm^{-1}).

Nakamoto, et al. [23]	*Pinchas, et al.* [3]		Present Work [22]		*Mikami, et al.* [25]
		Δν̃ [a]	^{50}Cr	Δν̃ [b]	
778, 772 π(CH)	801, 766 π(CH)		791.5	0.0	
			776.0	0.0	π(CH)
			772.0	0.0	
667, ring + ν(Cr—O)	678, ring + ν(CrO)	11	681.0	0.5	π(ring)
658, δ(CR) + ν(Cr—O)	661, π	3	659.5	0.0	π(ring)
609, 594 π?			613.2	1.0	ring + ν(Cr—O)
	592, ν(Cr—O)	19	596.5	0.7	π(ring)
459, ν(CrO)	456, δ(CR) + ν(CrO)	5	463.4	3.0	ν(Cr—O) + ν(CR)
416, π?	416, δ(OCrO)	8	417.8	0.0	ring
(373) [d], ring					
(207) [d], ν(Cr—O)			358.4	3.9	ν(Cr—O)
(277) [d], δ(CR)			250.0 [c]	—	
(202) [d], ring			224.0 [c]	—	
			179.0 [c]	—	

[a] $\tilde{\nu}(^{16}O) - \tilde{\nu}(^{18}O)$.
[b] $\tilde{\nu}(^{50}Cr) - \tilde{\nu}(^{53}Cr)$.
[c] Cr natural abundance. The spectra of the complexes containing pure metal isotopes were not obtained below 300 cm^{-1} because the amount of the sample available was not sufficient to run the Nujol mull spectrum on our instrument.
[d] Calculated frequencies.
Abbreviations: ν, stretching; π, out-of-plane bending; ring, in-plane ring deformation.

isotope method[26,27]. The M—N stretching frequencies thus determined are listed in Table 7 together with their electronic configurations and magnetic moments.

Table 7. Electronic configuration, magnetic moment and M—N stretching frequencies of tris(bipyridyl) complexes.

Metal	Electronic Configuration	Magnetic Moment [μ_B]	M—N Stretching Frequencies [cm^{-1}]
Cr^{III}	$(t_{2g})^3$	3.78	385, 349
Cr^{II}	$(t_{2g})^4$	2.9	351, 343
Cr^{I}	$(t_{2g})^5$	2.0	371, 343
Mn^{II}	$(t_{2g})^3(e_g)^2$	5.95	224, 191
Fe^{III}	$(t_{2g})^5$		384, 367
Cr^{0}	$(t_{2g})^6$	0	382, 308
Fe^{II}	$(t_{2g})^6$	0	386, 376
Co^{III}	$(t_{2g})^6$	0	378, 370 [a]
Mn^{0}	$(t_{2g})^5(e_g)^2$	4.10	258, 227
Co^{II}	$(t_{2g})^5(e_g)^2$	4.85	266, 228
Mn^{-I}	$(t_{2g})^6(e_g)^2$	3.71	235, 184
Co^{I}	$(t_{2g})^6(e_g)^2$	3.3	244, 194
Ni^{II}	$(t_{2g})^6(e_g)^2$	3.1	282, 258
Co^{0}	$(t_{2g})^6(e_g)^3$	2.23	280, 257
Cu^{II}	$(t_{2g})^6(e_g)^3$		291, 268
Zn^{II}	$(t_{2g})^6(e_g)^4$	0	230, 184

[a] Values obtained for $[Co(phen)_3](ClO_4)_3$.

As is seen in Table 7, each complex exhibits two M—N stretching bands and their frequencies are governed by the electronic structure of the central metal. All the complexes which have filled or partially filled t_{2g} (bonding) orbitals and empty e_g (anti-bonding) orbitals exhibit the M—N stretching bands in the 390—300 cm^{-1} region, whereas other complexes which have filled or partly filled e_g orbitals exhibit the M—N stretching bands in the 290—180 cm^{-1} region. Thus, a dramatic decrease in the M—N stretching frequency is seen in going from Co^{III} to Co^{II}. However, the M—N stretching frequencies do not change appreciably in the series Cr^{III}, Cr^{II}, Cr^{I} and Cr^{0} although the oxidation state of the metal changes in a wide range. This result may suggest that, as the formal oxidation state is lowered, σ-bonding becomes weaker and π-bonding becomes stronger so that the overall M—N bond strength is approximately constant. If this is the case, there will be considerable interaction between metal dπ orbitals and the anti-bonding ligand π* orbitals so that increasing amounts of electrons of the metal will reside essentially in ligand orbitals as the oxidation state is lowered. Thus, Cr(bipy)$_3$ may be represented as $Cr^{3\delta+}$ $(bipy^{\delta-})_3$ as suggested by *Koenig* and *Herzog*[30] who studied the electronic spectra of these complexes.

6. Complexes of Pyridine[31,32]

Thus far, the application of the metal isotope technique has been limited to infrared spectroscopy. This technique is also useful in assigning the metal-ligand vibrations in Raman spectra. If a molecule contains one metal atom at the center of symmetry, no metal isotope shifts are expected for all Raman-active fundamentals. Therefore, the lack of metal isotope shifts in the Raman spectrum proves the presence of a center of symmetry. As an example, Table 8 lists the Raman frequencies of $SnCl_4(py)_2$ (py = pyridine). The structure of this complex must be *trans*-octahedral since no isotopic shifts have been observed in the Raman spectrum. This is also supported by the fact that the mutual exclusion rule holds between infrared and Raman spectra of this compound (Table 8 and Fig. 4). For the *trans*-octahedral structure, one Sn—Cl and one Sn—N(py) stretching mode should be infrared-active and both bands are expected to show relatively large shifts by ^{116}Sn-^{124}Sn substitution. In agreement with this, two bands at 323.0 and 227.5 cm^{-1} of the ^{116}Sn complex are shifted by *ca.* 4 to 5 cm^{-1} while other bands show almost no shifts by the metal isotope substitution in the infrared spectra. Since the former band is strong and insensitive to the py-[D_5]py substitution, it can be assigned to the Sn—Cl stretching mode. The latter band is relatively weak and sensitive to the ligand deuteration. Hence, this band is assigned to the Sn—N stretching mode. These and other band assignments listed in Table 8 have been confirmed by an approximate normal coordinate analysis on a *trans*-SnX_4Y_2 model where Y (single atom) represents a pyridine ligand[31].

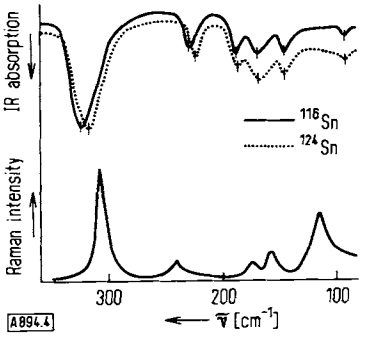


Fig. 4. Low-frequency infrared and Raman spectra of *trans*-$SnCl_4(py)_2$.

Table 8. Vibrational spectra of *trans*-$SnCl_4$(pyridine)$_2$ (cm^{-1}).

$\tilde{\nu}(^{116}Sn)$	Infrared $\Delta\tilde{\nu}$ [a]	$\Delta\tilde{\nu}$ [b]	Raman $\Delta\tilde{\nu}$(Sn)	Assignment
323.0	5.0	0	—	ν(Sn—Cl), E_u
—	—	—	307.0	ν(Sn—Cl), A_{1g}
—	—	—	244.8	ν(Sn—Cl), B_{1g}
227.5	4.0	3	—	ν(Sn—N), A_{2u}
187.0	1.0	9	—	δ(ClSnN), E_u
—	—	—	173.5	δ(ClSnCl), B_{2g}
170	1.0	0	—	δ(ClSnCl), E_u
—	—	—	157.3	ν(Sn—N), A_{1g}
144.5	0	1	—	δ(ClSnN), A_{2u}
—	—	—	116.0	δ(ClSnN), E_g
90	—	—	—	lattice

[a] $\Delta\tilde{\nu} = \tilde{\nu}(^{116}Sn) - \tilde{\nu}(^{124}Sn)$.
[b] $\Delta\tilde{\nu} = \tilde{\nu}$(Sn, py) − $\tilde{\nu}$(Sn, [D_5]py).

In a tetrahedral $ZnX_2(py)_2$ type complex, two Zn—X and two Zn—N(py) stretching modes are infrared as well as Raman active. Furthermore, all these four modes should be sensitive to ^{64}Zn-^{68}Zn substitution. As is seen in Table 9 and Fig. 5, four infrared bands at 329.2, 296.5, 222.4 and 203.9 cm^{-1} of $^{64}ZnCl_2(py)_2$ show relatively large shifts when ^{64}Zn is substituted by ^{68}Zn. The former two bands are strong and show little

shifts by the py-[D_5]py substitution. Therefore, these bands can be assigned to the Zn—Cl stretching modes. The latter two bands are relatively weak and sensitive to the ligand deuteration. Thus, these two bands can be assigned to the Zn—N stretching modes.

Similar results are seen in the Raman spectra of these compounds. In general, the antisymmetric mode is stronger in the infrared and weaker in the Raman spectrum than the symmetric mode. Therefore, the bands at *ca.* 329 and 222 cm^{-1} are assigned to the antisymmetric whereas the bands at *ca.* 297 and 204 cm^{-1} are assigned to the symmetric types[32].

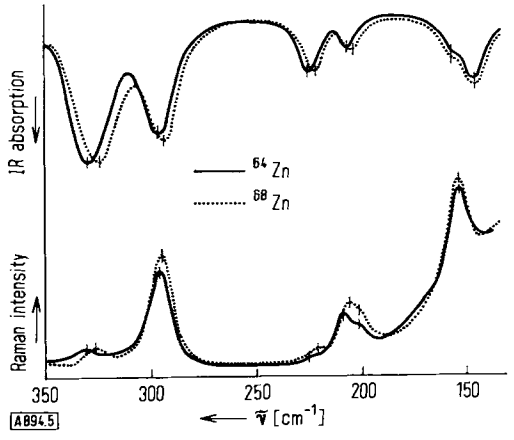


Fig. 5. Low-frequency infrared and Raman spectra of $ZnCl_2(py)_2$.

Table 9. Vibrational spectra of $Zn(pyr)_2Cl_2$ (cm^{-1}).

Infrared			Raman			
$\tilde{\nu}(^{64}Zn)$	$\Delta\tilde{\nu}$ [a]	$\Delta\tilde{\nu}$ [b]	$\tilde{\nu}(^{64}Zn)$	$\Delta\tilde{\nu}$ [a]	$\Delta\tilde{\nu}$ [b]	
329.2	4.8	0.8	330.3	3.9	1.0	ν(Zn—Cl), B_2
296.5	2.4	0.2	294.8	1.3	0.4	ν(Zn—Cl), A_1
222.4	3.6	3.8	224.1	4.4	5.0	ν(Zn—N), B_1
203.9	2.4	4.1	207.6	3.2	4.2	ν(Zn—N), A_1
—	—	—	200	0.0	1.0	δ(ClZnN), A_2
154	— [c]	7	151.2	0.0	6.6	δ(NZnN), A_1
143.3	0.3	4.7	—	—	—	δ(ClZnN), B_1, B_2
109.9	0.0	0.7	—	—	—	δ(ClZnCl), A_1

[a] $\tilde{\nu}(^{64}Zn) - \tilde{\nu}(^{68}Zn)$.
[b] $\tilde{\nu}(py) - \tilde{\nu}([D_5]py)$.
[c] Isotopic shifts were not determined due to poor shape of the band.

7. Ammine Complexes[33]

Theoretically, two metal-nitrogen stretching vibrations (A_1 and F_2) should be Raman-active for tetrahedral (T_d) ammine complexes. The totally symmetric A_1 mode involves no motion of the central metal atom and should thus be independent of the ^{64}Zn-^{68}Zn isotopic substitution. On the other hand, the F_2 mode involves the motion of the central metal atom and should be sensitive to the isotopic substitution. Fig. 6 shows the Raman spectra of crystalline $[^{64}Zn(NH_3)_4]I_2$ and its ^{68}Zn analog in the Zn—N stretching region. It is seen that the 432.0 cm^{-1} band of the ^{64}Zn complex gives a shift of 0.5 cm^{-1} which is within the experimental error, whereas the 412.0 cm^{-1} band gives a large shift of 2.0 cm^{-1}. Thus, it is possible to assign the former to the A_1 and the latter to the F_2 species on the basis of observed isotopic shifts alone. This assignment has also been confirmed by the observation that the 427 cm^{-1} band of an approximately 4.0 M ammonia solution of $[Zn(NH_3)_4]I_2$ is strongly polarized.

Other vibrations such as N—H stretching, NH_3 degenerate and symmetric deformation, and NH_3 rocking modes do not involve the motion of the metal atom and show little shifts by the ^{64}Zn-^{68}Zn substitution. In order to calculate theoretical isotopic shifts, we have carried out a normal coordinate analysis on the whole $[Zn(NH_3)_4]^{2+}$ ion (T_d symmetry). As is seen in Table 10, the results are in good agreement with those observed.

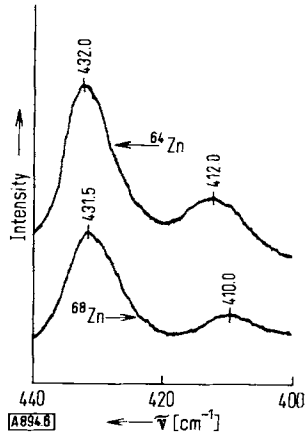


Fig. 6. Low-frequency Raman spectra of $[^{64}Zn(NH_3)_4]I_2$ and its ^{68}Zn analog.

8. Other Complexes

In addition to those complexes listed above, the metal isotope method has been applied to mercaptoalkylamine complexes (Ni^{II} and Pd^{II})[34], allyl-Pd complexes[35] and ferrocene[36]. Recently, this method has also been applied to metal complexes of octaethylporphin (Ni^{II} and Zn^{II}) by *Buerger et al.*[37].

In principle, the metal isotope method is applicable to any inorganic and coordination compounds. Practically, however, its application may be limited by several factors:

1. Pure and stable metal isotopes are available only for certain elements.

2. Some metal isotopes are too expensive even for a small scale synthesis.

3. Some compounds are difficult to prepare on a small scale. This is particularly true if a compound is gaseous or liquid.

Table 10. Comparison of observed Raman and calculated frequencies for the $[Zn(NH_3)_4]^{2+}$ ion (cm^{-1}).

		$[^{64}Zn(NH_3)_4]^{2+}$		$[^{68}Zn(NH_3)_4]^{2+}$		Band assignment
		obs.	calc. [a]	obs.	calc. [a]	
A_1	ν_1	3233	3213.5	3233	3213.5	ν(N—H)
	ν_2	1253	1262.1	1253	1262.1	$\delta_s(NH_3)$
	ν_3	432.0	432.9	431.5	432.9	ν(Zn—N)
E	ν_4	3275	3270.5	3275	3270.5	ν(N—H)
	ν_5	1596	1595.3	1596	1595.3	$\delta_d(NH_3)$
	ν_6	685	680.8	685	680.8	$\rho_r(NH_3)$
	ν_7	156	162.2	155	162.2	δ(NZnN)
F_1	ν_8	—	3270.0	—	3270.0	ν(N—H)
	ν_9	—	1594.8	—	1594.8	$\delta_d(NH_3)$
	ν_{10}	—	678.0	—	678.0	$\rho_r(NH_3)$
F_2	ν_{11}	3275	3270.3	3275	3270.3	ν(N—H)
	ν_{12}	3150	3214.4	3150	3213.4	ν(N—H)
	ν_{13}	1596	1595.2	1596	1595.2	$\delta_d(NH_3)$
	ν_{14}	1239	1259.5	1239	1259.5	$\delta_s(NH_3)$
	ν_{15}	685	686.0	685	686.0	$\rho_r(NH_3)$
	ν_{16}	412.0	410.1	410.0	407.6	ν(Zn—N)
	ν_{17}	156	158.8	155	157.4	δ(NZnN)

[a] The molecular parameters used were: Zn—N, 2.01 Å; N—H, 1.00 Å. All the angles were taken to be tetrahedral. The Urey-Bradley force constants used were: K (stretching), 5.66 (N—H) and 0.54 (Zn—N); H (bending), 0.018 (NZnN), 0.048 (ZnNH) and 0.43 (HNH); F (repulsive), 0.19 (N...N), 0.24 (Z...H) and 0.09 (H...H), all in units of mdyn/Å.

4. Observed shifts may be too small for complexes containing heavy elements such as Os, Pt and Pb.

The work described above was mainly supported by the Petroleum Research Fund administered by the American Chemical Society (ACS-PRF-3318-C3,5) and the U.S. Army Research Office (DA-ARO-D-31-124-G1130). The author wishes to express his thanks to his colleagues, former students and postdoctoral fellows for their contribution to this project.

Received: January 4, 1972 [A 894 IE]
German version: Angew. Chem. *84*, 755 (1972)

[1] *L. Sacconi, A. Sabatini*, and *P. Gans*, Inorg. Chem. *3*, 1772 (1964).

[2] *P. X. Armendarez* and *K. Nakamoto*, Inorg. Chem. *5*, 796 (1966).

[3] *S. Pinchas, B. L. Silver*, and *I. Laulicht*, J. Chem. Phys. *46*, 1506 (1967).

[4] *K. Nakamoto, K. Shobatake*, and *B. Hutchinson*, Chem. Commun. *1969*, 1451.

[5] *K. Shobatake* and *K. Nakamoto*, J. Amer. Chem. Soc. *92*, 3332 (1970).

[6] *P. L. Goggin* and *R. J. Goodfellow*, J. Chem. Soc. *A 1966*, 1462.

[7] *G. E. Coates* and *C. Parkin*, J. Chem. Soc. *1963*, 421.

[8] *D. M. Adams* and *P. J. Chandler*, Chem. Commun. *1966*, 69.

[9] *R. J. Goodfellow, P. L. Goggin*, and *L. M. Venanzi*, J. Chem. Soc. *A 1967*, 1897.

[10] *R. J. Goodfellow, P. L. Goggin*, and *D. A. Duddell*, J. Chem. Soc. *A 1968*, 504.

[11] *P. J. Park* and *P. J. Hendra*, Spectrochim. Acta *25 A*, 227, 909 (1969).

[12] *J. H. S. Green*, Spectrochim. Acta *24 A*, 137 (1968).

[13] *C. Udovich, J. Takemoto*, and *K. Nakamoto*, J. Coord. Chem. *1*, 89 (1971).

[14] *P. M. Boorman* and *A. J. Carty*, Inorg. Nucl. Chem. Lett. *4*, 101 (1968).

[15] *R. G. Hayter* and *F. S. Humic*, Inorg. Chem. *4*, 1701 (1965).

[16] *J. T. Wang, C. Udovich, K. Nakamoto, A. Quattrochi*, and *J. R. Ferraro*, Inorg. Chem. *9*, 2675 (1970).

[17] *N. Ohkaku* and *K. Nakamoto*, Inorg. Chem. *10*, 798 (1971).

[18] *R. C. Hoy* and *R. H. Morris*, Acta Crystallogr. *22*, 476 (1967).

[19] *F. Kanakubo, K. Ogawa*, and *I. Nitta*, Bull. Chem. Soc. Japan *36*, 422 (1963).

[20] *G. J. Palenik*, Acta. Crystallogr. *17*, 687 (1964).

[21] *W. Matoush* and *F. Basolo*, J. Amer. Chem. Soc. *75*, 5663 (1953).

[22] *K. Nakamoto, C. Udovich*, and *J. Takemoto*, J. Amer. Chem. Soc. *92*, 3973 (1970).

[23] *K. Nakamoto, P. J. McCarthy, A. Ruby*, and *A. E. Martell*, J. Amer. Chem. Soc. *83*, 1066 (1961).

[24] *R. D. Gilland, H. G. Silver*, and *J. L. Wood*, Spectrochim. Acta. *20*, *63 (1964)*.

[25] *M. Mikami, I. Nakagawa*, and *T. Shimanouchi*, Spectrochim. Acta *23 A*, 1037 (1967).

[26] *B. Hutchinson, J. Takemoto*, and *K. Nakamoto*, J. Amer. Chem. Soc. *92*, 3335 (1970).

[27] *J. Takemoto, B. Hutchinson*, and *K. Nakamoto*, Chem. Commun. *1971*, 1007.

[28] *R. G. Inskeep*, J. Inorg. Nucl. Chem. *24*, 763 (1962).

[29] *R. J. H. Clark* and *C. S. Williams*, Spectrochim. Acta *23 A*, 1055 (1967).

[30] *E. Koenig* and *S. Herzog*, J. Inorg. Nucl. Chem. *32*, 585 (1970).

[31] *N. Ohkaku* and *K. Nakamoto*, to be published.

[32] *Y. Saito* and *K. Nakamoto*, to be published.

[33] *J. Takemoto* and *K. Nakamoto*, Chem. Commun. *1970*, 1017; *K. Nakamoto, J. Takemoto*, and *T. L. Chow*, Appl. Spectry. *25*, 352 (1971).

[34] *C. W. Schläpfer* and *K. Nakamoto*, to be published.

[35] *K. Shobatake* and *K. Nakamoto*, J. Amer. Chem. Soc. *92*, 3339 (1970).

[36] *K. Nakamoto, C. Udovich, J. R. Ferraro*, and *A. Quattrochi*, Appl. Spectry. *24*, 606 (1970).

[37] *H. Buerger, K. Burczyk*, and *J. H. Fuhrhop*, Tetrahedron *27*, 3257 (1971).

Shift Reagents in NMR Spectroscopy

By Reinhard von Ammon and R. Dieter Fischer[*]

The number of possible applications of NMR spectroscopy has rapidly increased during the past few years. New fields of applications have been opened by the development of supraconducting solenoids and various spin-decoupling techniques and by the method of "pulsed Fourier transform NMR-spectroscopy". These methods originate mainly from progress in instrumentation. Recently, another "technique" has been introduced into NMR spectroscopy, which—principally on the basis of chemical and spectroscopic experience—is much less expensive but nevertheless useful. The basic principles, background, and most important applications of this method, known as the "NMR-shift-reagent technique", form the subject of this paper.

1. Introduction

An NMR-spectrum can be analyzed the more easily the more pronounced the chemical shifts of the nuclei of a sample are in comparison to the spin-spin coupling effects. The ideal case is a first order spectrum where the shift difference of the multiplet centers are large compared to the components of the multiplets. Possible means of simplifying spectra are spin decoupling[1] or—in certain cases—the introduction of suitable isotopes into the molecule under investigation. Another way is the variation of the magnetic field acting on the various nuclear magnets. If we discern between increasing the homogeneous, external magnetic field of the spectrometer and superimposing the "primary field" by additional internal "secondary fields", two alternative possibilities are evident.

A consequence of choosing the first possibility is the aim of commercial suppliers to produce NMR spectrometers with higher field strengths and improved resolution. The present status has—by means of supraconducting solenoids—reached field strengths corresponding to proton resonance frequencies of approximately 300 MHz.

The development of the other alternative is based upon experience of the chemist with materials whose magnetic properties are strongly anisotropic[*]. An example is the ring current effect causing chemically not very different

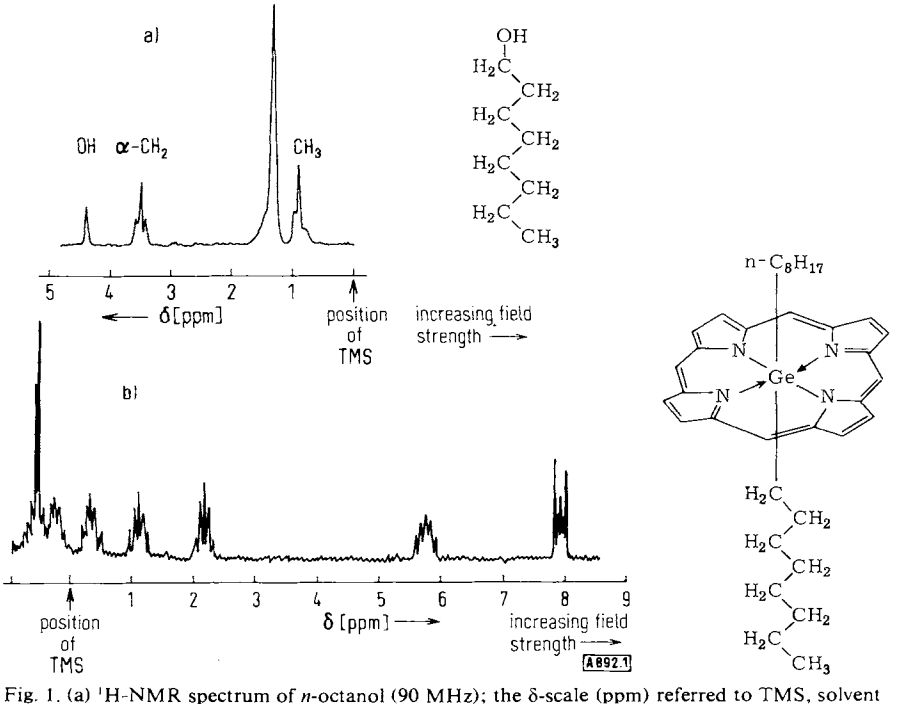


Fig. 1. (a) ^{1}H-NMR spectrum of *n*-octanol (90 MHz); the δ-scale (ppm) referred to TMS, solvent CCl_4; (b) ^{1}H-NMR spectrum (100 MHz) of the *n*-octyl part of dioctylgermanium-porphin [2]; δ-scale referred to TMS, solvent $CDCl_3$.

protons to exhibit a large separation of their resonance lines. Thus, in the diamagnetic porphin ring of the compound shown in Fig. 1, the primary field induces

[*] Dr. R. v. Ammon
Institut für Heisse Chemie des Kernforschungszentrums
75 Karlsruhe, Postfach 3640 (Germany)
Prof. Dr. R. D. Fischer
Institut für Anorganische Chemie der Universität Erlangen-Nürnberg
852 Erlangen, Egerlandstrasse (Germany)

[*] A secondary field is anisotropic if its magnitude and direction change with the direction of the primary field.

an additional anisotropic field which acts very differently upon the methylene proton pairs of the two axially coordinated *n*-octyl chains[2]. Similar signal spreadings are caused by the magnetic anisotropy of the phthalocyanine (= Pc) system in adducts of the type Fe(II)Pc·2S (S = amines *etc.*)[126] or by the weakly paramagnetic uranyl ion[3].

Any perceptible change of the structure of the substrate during the adduct formation is, however, to be avoided.

The molar ratio [S]:[R] does not necessarily have to be 1:1; it is important, however, that the mean lifetime of the adduct S—R is sufficiently small on the NMR time scale that only *one* averaged spectrum is observed for S and S—R.

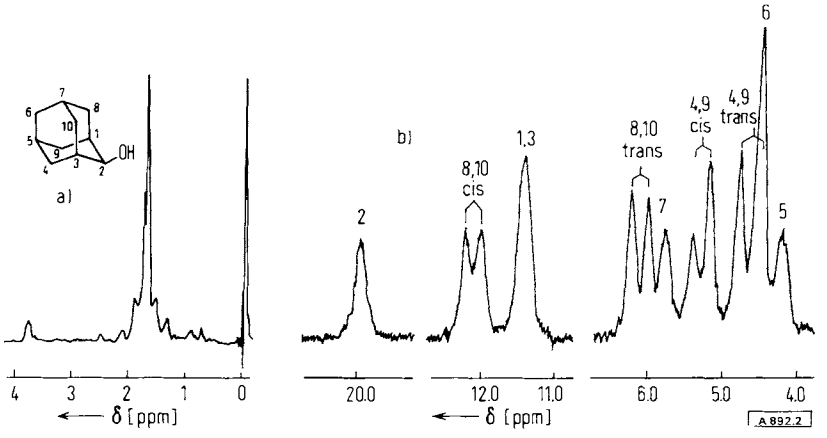


Fig. 2. ^{1}H-NMR spectra (60 MHz) of 2-adamantanol (a) before and (b) after addition of $Eu(dpm)_3$ as shift reagent; molar ratio shift reagent: substrate = 0.67, solvent $CDCl_3$ [4].

Much stronger secondary fields and therefore a still more pronounced expansion of the spectra can be induced, however, in paramagnetic systems with at least one unpaired electron. Fig. 2 illustrates the changes in the ^{1}H-NMR spectrum of adamantanol caused by the interaction of this substrate with the paramagnetic "shift reagent" tris(dipivalomethanato)europium(III), $Eu(dpm)_3$ (cf. Fig. 7), a system with six unpaired 4f electrons[4].

A further illustration is the ^{1}H-NMR spectrum of (−)-nicotine recorded at 60[5] and 220 MHz[6] in the absence (Fig. 3a and 3b) and at 90 MHz (Fig. 3c) in the presence of the organometallic shift reagent tricyclopentadienylpraseodymium(III)[7].

Whereas the enhancement of the external primary field causes a linear expansion of the spectra leaving the relative chemical shifts (in ppm) unchanged, the internal secondary field may also change the sequence of the signals. Since the strength of this field decreases with increasing distance from the origin of the magnetic field lines, "geometric shifts" (see below) become the ordering principle of the spectrum instead of the familiar chemical shifts in all cases where the influence of the secondary field is strong.

One may speak of an NMR shift reagent (R) if the NMR spectrum of a substance S is simplified (with respect to spectral analysis) through interaction with the reagent. The interaction between S and R should be prompted by addition of the reagent to the sample in the sense of at least one of the three equilibria (1a)—(1c).

$$S^{(1)} + R^{(1)} \rightleftharpoons S^{(1)}R^{(1)} \qquad (1a)^{[*]}$$

$$S^{(1)}R^{(1)} + S^{(2)} \rightleftharpoons S^{(2)}R^{(1)} + S^{(1)} \qquad (1b)^{[*]}$$

$$S^{(1)}R^{(1)} + R^{(2)} \rightleftharpoons S^{(1)}R^{(2)} + R^{(1)} \qquad (1c)^{[*]}$$

[*] For simplicity only 1:1 adducts are considered at the monent (cf. Section 3.2.1.2).

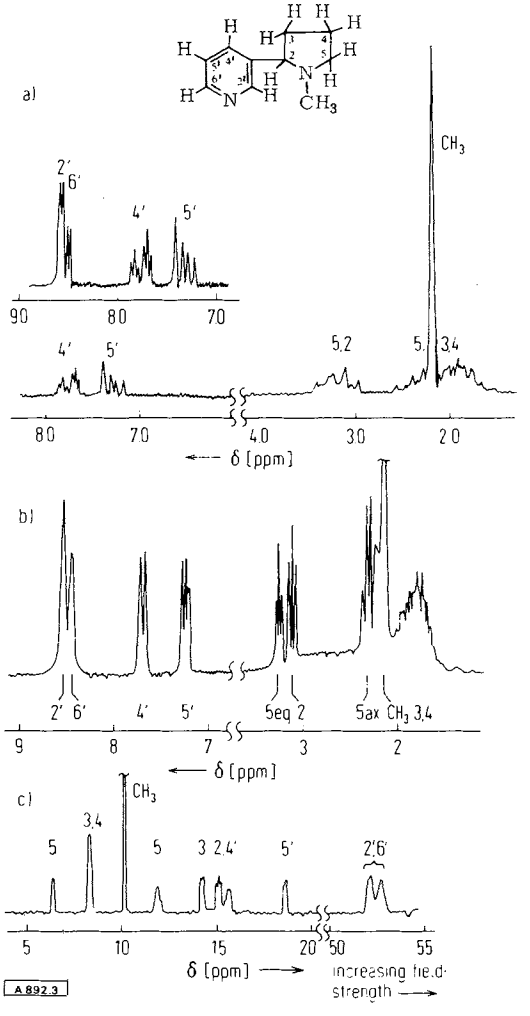


Fig. 3. ^{1}H-NMR spectra of (−)-nicotine, recorded under various conditions: (a) 60 MHz in CCl_4 [5]; (b) 220 MHz in $CDCl_3$ referred to TMS [6]; (c) 90 MHz in D_8-toluene after adduct formation with an equimolar amount of $Pr(C_5H_5)_3$; δ-scale referred to C_6H_6 [7].

2. Theory

Although the principle of the shift reagent technique has been known for some time and, in several cases, has been applied before[8-11,155], it was not until 1969 that *Hinckley*[12] initiated the systematic development of this branch of NMR spectroscopy[13,14,127,128,158,160]. The following survey of the theoretical background, which has been treated elsewhere in several detailed articles[15-21], concentrates on the most important aspects necessary for an understanding of the quantitative correlations between the properties of a shift reagent, the substrate, and the observed spectra.

2.1. The "Isotropic" Shift

The contribution Δ_i^{iso} of an internal secondary field to the resonance frequencies δ_i of a substance S within the adduct S—R in solution is experimentally obtained as the difference of the resonance frequencies under the influence of and without the secondary field:

$$\Delta_i^{iso} = \delta_i(S—R) - \delta_i(S) \tag{2}$$

Although the internal secondary field is practically always anisotropic, Δ_i^{iso} is generally called the "isotropic" shift, because it is the averaged result over all orientations of a molecule moving freely in solution. In the case of a paramagnetic shift reagent the term "paramagnetic shift" is also used.

If the shift reagent does not contain unpaired electrons, Δ_i^{iso} is identical with the dipolar or "pseudocontact" term Δ_i^{dip}, which takes into account all magnetic dipolar interactions of the magnetic moment of the i^{th} nucleus with the anisotropic magnetic field of the valence electron shell of the shift reagent. If unpaired electrons are present, Δ_i^{iso} is composed of the dipolar contribution and a (Fermi-)contact term Δ_i^{con} taking into account the influence of a possible spin delocalization within the adduct S—R:

$$\Delta_i^{iso} \equiv \Delta_i^{para} = \Delta_i^{dip} + \Delta_i^{con} \tag{3}$$

2.1.1. Magnetic Dipolar Interactions

It often seems justified to relate the internal secondary field of a molecule in solution for any orientation relative to the direction of the external primary field to a magnetic "point dipole" of well defined position within the molecule. (The center of this point dipole is generally at the nucleus of a paramagnetic transition metal ion, but not necessarily at the center of a cyclic π-electron system.) Δ_i^{dip} can then be expressed as a function of the internal molecular coordinates r_i, ϑ_i and ω_i (see Fig. 4) and the three principal components χ_x, χ_y and χ_z of the measurable magnetic susceptibility[23,24] (N_L = Loschmidt's constant).

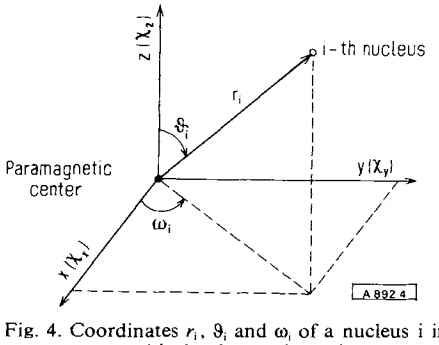


Fig. 4. Coordinates r_i, ϑ_i and ω_i of a nucleus i in the coordinate system x, y, z with the three principal components χ_x, χ_y, and χ_z of the magnetic susceptibility.

$$\Delta_i^{dip} = -D'G_i - D''G_i' \tag{4}$$

$$D' = \frac{1}{3N_L}(\chi_z - 1/2\chi_x - 1/2\chi_y) \quad (5a); \qquad D'' = \frac{1}{2N_L}(\chi_x - \chi_y) \tag{5b}$$

$$G_i = \frac{3\cos^2\vartheta_i - 1}{r_i^3} \quad (6a); \qquad G_i' = \frac{\sin^2\vartheta_i \cos 2\omega_i}{r_i^3} \tag{6b}$$

The equations (5a)—(6b) are valid for certain types of relaxation conditions which are particularly frequently encountered[22].

Particularly important for the shift reagent technique is the special case of an *axially* symmetric secondary field, defined by: $\chi_z \equiv \chi_\parallel$; $\chi_x = \chi_y \equiv \chi_\perp$.

This case applies, for instance, to metal complexes with axially symmetric ligand fields, but also to the example in Fig. 1b. Since $D'' = 0$, equation (4) reduces to

$$\Delta_i^{dip}(ax) = -D'G_i \tag{7}$$

Contrary to the non-axially symmetric case the $\Delta_i^{dip}(ax)$-values of a system are directly proportional to the corresponding "geometric factors" G_i:

$$\Delta_1^{dip} : \Delta_2^{dip} : \Delta_3^{dip} \; etc. = G_1 : G_2 : G_3 \; etc. \tag{8}$$

Unfortunately, the rigorously axially symmetric case is rarely met in practice[161,162]. However, in a number of S—R systems with lower symmetry the second term in equation (4) should average to zero because of the rotations of S relative to R which are often very fast on the NMR time scale. It is, nevertheless, most essential that—in accordance with equations (4) and (7)—Δ_i^{dip} is proportional to r_i^{-3} in all cases (cf. Section 4.1).

For the case of a non-axially symmetric complex where the substrate rotates freely around an axis running through the metal ion, the following equation has been proposed[162]:

$$\Delta^{dip} = \frac{1}{2r^3}[-D'(3\cos^2\alpha - 1) - D''\sin^2\alpha\cos 2\beta](3\cos^2\gamma - 1) \tag{9}$$

The angle γ is included by the radius vector r_i (Fig. 4) and the rotation axis of the substrate; α and β refer to the position of the rotation axis in analogy to ϑ and ω.

The spectral shifting potential of a shift reagent is determined by its anisotropy parameters D' and D'', which are usually temperature dependent[163]. In the series of axially symmetric, organometallic shift reagents of the type $(C_5H_5)_3Ln(III)$[27,144] with Ln = La through Lu, the parameter $D'(ax)$ is proportional to the para-

magnetic shift Δ_j^{para} of a specified proton of the substrate S. If S = cyclohexylisonitrile, the variation of $D'(ax) = -\Delta_\delta^{para}/G_\delta$ is quite pronounced (Fig. 5).

A similar periodicity has been found for a series of homologous chelate adducts $Ln(dpm)_3S_2$[14]. The same very characteristic dependence of Δ^{dip} on the number of f electrons of Ln was confirmed with the magnetic anisotropy parameters very recently determined for the crystalline adducts[162]. It is remarkable that, according to available data for homologous series of lanthanoid complexes, the ions of each of the three "triads" [Ce, Pr, Nd], [Tb, Dy, Ho], and [Er, Tm, Yb] induce dipolar shifts of the same sign[28]. *Bleaney et al.*[163] have just recently given a theoretical explanation for this periodicity.

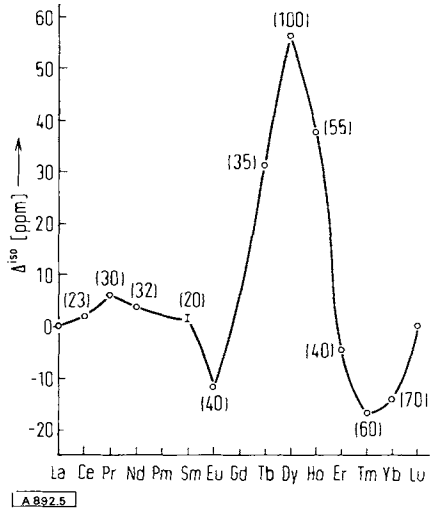


Fig. 5. Isotropic shifts (in ppm) of the C_6H_{11}-protons in δ-position of the adducts between cyclohexylisonitrile and the lanthanoid(III)-tricyclopentadienides, $Ln(C_5H_5)_3$ [7]. Solvent D_8-toluene; $T = 302$ °K, 90 MHz. The linewidths at half-height (Hz) are given in parentheses.

The sign of Δ_i^{dip} can often be predicted more easily than its absolute magnitude: thus, in the example of Fig. 1b we have $\chi_{||}, \chi_\perp < 0$ (diamagnetism) and in the case of the UO_2^{2+} ion $\chi_\perp > 0$ (temperature-independent paramagnetism). Further, $G_i > 0$ and $G_i < 0$, respectively, for the two examples. If $\chi_{ii} < \chi_\perp$, then, according to equations (5a), (6a) and (7), Δ_i^{dip} has a positive sign in the first case (shift to high field) and a negative sign in the second case. Fairly reliable dipolar shifts of protons with known steric positions can be read from modified contour diagrams of the magnetic field of the type shown in Fig. 6 for these two examples.

2.1.2. Contact Interactions

The contact term Δ_i^{con} in equation (3) is proportional to the temperature dependent mean value of the spin polarization $\langle S \rangle$ at the paramagnetic central ion and to a hyperfine coupling parameter A_i (equation (10)).

$$\Delta_i^{con} = K \cdot A_i \cdot \langle S \rangle \qquad (10)$$

A_i is proportional to the transferred unpaired spin density at the nucleus $(r_i, \vartheta_i, \omega_i)$. Equation (10) becomes the more familiar equation (11) in the case of an isotropic "spin-only" system:

$$\Delta_i^{con} = -\frac{\gamma_e}{\gamma_N} A_i \cdot \frac{g_e \beta S(S+1)}{3kT} \qquad (11)$$

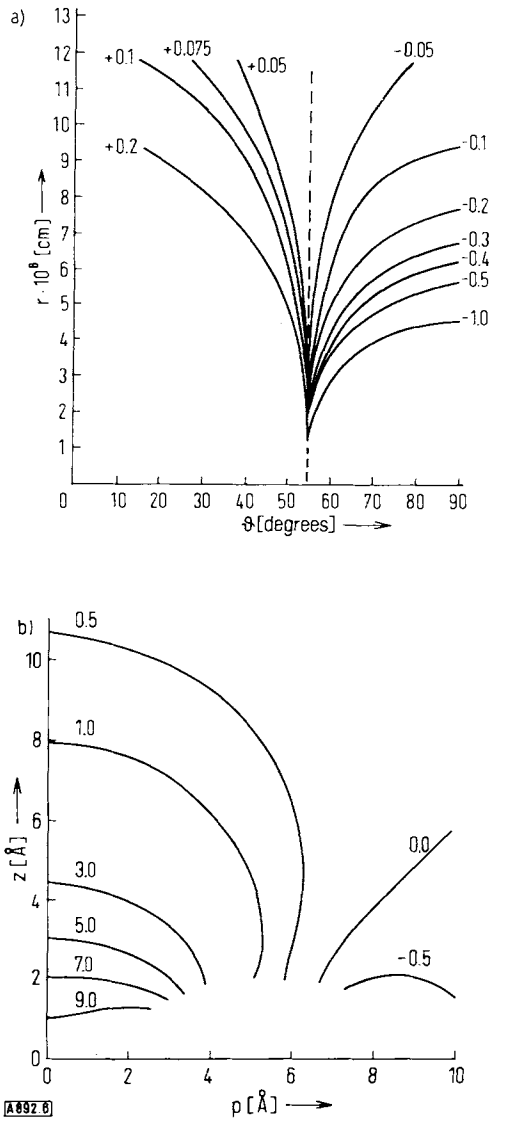


Fig. 6. (a) The anisotropic magnetic field in the vicinity of the UO_2^{2+} ion, expressed by lines of equal isotropic shift (in ppm) ("isoshielding lines") induced on protons in the coordination sphere of the UO_2^{2+} ion [3]. r = distance vector U—H; ϑ = angle formed by r and the principal axis of symmetry O—U—O; the number next to the curves indicate the isotropic shifts Δ^{iso} (ppm). The dashed vertical line corresponds to $\Delta^{iso} = 0$. (b) "Isoshielding lines" (in ppm) of protons under the influence of the anisotropic field of the ring current induced by the π-system of phthalocyanine [126]. Ordinate: distance from the ring center along the fourfold axis; abscissa: distance from the ring center in the ring plane.

In this equation γ_e and γ_N are the magnetogyric ratios of electron and nucleus, respectively; S is the spin quantum number, β the Bohr magneton, and k Boltzmann's constant. In anisotropic systems A_i includes all possible orientations of the molecule tumbling freely in solution, in complete analogy to the parameters D' and D''.

The calculation of A_i is even more difficult than the calculation of D' and D'' [26]. Since there is no means of correlating the contact shift with geometric coordinates, as was shown for the pseudocontact shift, and since a reliable factorization of the experimental shift into the dipolar and contact contributions is not possible in many cases, noticeable contact contributions in the shift reagent technique usually prevent quantitative structural evaluations.

Paramagnetic lanthanoid complexes fulfil the requirement of negligible contact interactions particularly well [60], because the radial extension of the 4f orbitals is exceedingly small. According to experience, however, it is safe to neglect contact contributions even in 4f-systems only if at least three atoms (*i. e.* four bonds) are situated between the nucleus under investigation and the paramagnetic center. From extensive ^{17}O- and ^{1}H-NMR studies of lanthanoid aquo-complexes [29] it was concluded that $\Delta_O^{con} \gg \Delta_O^{dip}$ holds for the O-atoms in the first coordination sphere, whereas the overall shift Δ_H^{iso} of the neighboring H-atoms still contains a contact contribution of at most 60%.

2.2. Dynamic Effects

The equations given in Section 2.1 allow quantitative predictions as to magnitude and sign of the isotropic shifts; they do not, however, contain a term including the linewidth allowing predictions referring to the chances of a signal to be observed. Unfortunately, drastic signal broadenings have to be expected frequently in paramagnetic samples containing unpaired electrons. These may be caused not only by intramolecular spin delocalization, but also by time-dependent intermolecular interactions [19].

These undesirable line broadenings may be partially compensated for if the mean lifetime of the electronic spin states (electron spin-lattice relaxation time T_{1e}) is drastically reduced with respect to the correlation time for the thermal motion of the molecules. Besides extremely low T_{1e} values, rapid changes of the ligand field at the paramagnetic metal ion can also give rise to narrow linewidths.

The term T_{1e}^{-1} clearly corresponds to the rate of transforming the excitation energy of a discrete spin level into thermal energy of the surrounding "lattice" (*i.e.* coordination + solvation sphere). T_{1e}^{-1} increases with increasing temperature and with the strength of the external magnetic field, and, at the same time, with increasing magnitude of the spin-orbit coupling constant, but with decreasing energetic difference between the electronic ground state and the next excited (= ligand field) states. The last two requirements are again fulfilled particularly well by systems containing unpaired 4f or 5f electrons.

Apart from the spin-only system Gd^{3+} (f^7), lanthanoid and actinoid complexes actually exhibit NMR linewidths between a few Hz and several hundred Hz [14, 30, 165]. According to systematic study of the linewidths in the spectra of the adducts $Ln(dpm)_3S_x$ by *Horrocks* [14] and according to general experience complexes of Eu and Pr exhibit the sharpest signals. On the other hand, the signals of most d^n-transition metal complexes are sufficiently narrow only in exceptional cases (Co^{2+} and Ni^{2+}). The detection of the NMR signals of paramagnetic organic radicals is usually prevented by their excessive linewidths.

Chemically, the lifetime of the relevant electronic states can also be reduced by rapid reactions of type (1a)—(1c). Signal narrowing is also to be expected if the adduct S—R is able to alternate between several conformations $(S—R)^I$, $(S—R)^{II}$... *etc.*

3. Systematic Approach to Shift Reagents

3.1. General Requirements

An effective and versatile shift reagent should fulfil at least four requirements:

1. Optimal shifting potential combined with minimal signal broadening effect;

2. ability to interact with a great number of substrates, *i.e.* marked acidic or basic properties;

3. sufficient solubility;

4. absence of interfering absorptions in the usual range of substrate spectra.

Ideal, universally applicable shift reagents cannot be realized: Lewis-acid shift reagents are effective only with basic substrates (and *vice versa*). High reactivity (for instance towards extremely weak bases) is not compatible with the chemical stability required at the same time. A high reactivity even excludes the use of polar solvents, since their functional groups would compete with the substrate.

Requirements 1 to 4 do not yet take into consideration that quantitative information about the molecular structure or the conformational behavior of a substrate is sometimes desirable. With regard to such studies the following requirements should also be fulfilled:

5. Pseudocontact should dominate over Fermi-contact interactions;

6. the secondary fields should have axial symmetry, and the point-dipole approximation should be valid;

7. the adduct S—R should be conformationally uniform (whereas the substrate itself may have several conformations);

8. a straightforward temperature dependence of the isotropic shifts (*e. g.* temperature-independence or linear variation of Δ^{iso} with $1/T$).

Whereas postulates 5 to 7 are the prerequisites for the applicability of equations (4) to (8), postulate 8 is particularly advantageous for conformational studies within wide temperature ranges [27]. This last point, however, has rarely been found to be true [97, 123, 124, 152].

3.2. Types of Shift Reagents Applied

3.2.1. Coordination Compounds Containing Unpaired d of f Electrons

Although numerous examples of the application of d^n-complexes as shift reagents have become known[8-11,34-38,129-131,155], coordination compounds of the rare earth elements have more favorable properties.

The special features of the 4f radial functions[39] of these elements result in an optimal fulfilment of requirements 1 and 5. In addition, the characteristic flexibility of the rare earth ions with regard to their preferential coordination number[146] ensures the spontaneous formation of sufficiently stable adducts.

With respect to their various applications and their chemical nature we classify shift reagents containing unpaired d or f electrons as typical salts, chelates, and organometallics.

3.2.1.1. Salts

Most representatives of this class are simple salts of transition element or lanthanoid ions forming solvated ions—mainly in aqueous solution—which are capable of additionally coordinating a polar substrate (cf. Table 1). Shift reagents of this type are suited only in rare cases to quantitative spectral analyses because of inadequate fulfilment of postulations 1, 6, and 7[115,156]. Such reagents had already been employed for more than a decade[8] before *Hinckley*'s first paper[12].

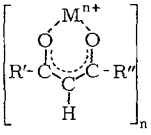
Table 1. Some examples for the application of shift reagents of the salt type to studies on substrates in aqueous solution.

Shift reagent	Substrate	Ref.
$CoCl_2$	*n*-propanol	[8]
$CuCl_2$	carnosine	[40]
$(FeNH_4)_2(SO_4)_3$	amino acids	[41]
$Eu(NO_3)_3 \cdot 6D_2O$	organophosphorus compounds	[42]
$Ln(ClO_4)_3 \cdot 6H_2O$ (Ln = Pr, Eu)	amino acids, carboxylic acids	[43]
$EuCl_3 \cdot 6H_2O$	carboxylic acids	[44]
$EuCl_3$	ribose 5-phosphate	[115]
$EuCl_3$	mononucleotides	[156]

3.2.1.2. Chelates

This category comprises the systems best known and most widely used, including also *Hinckley*'s original reagent $Eu(dpm)_3 \cdot 2pyr$[12]. All representatives of this class (Fig. 7) constitute β-diketonato complexes of the general formula $L_m MX_n$ (L = chelate ligand). In the case of transition metal complexes L_2M at best two coordination sites are available for the substrate. Lanthanoid complexes L_3MX_n with $n = 0$ provide several free, acidic coordination sites. Because of the variability of the coordination number of rare earth elements[146,147], complexes with $n = 1$ or 2 may still exhibit at least one free coordination site, even in the case of *Hinckley*'s reagent (M = Eu, X = pyridine, $n = 2$, formal coordination number: 8).

Voluminous substituents of simple structure are preferably chosen as substituents R (Fig. 7), *e.g.* CH_3, C_6H_5, n-C_3F_7 or $C(CH_3)_3$. Thus postulations 3, 4, and 7 are accounted for.



A 892 7

dpm or tmhd: R' = R'' = $-C(CH_3)_3$

fod: R' = $-C(CH_3)_3$, R'' = $-CF_2-CF_2-CF_3$

Fig. 7. General structure of shift reagents of the chelate type.

The accumulation of voluminous substituents R should limit the number of possible conformations of the shift reagent, especially if $m = 3$[45]. It also diminishes the affinity of the reagent toward water, which, if absorbed, decreases its shifting ability[46-48]. Fluorinated substituents[49,157] enhance the solubility and—presumably through inductive effects—the acceptor strength of the reagent.

For the chelate ligand with $R' = R'' = C(CH_3)_3$[50] the notation "dpm" (from: "*dip*ivalo-*m*ethanato-") or "tmhd" (from: "*t*etra*m*ethyl*h*eptane*d*ionato-") has come into current use in the literature. The ligand with $R' = C(CH_3)_3$ and $R'' = n$-C_3F_7[49,154] is written "fod" (from: "hepta*f*luoro-dimethyl*o*ctane*d*ionato-"). "Fod" complexes are also in use in their perdeuterated forms (postulate 4). A good account of the practical problems connected with the application of lanthanoid shift reagents is given in Ref.[127].

The composition of the adducts formed in solution between a shift reagent and a monofunctional substrate is by no means uniform. Obviously it also depends on the nature of the substrate. Thus, the existence of 1:1 adducts[31b,141] and 2:1 adducts[133] has definitely been proven. So far little is known about the conformations of the adduct in solution. According to recent observations it cannot be excluded that the preferential conformation of an adduct is influenced by the nature of the coordinated substrate[51].

In the crystalline state evidence exists for well-defined adducts between tris(β-diketonato)lanthanoid complexes and 1 to 4 additional ligands, especially water[146,147]. X-ray structure analyses of the 1:2 adducts $Ho(dpm)_3 \cdot 2$(4-picoline)[45] and $Eu(dpm)_3 \cdot 2pyr$[87] provided evidence that the two substrate molecules do not have coaxial positions in the adduct. The symmetry of the complexes is only C_2[162]. Analogous results are provided by the known structures of several crystalline 1:1 adducts[146]. If these results would hold also in solution, axially symmetric ligand fields at the central ion could be expected only in rare cases.

Most chelate reagents are more or less hygroscopic and chemically unstable towards weak acids such as carbonic acids and phenols, and sometimes even alcohols[164]. They are, nevertheless, the shift reagents most widely used today and are certainly the ones best suited for standard applications.

3.2.1.3. Organometallics

The tricyclopentadienyl complexes of several lanthanoids $(C_5H_5)_3Ln(III)$[52] belong to this category. These compounds can coordinate only a single unidentate ligand S:

$$(C_5H_5)_3Ln + S \rightleftharpoons (C_5H_5)_3LnS$$

The acceptor strength of these compounds generally exceeds the acidity of the chelate complexes[125,148]. Thus it is often possible to isolate well-defined 1:1-adducts free of the components. On the other hand, the sensitivity of the organometallic shift reagents towards acids, water, and oxygen exceeds the sensitivity of the chelate complexes considerably. Therefore they have to be manipulated in an inert gas atmosphere and in carefully purified solvents.

Apart from the fact that the shifting potential of the tricyclopentadienyl complexes sometimes exceeds the corresponding chelate complexes, a particular advantage of many adducts $(C_5H_5)_3LnS$ is the C_{3v} point symmetry of the effective ligand field at the central ion[*]. Such systems fulfil postulates 6 and 7 and thus often allow quantitative evaluations of the observed spectra with respect to refined structural and conformational analyses[7,27,144].

Although the solubility of the free complexes $(C_5H_5)_3Ln$ in inert media like benzene or toluene is often rather limited, the solubilities of the adducts often turn out to be quite high, depending on the substrate [*e.g.* $(C_5H_5)_3Nd$: *ca.* 1 mg/ml; $(C_5H_5)_3Nd$·nicotine: *ca.* 100 mg/ml].

3.2.2. Shift Reagents without Unpaired d or f Electrons

3.2.2.1. Metal-free Radical Systems

Organic nitroxide radicals often exhibit electron spin-lattice relaxation times which—in contrast to other stable organic radicals—allow relatively sharp NMR signals to be observed. Therefore utilization of systems like $(CH_3)_2NO$ or $[(CH_3)_3C]_2NO$ as shift reagents was attempted[53,54]. In contrast to the acidic metal complexes these compounds tend to interact with acidic substrates. This fact has been made use of in the investigation of hydrogen bonds.

Moreover, nitroxide radicals can weakly interact with other organic radicals thus reducing drastically the originally very large T_{1e} values of these compounds. By this means the NMR spectra of several organic radicals could be observed[55,56].

3.2.2.2. Non-radical Shift Reagents

This category comprises those systems which develop a noticeable anisotropy either through a strong induced diamagnetism (*e.g.* in cyclic π-electron systems, Fig. 1b) or through temperature-independent paramagnetism (*e.g.* UO_2^{2+}). Another shift reagent of this class is iron(II)phthalocyanine, FePc, which is paramagnetic. On axial coordination of two bases like amines, however, the resulting quasi-octahedral, low-spin complex $FePcS_2$ is diamagnetic[126].

The advantages of shift reagents of this category are sharp signals and temperature-independent isotropic shifts. Their resolving power, however, is only exceptionally equivalent to shift reagents with unpaired electrons.

Recently, the use of some anionic π-electron systems as shift reagents (*e.g.* $[B(C_6H_5)_4]^-$ or $[P(C_{12}H_8)_3]^-$) has been reported[57]. These compounds are especially suited to reaction with cationic substrates in strongly polar solvents. The results published so far deal mainly with short-lived ion pairs of these anions with various—in some cases chiral—quaternary phosphonium ions.

4. Analysis of Shifted Spectra

4.1. Concentration Dependence of the Isotropic Shifts

The concentration dependence of the isotropic shift of a substrate signal averaged over all possible species present in solution can be expressed most clearly by the equilibrium concentrations of the free and complexed substrate:

$$\delta_{exp} = n_{R-S} \cdot \delta_{R-S} + n_S \cdot \delta_S = n_{R-S}(\delta_{R-S} - \delta_S) \quad (12)$$

In this equation, n_{R-S} and n_S are the molar fractions of the adduct and the substrate, respectively.

Practically, however, only the initial concentrations $[R]_0$ and $[S]_0$ of the shift reagent and substrate are usually known. One is forced, therefore, to express δ_{exp} as a function of $L = [R]_0/[S]_0$ instead of the molar fractions. In diagrams of both $\delta_{exp} = f(n_{R-S})$ and $\delta_{exp} = f(L)$ curves of the type shown in Fig. 8a are obtained.

In the first case, the extrapolated ordinate intercept and the slope of the linear part are always equal to δ_S (= chemical shift of the free substrate) and $\delta_{R-S} - \delta_S$, the "molar isotropic shift" of the 1:1-adduct. The analogous correlation in the second case can be approximated only with the restriction that $[R]_0 \ll [S]_0$ and the formation constant K[31] of the adduct is sufficiently large. The main reason is that, as was observed experimentally[47,141], the slope of the linear sections in diagrams $\delta_{exp} = f(L)$ depend noticeably on the absolute substrate concentration.

Several authors have derived equations allowing the evaluation of δ_{R-S} and K with satisfactory accuracy[141-143,169]. According to *Armitage et al.*[141,159], a diagram $[S]_0 = f(\delta_{exp}^{-1})$ in the concentration range $[S]_0 \gg [R]_0$ at constant $[R]_0$ yields straight lines:

$$[S]_0 = [R]_0 \cdot \delta_{R-S} \cdot \delta_{exp}^{-1} - ([R]_0 + K^{-1}) \quad (13)$$

[*] The assumption of this relatively high symmetry is justified for the NMR experiment in view of the proven free rotation of the C_5H_5-rings.

From the slope and the y-intercept of such a straight line the chemical shift δ_{R-S} and the formation constant K of the adduct can easily be obtained. These two parameters are occasionally termed "intrinsic LIS parameters" (*l*anthanoid *i*nduced *s*hift)[143]. Fig. 8b is a diagram of $[S]_0 = f(\delta_{exp}^{-1})$ showing the straight lines obtained for the three different protons of *n*-propylamine in the presence of $Eu(dpm)_3$[159]. It is remarkable that for the three protons the intercepts are identical (thus resulting in an identical K value), although the slopes (and thus the values δ_{R-S}) vary markedly.

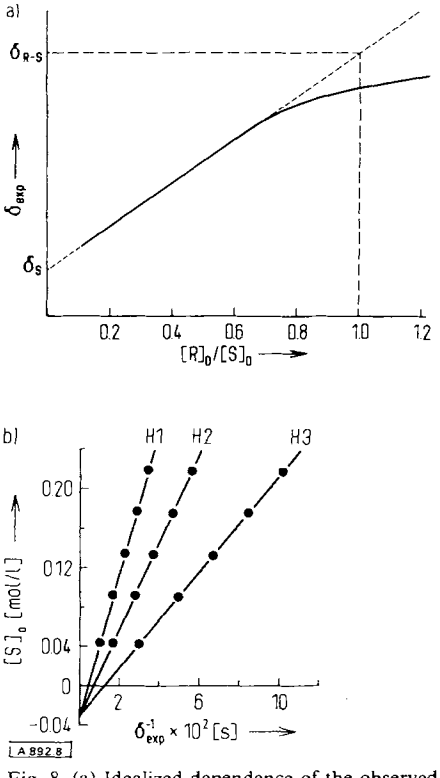


Fig. 8. (a) Idealized dependence of the observed shift δ_{exp} on the molar ratio of the initial concentrations of shift reagent $[R]_0$ and substrate $[S]_0$. δ_S = Chemical shift of the free substrate, $\delta_{R\ S}$ = shift of the 1:1-adduct. (b) Plot of $\delta_{exp}^{-1} = f([S]_0)$ for the three different protons of *n*-propylamine at constant $Eu(dpm)_3$ concentration (*ca.* 0.006 M in $CDCl_3$) [159].

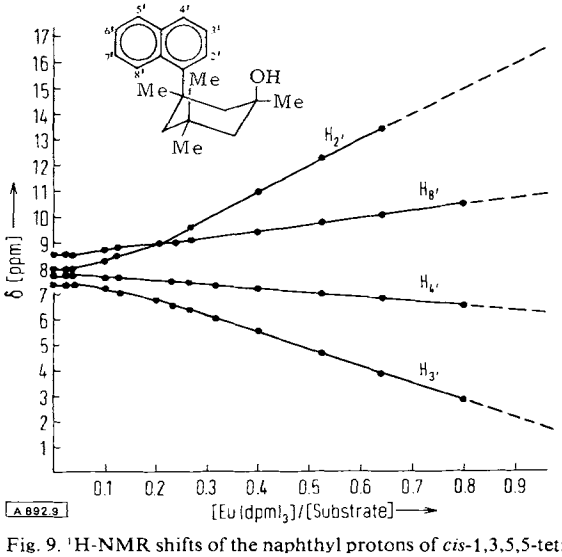


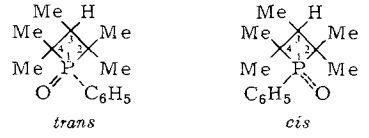
Fig. 9. ^{1}H-NMR shifts of the naphthyl protons of *cis*-1,3,5,5-tetramethyl-5-(1-naphthyl)cyclohexan-1-ol as a function of the $Eu(dpm)_3$ concentration [33].

Equation (13) is valid only for 1:1 adducts. Suitable modifications can be obtained, however, taking into account different stoichiometries. Unknown adduct compositions may thus be determined[151,159].

Deviations of the idealized curve shown in Fig. 8a at higher values of L may be caused by the finite magnitude of K or by the self-association of $Pr(dpm)_3$ and $Eu(dpm)_3$ which has been proved independently also in solution[32]. Occasionally curvatures at low L values are also observed (Fig. 9)[33]. However, a determination of the chemical shifts δ_S by extrapolation appears to be justified in most cases[10,34]. If either substrate or shift reagent are polyfunctional, the plots $\delta_{exp} = f(L)$ may be completely curved or may exhibit several linear parts (cf. Section 5.2).

4.2. Graphical Signal Assignment

Frequently the problem of signal assignment can rapidly be solved by making use of the fact that the isotropic shifts decrease with increasing distance of the respective nuclei from the bonding site between shift reagent and substrate. An example is the distinction between the *cis*- and the *trans* form[58,59,78,145,153] of geometric isomers, as in the case of a phosphetane (Fig. 10)[61].



Δ^{iso}(H-3) = 160 Hz Δ^{iso}(H-3) = 224 Hz

Fig. 10. Isotropic shift of the 3-proton in *cis*- and *trans*-2,2,3,4,4-pentamethyl-1-phenylphosphetan-1-one after addition of 0.48 equivalents of $Eu(dpm)_3$ in $CDCl_3$ [61].

Because of the direct proportionality between Δ_i^{dip} and r_i^{-3} [cf. equations (4) and (7)] it is usually practical to plot these quantities on a logarithmic scale[62,63]. In the case of axial symmetry one gets on taking the logarithms of equation (7):

$$\log|\Delta_i| = -3\log r_i + [\log|(3\cos^2\vartheta_i - 1)| + \log|D|] \qquad (14)$$

As long as the term in the brackets is constant, equation (14) is the function of a straight line with slope -3. The essential requirement for this term to be constant is:

$$\log|D| \gg \log|(3\cos^2\vartheta_i - 1)|$$

If this condition holds, ϑ may take all values between 0 and *ca.* 50°, and between 60 and *ca.* 90°. Since with $\vartheta = 54.7°$

$$\log(3\cos^2\vartheta_i - 1) = -\infty$$

large deviations from linearity are to be expected in the critical angular range $50° < \vartheta < 60°$.

Fig. 11 shows the diagram $\log\Delta_i = f(\log r_i)$ for the two conformers present at $-70\,^{\circ}C$ of the compound $(C_5H_5)_3PrCNC_6H_{11}$ with the cyclohexane ring equatorially or axially substituted[27]. The deviation from the best straight line with slope -3 of the points with ϑ-values close to the critical range is obvious.

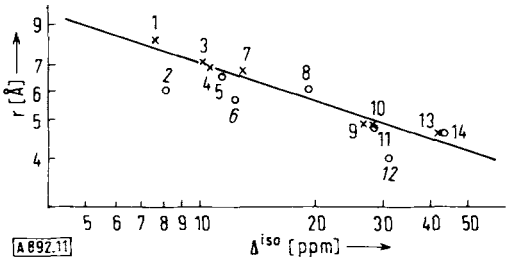


Fig. 11. The isotropic shifts Δ^{iso} of the C_6H_{11}-signals in the ^{1}H-NMR spectrum of $(C_5H_5)_3PrCNC_6H_{11}$ at $-70\,^{\circ}C$ as a function of the geometric parameters r(Å) and ϑ; slope of the best straight line: -3.2 [27].

1 = δ-H (Ee), $\vartheta = 9^{\circ}$	8 = β-H (Aa), $\vartheta = 14^{\circ}$
2 = δ-H (Ae), $\vartheta = 39^{\circ}$	9 = β-H (Ea), $\vartheta = 24^{\circ}$
3 = γ-H (Ee), $\vartheta = 20^{\circ}$	10 = β-H (Ee), $\vartheta = 24^{\circ}$
4 = δ-H (Ea), $\vartheta = 20^{\circ}$	11 = β-H (Ae), $\vartheta = 26^{\circ}$
5 = δ-H (Aa), $\vartheta = 24^{\circ}$	12 = γ-H (Aa), $\vartheta = 37^{\circ}$
6 = γ-H (Ae), $\vartheta = 35^{\circ}$	13 = α-H (E), $\vartheta = 13^{\circ}$
7 = γ-H (Ea), $\vartheta = 12^{\circ}$	14 = α-H (A), $\vartheta = 13^{\circ}$

A = axially substituted conformation
E = equatorially substituted conformation
a = axial proton
e = equatorial proton
Underlined numbers = points with greatest deviation from the best straight line.

In the case of protons separated from the metal ion by only three bonds (*e.g.* the α-protons in alcohols or epoxides[63–65]), the large deviations frequently encountered from the best straight line have been tentatively interpreted with the assumption of Fermi-contact interactions (see Section 2.1.2). *Farid et al.*[66], however, could prove for two such cases[62,67] that these deviations were due to the neglect of the angular dependence.

From equation (14) it can be deduced that a better fit of all points to the straight line should be achieved by appreciably increasing the anisotropy factor D (*i.e.* by replacing the Pr ion by Tb(III) or Dy(III), cf. Fig. 5).

Occasionally, in the diagram $\log\Delta_i = f(\log r_i)$ straight lines with slopes smaller than -3 have been found[67–75,137]. In spite of the approximations used which are responsible for this effect[76], reliable assignments were achieved in these cases also.

4.3. Position of the Metal Atom

The distances r_i can be determined from molecular models (*e.g.* Dreiding). The metal-ligand distances should be known for this procedure; if they are not, they must be approximated. In some cases sufficiently linear plots of $\log\Delta_i = f(\log r_i)$ were obtained even when r_i was put equal to the distance between the atom i of the substrate and the periphery of the lone pair at the donor atom[67–69]. Using this method, *Ernst*[75] found, *e.g.*, that the preferential conformation of 2,6-dimethylcyclohexylamine is that shown in Fig. 12. It appears to be somewhat more realistic to express the distance metal-donor atom as the sum of the two covalent radii[64].

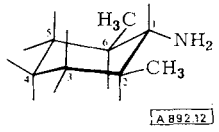


Fig. 12. Preferential conformation of 2,6-dimethylcyclohexylamine [75].

Sanders and *Williams*[77] found the distance between Eu ion and O atom in the adduct of 4-*tert*-butylcyclohexanone and $Eu(dpm)_3$ shown in Fig. 13a by iterative adjustment of the distances r with the isotropic

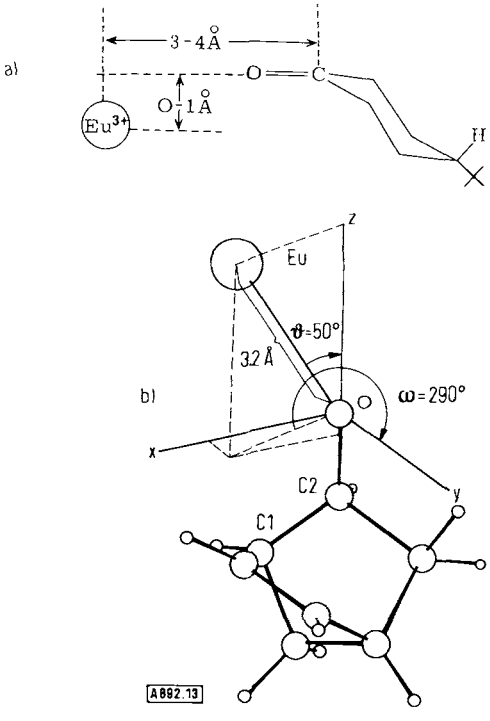


Fig. 13. (a) Probable position of the Eu(III) ion in the adduct between $Eu(dpm)_3$ and 4-*tert*-butylcyclohexanone [77]; (b) Most probable position of the Eu(III) ion in the adduct between $Eu(dpm)_3$ and *endo*-norbornenol [139]. The O atom is at the origin of the internal coordinate system, the O—C-2 bond is placed along the negative z axis, atom C-1 is placed in the x—z plane with the positive x coordinate.

shifts. Such iterations can conveniently be carried out by computer[66,139,140,156], especially if the angular term and internal rotations are also taken into consideration. The adduct of $Eu(dpm)_3$ with *endo*-norbornenol[139,140] is an example (Fig. 13b). The distances Eu—O or Yb—O thus obtained in adducts with shift reagents of the chelate type are generally between 3.0 and 3.5 Å[78–80]. In the case of fluorenone and 1-indanone, however, a satisfactory correlation was obtained with a distance Yb—O of 1.5 ± 0.2 Å[81] (Fig. 14). The results of two structure determinations by X-ray methods in the solid state are, for comparison: Ho—N in $Ho(dpm)_3(4\text{-picoline})_2$ 2.53 Å[45] and Eu—N in $Eu(dpm)_3(pyr)_2$ 2.65 Å[87].

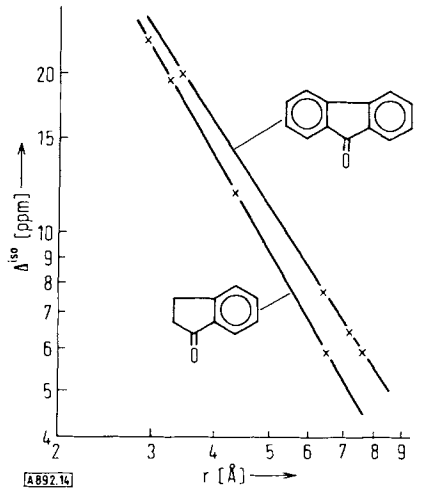


Fig. 14. The isotropic shifts as a function of the distance r in the adducts between Yb(dpm)$_3$ and fluorenone and 1-indanone, respectively [81].

4.4. Influence of the Angular Term

If the angular dependence of G_i [equation (6)] is taken into account, the correlation between the Δ_i-values and the geometric factors is generally improved[27,48,66,82,83,138].

Thus, in the case of the axially symmetric adduct $(C_5H_5)_3PrCNC_6H_{11}$[27] the standard deviation of the best straight line $\log\Delta_i = f(\log r_i)$ is 25.6% (Fig. 11), whereas it decreases to 2.8% in the plot $\Delta_i = f(G_i)$ (Fig. 15). A similar improvement by nearly an order of magnitude could be achieved with an adduct of a shift reagent of the chelate type[84]. This example shows that it is obviously advantageous not to neglect the term $3\cos^2\vartheta - 1$ also in cases of lower than axial symmetry.

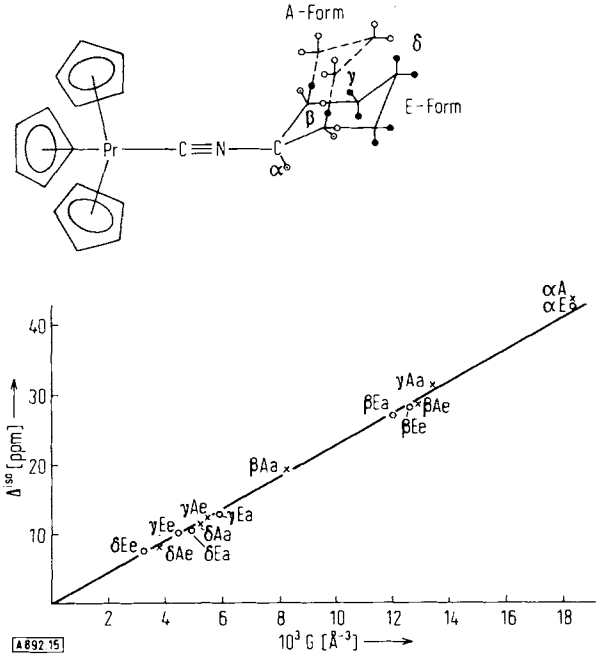


Fig. 15. Correlation between the isotropic shifts measured at -70 °C of the C_6H_{11}-protons and their G-values in the two chair conformers of the adduct $(C_5H_5)_3PrCNC_6H_{11}$ (solvent: D_8-toluene) [27]. The nomenclature used to label the protons belonging to the points of the plot is given in the caption to Fig. 11.

The change of sign of this term at $\vartheta = 54.7°$ is responsible for the occasional observation of shifts to high field using Eu complexes, which generally cause shifts to lower field[33,44,85,86,88,89]. For instance, in the alcohol shown in Fig. 9 the signals of the naphthyl protons 3′ and 4′ are shifted, contrary to the signals of all other protons, to high field[33]. These results are explained in a straightforward manner by the coordination of the Eu ion at the axial OH-group.

4.5. Internal Rotations

In substrate molecules with internal rotational degrees of freedom which cannot be frozen-in in the temperature range used for the measurements, the Δ_i-values have to be correlated with mean G_i values taking into account all possible rotamers. The mean G_i value is influenced most strongly by internal rotations whose rotational axes do not coincide with the principal axis of symmetry of the complex. Equation (9) has been proposed for the case that the metal ion lies within the rotation axis[162].

From the good correlation in the diagram $\Delta_i = f(G_i)$ of $(C_5H_5)_3PrCNC_6H_{11}$[27] (Fig. 15) a linear Pr—CN≡N arrangement along the threefold principal rotation axis of the complex can be deduced. For the analogous alkoxy-complex $(C_5H_5)_3UC_6H_{11}$[82], however, a quantitative correlation between Δ_i and G_i was not achieved, since the rotation axis O—C in the bent U—O—C group does not coincide with the principal molecular axis U—O. In most cases of this kind an exact determination of the mean G_i values is quite tedious and requires the use of a computer. In unfavorable cases, therefore, only qualitative signal assignments are possible, even if a powerful shift reagent is used.

5. Special Applications

5.1. Determination of Spin Coupling Constants

Shift reagents lowering the order of the spectrum of a substrate without broadening the signals excessively, simplify the determination of coupling constants[90–93].

Table 2. Coupling constants of *trans*-5-*tert*-butyl-2-methyl-1,3,2-dioxaphosphoran-2-one (Fig. 16).
Upper line: Numbers obtained with computer program LAOCN3.
Lower line: Numbers directly taken from the expanded spectrum.

[Eu(dpm$_3$)] / [substrate]	J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}
0	−11.1	10.5	4.47	4.14	20.2
0.5	11	11	4	3	20

Table 2 shows the coupling constants of a heterocyclic AA′BB′XY-system (Fig. 16)[94]. The data obtained from an iterative computer analysis of the spectrum of

the free substrate are listed in the upper line, and in the lower line the constants directly read off from the spectrum recorded in the presence of a shift reagent.

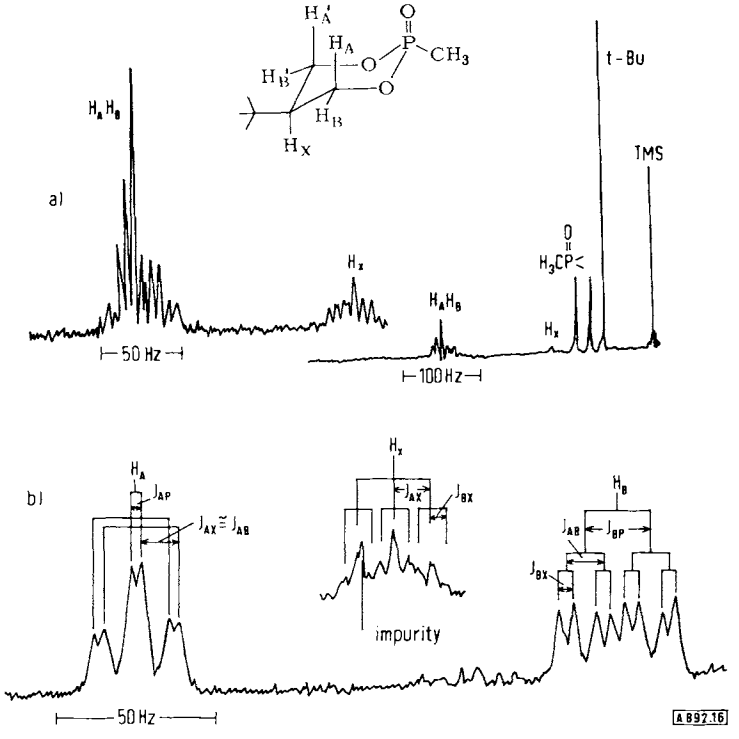


Fig. 16. ^{1}H-NMR spectrum of *trans*-5-*tert*-butyl-2-methyl-1,3,2-dioxophosphoran-2-one [94]. (a) 0.2 M in CCl_4; (b) With 0.5 equivalents of Eu(dpm)$_3$. The coupling constants directly taken from the spectrum are indicated.

The influence of adduct formation on the magnitude of the coupling constants of a substrate is comparable to a substituent effect in all cases where a change of the substrate conformation is negligible[157]. A linear increase of up to 10% in several geminal coupling constants in camphor and 3,5,5-trimethyl-3-(*p*-chlorophenyl)cyclohexane has been noted upon increasing the concentration of the reagents Eu(dpm)$_3$ or Eu(fod)$_3$ up to a molar ratio $L \approx 0.7$[157]. In the case of noticeable contact interactions additional changes of the coupling constants may possibly occur[95,96]. A closer examination of this effect is generally prevented by line broadening.

5.2. Influence of the Basicity of the Substrate; Polyfunctional Substrates

The formation constant of an adduct between a substrate and a shift reagent (cf. Section 4.1) and thus the isotropic shifts of the substrate depend markedly on the basicity of the substrate. Thus, the "molar shift" induced in substrate RX by Eu(dpm)$_3$ decreases in the order $X = NH_2 > OH > C{=}O > -O- > CO_2R > CN$[77]. This series could be extended by some very weakly basic molecules, such as $M{-}SO_2CH_3$, or the organometallics $(C_5H_5)_2Sn$ or $[(C_5H_5)Fe(CO)_2]_2$[98].

Ernst and *Mannschreck*[99] found a linear correlation between the pK_a-values of a series of *p*-substituted anilines and the shift of the phenyl protons in the *o*- and *m*-position obtained at constant Eu(dpm)$_3$ concentration (Fig. 17a).

As important as the basic strength of the substrate are the steric conditions in the vicinity of the basic center[79]. Thus, in the series aniline, *N*-methylaniline, and *N*,*N*-dimethylaniline the shifts decrease in spite of increasing pK_a-values (Fig. 17b)[99].

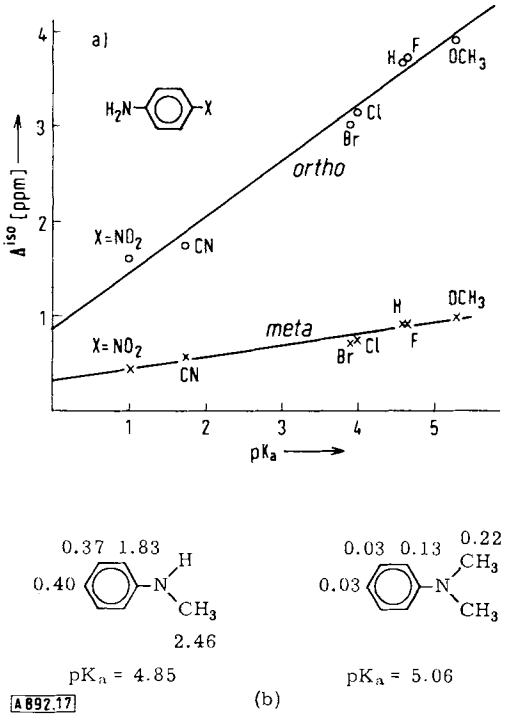


Fig. 17. (a) Correlation between the pK_a-values of *p*-substituted anilines and the isotropic shifts (in ppm) of the *o*- and *m*-protons (molar ratio Eu(dpm)$_3$/substrate = 0.2; solvent $CDCl_3$). (b) Influence of the substitution at the nitrogen of aniline on the isotropic shifts (in ppm) of the phenyl protons [99].

If a substrate molecule contains two donor functions whose equilibrium constants of complex formation with the shift reagent differ greatly (like —OH and $-CO_2R$[100] or P=O and C=O[101]), in the diagram $\delta = f(L)$, where δ is the additive isotropic shift[137], pronounced changes of the slope at the equimolar ratio ($L = 1.0$) for nuclei close to one of the two basic centers are observed. Evidently the weaker basic group does not coordinate before most or all of the stronger function has reacted. Figure 18 shows the results obtained with a substrate carrying an alcohol and an ester function[100].

According to *Hinckley*[63] the contributions of the two donor centers of a bifunctional substrate to the overall shift can be separated graphically in the following manner (Fig. 19): in the diagram $\log\Delta_A = f(\log r_A)$ of testosterone the Δ_A value of proton i very likely originates from Eu(dpm)$_3$ coordinated at the OH-group. It seems justified to draw a straight line of slope -3 through point i, since such a line was experimentally found for the protons of the structurally very similar, but monofunctional cholesterol[12]. The vertical differences of the experimental shifts of protons j and l from this line are equal to the contribution Δ_B resulting from

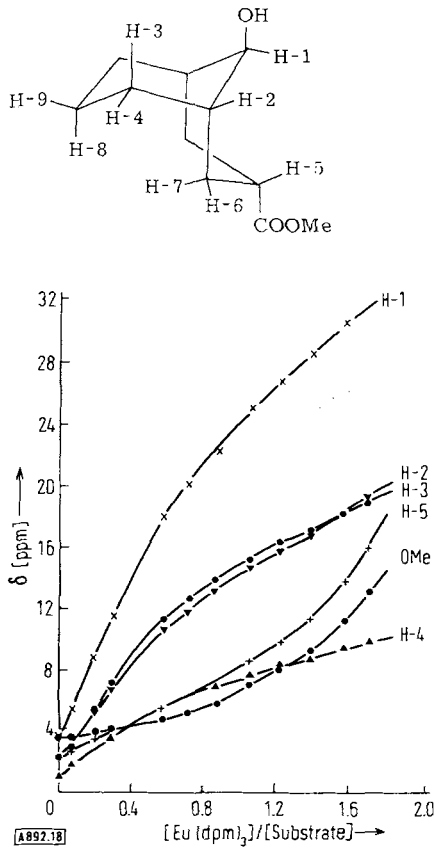


Fig. 18. The chemical shifts (ppm relative to TMS) of the protons of methyl-*trans*-9-hydroxybicyclo(3.3.1)nonane-*endo*-3-carboxylate as a function of the molar ratio $Eu(dpm)_3$/substrate [100].

$Eu(dpm)_3$ coordinated at the carbonyl group. These shifts again fall approximately on a straight line $\log \Delta_B = f(\log r_B)$ of slope -3. The shifts $-\Delta_A$ and Δ_B corresponding to the same distance r are proportional to the complex formation constants K_{CO} and K_{OH}. In this case the ratio $\Delta_A/\Delta_B = K_{CO}/K_{OH} = 0.47$.

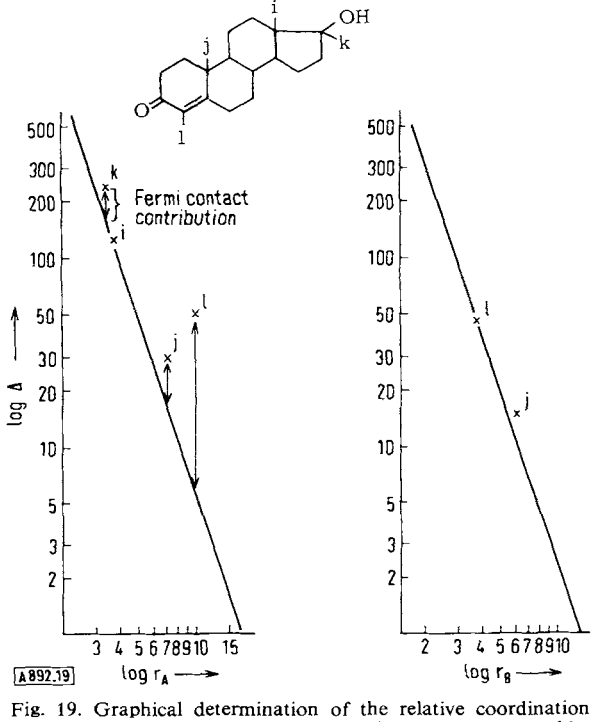


Fig. 19. Graphical determination of the relative coordination strength of the OH and C=O functions in testosterone: double-logarithmic plot of the isotropic shifts Δ (in Hz) of protons i, j, k, and l as a function of the distances r_A and r_B (in Å) (cf. text) [63].

Hart and *Love*[102] determined the relative basic strength of functional groups by inter- or intramolecular competition: under the influence of $Eu(dpm)_3$ an equimolar mixture of acetone-tetrahydrofuran exhibits the molar shifts indicated in Fig. 20a and b. From the changes of the shifts one can deduce that $Eu(dpm)_3$ coordinates tetrahydrofuran about 8 times better than acetone.

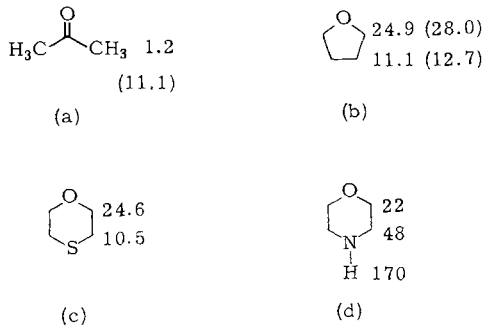


Fig. 20. Extrapolated molar isotropic shifts (in ppm) of the protons of two monofunctional substrates in an equimolar mixture and of two bifunctional substrates on addition of $Eu(dpm)_3$ [102]. In parentheses: values of the pure substances. (a) acetone, (b) tetrahydrofuran, (c) thioxane, (d) morpholine.

Similar competition experiments were carried out with bifunctional molecules (Fig. 20c and d). From a large number of data a series of basicity was deduced which was practically identical to the one cited above.

5.3. Polymers

Solutions of polymers such as polyethylene oxide[103] and poly(methyl methacrylate)[103,104] also display induced shifts upon the addition of lanthanoid chelates leading to a substantial improvement of the resolution of their rather complex NMR spectra. In the case of polypropylene glycol[105] it was possible to separate the ^{1}H-NMR bands of the end methyl groups from the bands of the methyl groups in the polymeric chain, thus allowing determination of the molecular weight by direct comparison of signal intensities.

5.4. Dynamic Processes

Dynamic processes whose reaction rates are in a favorable range on the NMR time scale (rate constant k: 3 to 300 s^{-1}) cause line broadening, and finally line splitting, if the temperature is lowered. At the splitting or coalescence temperature T_c the following approximate correlation holds between the rate constant k_c and the maximum peak separation $\Delta\nu$[106]:

$$k_c = \Delta\nu/\sqrt{2} \qquad (15)$$

Apart from the fact that the rate of such a process can be changed by complex formation with a shift reagent,

the temperature T_c rises if $\Delta\nu$ is increased by the paramagnetic effect. Some processes can therefore be observed better in the presence of a shift reagent, because the broadening and splitting of the signals occurs in a more suitable temperature range.

One has to distinguish between intra- and intermolecular dynamic processes. Intramolecular processes within the substrate are sometimes obscured in the NMR spectrum by intermolecular ligand exchange phenomena[107,108].

Ligand exchange in a system lanthanoid chelate-substrate was observed for the first time by *Evans* and *Wyatt*[133]: in a mixture of $Eu(fod)_3$ with an excess of dimethyl sulfoxide in CD_2Cl_2 the CH_3 signal broadens considerably on cooling the solution to -45 °C (Fig. 21).

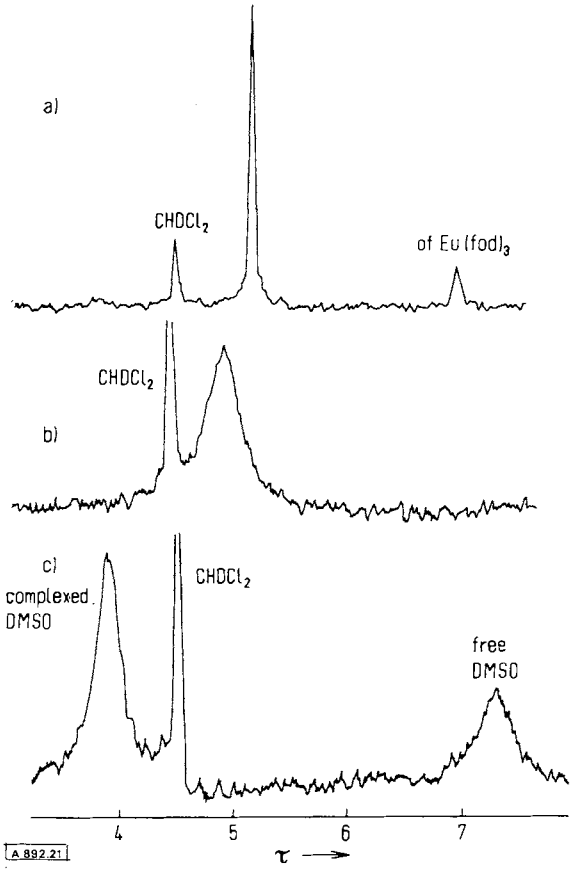


Fig. 21. ^{1}H-NMR spectra of a 0.131 M solution in $CHDCl_2$ of dimethyl sulfoxide (DMSO) after addition of 0.044 M $Eu(fod)_3$ at (a), 38 °C; (b) -45 °C; and (c) -80 °C [133].

At -80 °C this signal splits into signals corresponding to the free and complexed substrate. A stoichiometric ratio S:R = 2:1 can be deduced from the relative intensities of these lines.

The determination of solvation numbers of metal ions (*e.g.* UO_2^{2+}) in solution by the separate observation of the NMR signal of the free and the shifted signal of the complexed solvent at low temperature is a well established technique[111,112].

An intramolecular process observable without the interference of ligand exchange is the rotational isomerism of amides whose coalescence temperature is rather high (50 to 127 °C[20,109]). On addition of $Yb(dpm)_3$ *Beaute et al.*[109] noticed an appreciable increase in the coalescence temperature, but no significant change in the

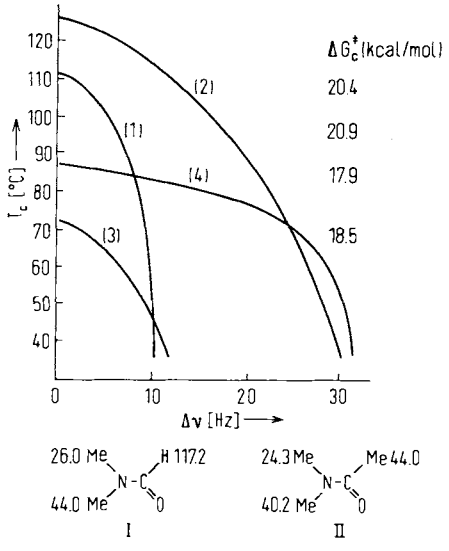


Fig. 22. Coalescence temperatures (T_c) and free enthalpies of activation ($\Delta G_c^{\ddagger}$) for *N,N*-dimethylformamide (I) and *N,N*-dimethylacetamide (II) without and with addition of $Yb(dpm)_3$. The curves represent the temperature dependence of the frequency difference $\Delta\nu$ of the methyl signals [109]. Molar ratio [$Yb(dpm)_3$]/[I]: (1) = 0, (2) = 0.06; [$Yb(dpm)_3$]/[II]: (3) = 0, (4) = 0.05. The numbers at the formulas represent the extrapolated molar shifts (in ppm) of the respective protons.

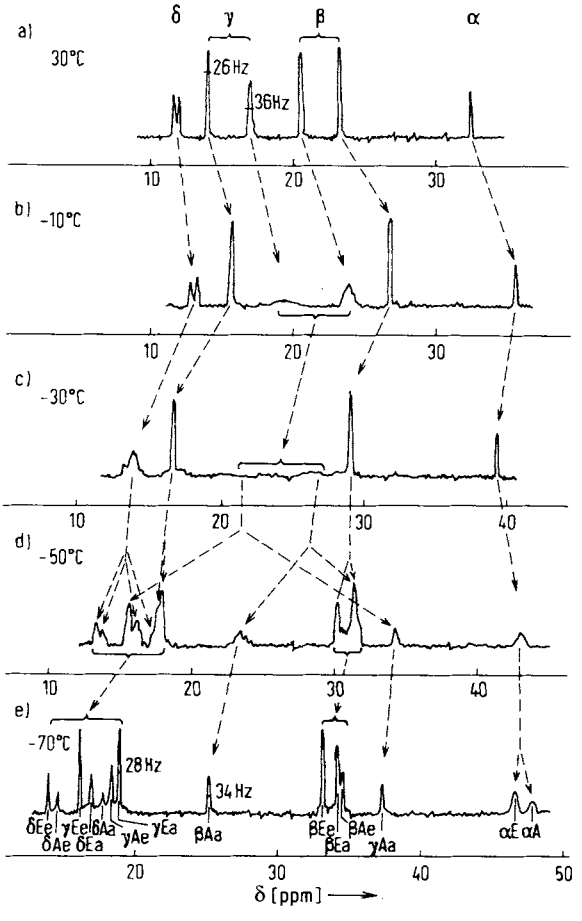


Fig. 23. Temperature dependence of the ^{1}H-NMR spectrum (C_6H_{11}-part) of the adduct between $(C_5H_5)_3Pr$ and CNC_6H_{11} [27]; δ-scale (abscissa) relative to C_6H_6; solvent: D_8-toluene. Nomenclature of the protons the same as in Fig. 11.

free enthalpy of activation of this rotation (Fig. 22). *Schwarzhans*[20], however, found the coalescence temperature in the spectrum of *N,N*-dimethylacetamide unchanged upon complex formation with UBr_4[110]. Thence he deduced that the CO group and not the nitrogen atom is the center of coordination.

The chair-chair interconversion of a monosubstituted cyclohexane (cyclohexylisonitrile) upon adduct formation with $(C_5H_5)_3Pr$[27] was studied by observing the temperature dependence of seven signals of the C_6H_{11} protons. The coalescence temperatures of several signal pairs with particularly large $\Delta\nu$ are raised so much that large signal broadenings occur already at a little below room temperature (Fig. 23).

5.5. Reaction Mechanisms

The mechanism of a reaction which is catalyzed by lanthanoid ions can be studied with the shift reagent technique if these ions can act at the same time as paramagnetic shift reagents on the NMR spectrum of the substrate. Thus, during the decarboxylation of oxaloacetic acid either of the complexes I and II

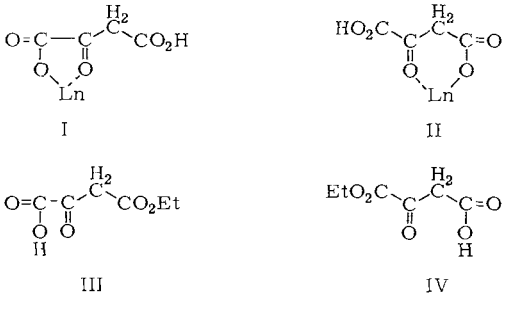


Fig. 24. Possible intermediates (I and II) during the decomposition of oxaloacetic acid catalyzed by Ln(III) ions [44]. III and IV: Substances of comparable structure.

(Fig. 24) can be formed as an intermediate. For the elucidation of the mechanism, *Reyes-Zamora* and *Zsai*[44] prepared the half esters III and IV (Fig. 24). Upon addition of $EuCl_3$ the CH_2 protons of III exhibited the usual low field shift in the ^{1}H-NMR spectrum, in contrast to the signals of IV which were shifted to high field. As oxaloacetic acid shows a low field shift on addition of $EuCl_3$, the authors concluded that the intermediate must have structure I which is the only possible one that the half ester III can form with the metal.

The kinetics of the catalytic deuteration of 4-*tert*-butylhexanone were studied by measuring the intensity decrease of the various ^{1}H-NMR signals of that substrate after spectral simplification with $Eu(dpm)_3$[134].

5.6. Pulsed Fourier-Transform ^{13}C-NMR Spectroscopy

Shift reagents have hitherto been employed almost exclusively in ^{1}H-NMR spectroscopy, not only because the proton is still the nucleus most widely used, but also because the spectral resolution efficiency of the shift reagents is greatest here. However, there are interesting applications in the NMR-spectroscopy of other nuclei, *e.g.* in pulsed Fourier-transform (=P.F.T) ^{13}C-NMR-spectroscopy[113]. The investigation of cholesterol in the presence of $Eu(dpm)_3$[166] is an example.

Gansow et al.[114] assigned the P.F.T. ^{13}C-NMR spectrum of isoborneol, recorded by the common ^{1}H-broadband decoupling technique (Fig. 25). British

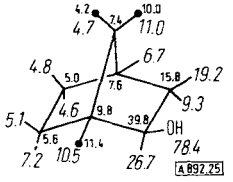


Fig. 25. Isotropic ^{13}C-NMR [114] and ^{1}H-NMR [64, 114] shifts (in ppm) of isoborneol (0.34 M) in an equimolar mixture with $Eu(dpm)_3$ in CCl_4. CH_3 groups = •; all shifts are to low field; the ^{1}H data are written in italics.

authors[115] expanded the relatively complex ^{13}C-NMR spectrum of ribose-5-phosphate by adding Eu^{3+} ions in aqueous solution. The assignment of the signals was achieved by means of hetero-spin-decoupling: the selective irradiation of definite ^{1}H-decoupling frequencies was feasible only in the spectrum simplified by the Eu ions (Fig. 26).

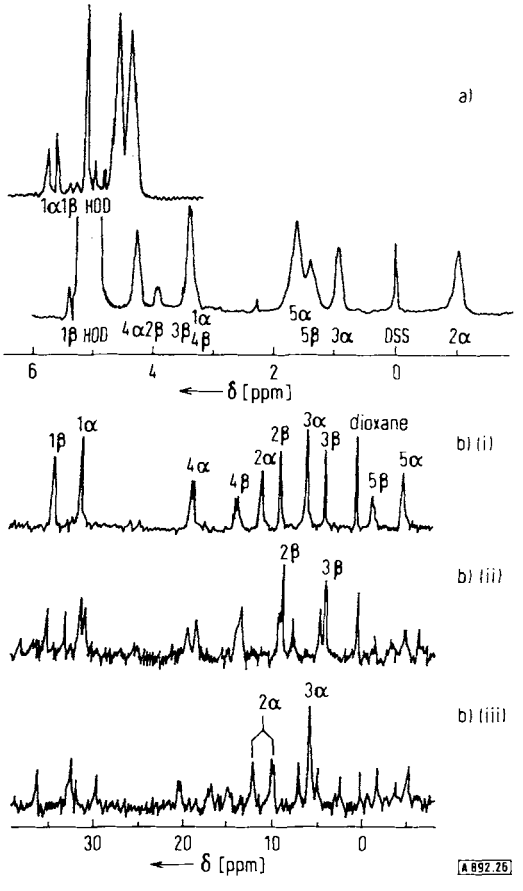


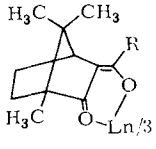
Fig. 26 (a) ^{1}H-NMR spectrum (100 MHz) of ribose-5-phosphate (0.7 M in D_2O) in the absence (above) and in the presence of 0.97 M Eu^{3+} ions at pH = 1.1. DSS = sodium salt of 2,2-*dimethyl*-2-*silapentane*-5-*sulfonic* acid; 1 α to 5 β = nuclei in position 1 to 5 with respect to the phosphate group of the α- and β-anomer, respectively. (b) ^{13}C-NMR spectra (25.2 MHz, P.F.T. technique) of ribose-5-phosphate (0.6 M) with an addition of 0.72 M Eu^{3+} ions [115]; (i) ^{1}H-broad band decoupling; (ii) selective irradiation of the 2β-^{1}H frequency; (iii) selective irradiation at the 3α-^{1}H frequency.

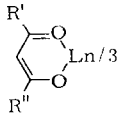
5.7. Chiral Shift Reagents

Pirkle et al.[116,132] noticed that the NMR spectra of the enantiomers of asymmetric compounds (particularly alcohols, α-hydroxy-acids, amines, amino acids and sulfoxides) differ appreciably in optically active solvents, *e.g.* (*R*)-(−)-2,2,2-trifluorophenylethanol. These differences are presumably caused by the formation of diastereomeric adducts between the substrate and the optically active solvent. The latter is to be considered as a chiral shift reagent. The splitting of the spectra results from a different position of the substrate nuclei in the diastereomers with respect to the magnetic field produced by the ring current of the π-system of the solvent.

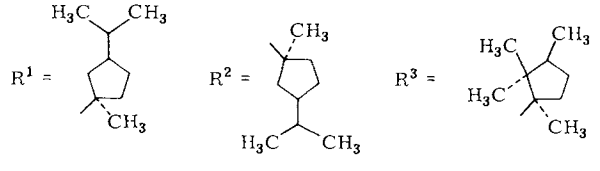
Prior to the introduction of more efficient chiral shift reagents of the chelate type numerous NMR studies were conducted on paramagnetic complexes of the d-transition elements with asymmetric chelate ligands[117,118]. Primary concern in investigations of this type is directed, however, at the spectra of the chelate ligands. The first chiral shift reagent of the chelate type with a lanthanoid central ion was prepared by *Whiteside* and *Lewis*[119]. Other, similar reagents with praseodymium and europium as central ions were described later[120,121]. Fig. 27 illustrates the effect of the chiral shift reagent *(1)* (Table 3) on the ^{1}H-NMR spectrum of pure (*S*)-α-phenylethylamine and on a mixture of both enantiomers of this substrate. All signals in the spectrum of the pure (*S*)-enantiomer appear doubled in the spectrum of the mixture with the splitting Δ_{chir} being largest for nuclei in the vicinity of the asymmetric center of the substrate. Whereas the utilizability of *(1)* is limited to relatively strong donors like amines, chiral splitting is also induced in the spectra of alcohols, ketones, esters, and sulfoxides by the more acidic chiral shift reagents *(2)* to *(8)* (Table 3). Table 4 gives a survey of the chiral shifting potential of such reagents. A particularly straightforward synthesis of the ligand of chiral shift reagent *(2)* (Table 3) is given in Ref.[149].

Table 3. Chiral shift reagents of the β-diketonato type.





(1) R = $-C(CH_3)_3$
(2) R = $-CF_3$
(3) R = R^1
(4) R = 77% R^2 + 23% R^1
(5) R′ = R″ = R^1
(6) R′ = R^1, R″ = R^3
(7) R′ = 77% R^2 + 23% R^1; R″ = R^3
(8) R′ = R^1; R″ = 77% R^2 + 23% R^1.



The absence of chiral splitting in the case of enantiotopic[150] pairs of nuclei in otherwise nonchiral substrates (*e.g.* the methyl groups in 2-propanol or dimethyl sulfoxide)[120] as well as the dependence of Δ_{chir} on the concentration ratio reagent: substrate[119] is consistent with the assumption that the formation of conformationally stable diastereomers is an essential requirement for the spectral splitting. In particular, if the formation constants of the diastereomers differ measurably, the assumption seems justified that different geometric factors correspond to analogous nuclei of the substrate in the diastereomeric pair. A comparison of the Δ_{chir} values given in Table 4 with comparable data of diastereomeric systems without unpaired electrons[122]

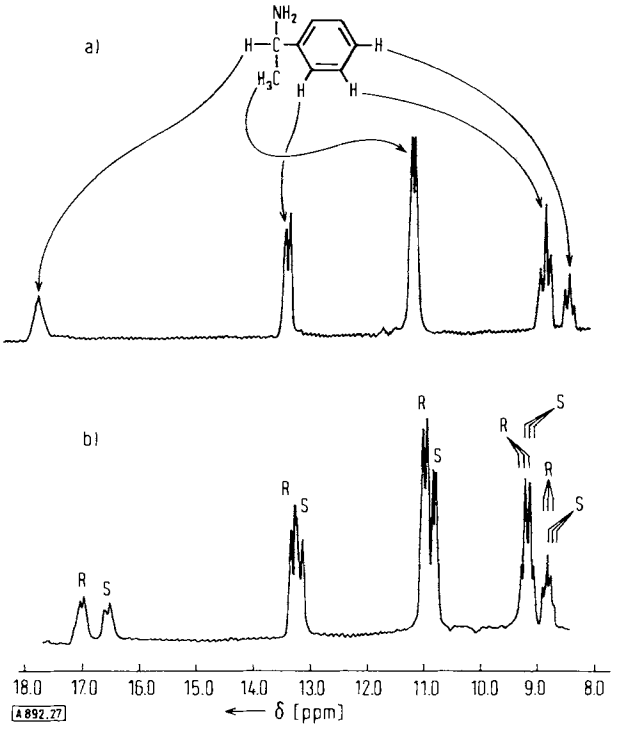


Fig. 27. ^{1}H-NMR spectra of α-phenylethylamine in CCl_4 after addition of tris[(3-*tert*-butylhydroxymethylene)-D-camphorato]-europium(III) [119]. Molar ratio [Eu-complex]/[substrate]: 0.5 to 0.6. (a) Pure (*S*)-form of the amine; (b) mixture of (*S*)- and (*R*)-form.

Table 4. Signal shifts Δ_{chir} induced by chiral shift reagents (R).

Substrate	Proton	R [a]	Δ_{chir} (ppm)	[R] / [substrate]
2-octanol	α-CH_2	*(2)*	0.11	>0.6
1-phenylethyl acetate	—CO_2—C(H)—CH_3	*(2)*	0.18	>0.6
1-methyl-2-norbornanone	1-CH_3	*(2)*	0.17	>0.6
1-phenylethylamine	—CH—	*(3)*	1.13	*ca.* 1.3
		(8)	1.65	*ca.* 0.8
2-phenyl-2-butanol	—C(CH_3)—	*(3)*	0.32	*ca.* 1.3
		(8)	0.25	*ca.* 0.8
benzyl methyl sulfoxide	—CH_2S—	*(3)*	0.32	*ca.* 1.3
		(8)	0.40	*ca.* 0.8
2-butyl formate	O—C(H)—CH_3	*(3)*	0.00	*ca.* 1.3
		(8)	0.10	*ca.* 0.8

[a] The numbers refer to the compounds in Table 3.

shows that the anisotropic field of the lanthanoid ion improves the splitting of the spectrum by approximately an order of magnitude.

5.8. Isotope Effects

A further interesting application of shift reagents of the chelate type was found by *Hinckley et al.*[135,136] and other authors[151,167,168]: the ^{1}H-NMR spectra of alcohols partially deuterated at the position geminal to the OH-group are doubled under the influence of Eu complexes. The isotropic shifts of the doubled signals differ by 1 to 3.5%. The authors discuss as possible reasons for this splitting a change in the basicity of the hydroxyl oxygen by the deuterium substitution or differences in the strength of a secondary hydrogen bonding between the geminal H (or D) and the ring oxygens of the metal chelate ligands.

Received: May 9, 1972 [A 892 IE]
German version: Angew. Chem. *84*, 737 (1972)

[1] *W. v. Philipsborn*, Angew. Chem. *83*, 470 (1971); Angew. Chem. internat. Edit. *10*, 472 (1971).

[2] *J. E. Maskasky* and *M. E. Kenney*, J. Amer. Chem. Soc. *93*, 2060 (1971).

[3] *T. H. Siddall, III* and *C. A. Prohaska*, Inorg. Chem. *4*, 783 (1965).

[4] *G. H. Wahl, Jr.* and *M. R. Peterson, Jr.*, Varian Instr. Appl. *4*, 6 (1970).

[5] NMR Spectra Catalog, Varian Associates, Palo Alto (1963), Spectrum No. 269.

[6] *M. Ohashi, I. Morishima*, and *T. Yonezawa*, Bull. Chem. Soc. Japan *44*, 576 (1971).

[7] *R. D. Fischer* and *R. v. Ammon*, unpublished work.

[8] *W. D. Phillips, C. E. Looney*, and *C. K. Ikeda*, J. Chem. Phys. *27*, 1435 (1957).

[9] *R. W. Kluiber* and *W. D. Horrocks*, J. Amer. Chem. Soc. *87*, 5350 (1965).

[10] a) *K. Fricke* and *H. Suhr*, Ber. Bunsenges. phys. Chem. *72*, 434 (1968); b) *K. Fricke*, Tetrahedr. Letters *1971*, 1237.

[11] *W. A. Szarek, E. Dent, T. B. Grindley*, and *M. C. Bird*, Chem. Commun. *1969*, 953.

[12] *C. C. Hinckley*, J. Amer. Chem. Soc. *91*, 5160 (1969).

[13] *L. Ernst*, Nachr. Chem. Techn. *18*, 459 (1970).

[14] *W. DeW. Horrocks, Jr.* and *J. P. Sipe, III*, J. Amer. Chem. Soc. *93*, 6800 (1971).

[15] *D. R. Eaton* and *W. D. Phillips*, Advan. Magn. Resonance *1*, 103 (1965).

[16] *E. de Boer* and *H. van Willigen*, Progr. NMR Spectroscopy *2*, 111 (1967).

[17] *D. R. Eaton* in *H. A. O. Hill* and *P. Day:* Physical Methods in Advanced Inorganic Chemistry. Interscience, New York 1968.

[18] *R. H. Holm*, Accounts Chem. Res. *2*, 307 (1969).

[19] *H. J. Keller* and *K. E. Schwarzhans*, Angew. Chem. *82*, 227 (1970); Angew. Chem. internat. Edit. *9*, 196 (1970).

[20] *K. E. Schwarzhans*, Angew. Chem. *82*, 975 (1970); Angew. Chem. internat. Edit. *9*, 946 (1970).

[21] *H. J. Keller* in *P. Diehl, E. Fluck*, and *R. Kosfeld:* NMR-Basic Principles and Progress. Springer, Berlin 1970.

[22] *W. DeW. Horrocks, Jr.*, Inorg. Chem. *9*, 690 (1970).

[23] *W. DeW. Horrocks, Jr.* and *D. DeW. Hall*, Coord. Chem. Rev. *6*, 147 (1971).

[24] The formulation of D' and D'' as a function of spectroscopic splitting factors (g-factors [25, 26]), which is still frequently encountered in the literature, neglects the influence of the Van Vleck paramagnetism and is therefore inferior to the formulation used here [22].

[25] *J. B. Jesson*, J. Chem. Phys. *47*, 579, 582 (1967).

[26] *A. J. Kurland* and *B. R. McGarvey*, J. Magn. Resonance *2*, 286 (1970).

[27] *R. v. Ammon, R. D. Fischer*, and *B. Kanellakopulos*, Chem. Ber. *104*, 1072 (1971).

[28] *R. D. Fischer* in *R. H. Holm, W. D. Horrocks, Jr.*, and *G. N. LaMar:* Chemical Applications of NMR-Resonance in Paramagnetic Molecules. Academic Press, in press.

[29] *J. Reuben* and *D. Fiat*, J. Chem. Phys. *51*, 4909 (1969).

[30] *R. v. Ammon, B. Kanellakopulos, R. D. Fischer*, and *P. Laubereau*, Inorg. Nucl. Chem. Lett. *5*, 315 (1969).

[31] a) *H. Huber* and *J. Seelig*, Helv. Chim. Acta *55*, 135 (1972); b) *K. Roth, M. Grosse*, and *D. Rewicki*, Tetrahedron Lett. *1972*, 435.

[32] *M. K. Archer, D. S. Fell*, and *R. W. Jotham*, Inorg. Nucl. Chem. Lett. *7*, 1135 (1971).

[33] *B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan*, and *L. F. Johnson*, J. Amer. Chem. Soc. *93*, 3281 (1971).

[34] *R. W. Kluiber* and *W. D. Horrocks*, J. Amer. Chem. Soc. *88*, 1399 (1966).

[35] *I. Morishima* and *T. Yonezawa*, J. Chem. Phys. *54*, 3238 (1971).

[36] *I. Morishima, K. Okada, M. Ohashi*, and *T. Yonezawa*, Chem. Commun. *1971*, 33.

[37] *Y. N. Molin* and *E. E. Zaev*, Zh. Strukt. Khim. *8*, 140 (1967).

[38] *E. E. Zaev, V. K. Voronov, M. S. Shvartsberg, S. F. Vasilevsky, Y. N. Molin*, and *I. L. Kotljarevsky*, Tetrahedron Lett. *5*, 617 (1968).

[39] *H. G. Friedman, Jr., G. R. Choppin*, and *D. G. Feuerbacher*, J. Chem. Educ. *41*, 354 (1964).

[40] *M. Ihnat* and *R. Bersohn*, Biochemistry *9*, 4555 (1970).

[41] *A. M. Bowles, W. A. Szarek*, and *M. C. Baird*, Inorg. Nucl. Chem. Lett. *7*, 25 (1971).

[42] *J. K. M. Sanders* and *D. H. Williams*, Tetrahedron Lett. *1971*, 2813.

[43] *F. A. Hart, G. P. Moss*, and *M. L. Staniforth*, Tetrahedron Lett. *1971*, 3389.

[44] *C. Reyes-Zamora* and *C. S. Tsai*, Chem. Commun. *1971*, 1047.

[45] *W. DeW. Horrocks, Jr., J. P. Sipe, III*, and *J. R. Luber*, J. Amer. Chem. Soc. *93*, 5258 (1971).

[46] *J. K. Przystal, W. G. Bos*, and *I. B. Liss*, J. Inorg. Nucl. Chem. *33*, 679 (1971).

[47] *D. R. Crump, J. K. M. Sanders*, and *D. H. Williams*, Tetrahedron Lett. *1970*, 4419 and 4949.

[48] *J. Armitage* and *L. D. Hall*, Canad. J. Chem. *49*, 277 (1971).

[49] *R. E. Rondeau* and *R. E. Sievers*, J. Amer. Chem. Soc. *93*, 641 (1971).

[50] *K. J. Eisentraut* and *R. E. Sievers*, J. Amer. Chem. Soc. *87*, 5254 (1965).

[51] *M. McCreary*, cited in Ref. [120].

[52] *E. O. Fischer* and *H. Fischer*, J. Organometal. Chem. *6*, 141 (1966).

[53] *I. Morishima, K. Endo*, and *T. Yonezawa*, J. Amer. Chem. Soc. *93*, 2048 (1971).

[54] *I. Morishima, K. Endo*, and *T. Yonezawa*, Chem. Phys. Lett. *9*, 143, 203 (1971).

[55] *H. Brunner, K. M. Hausser*, and *F. A. Neugebauer*, Tetrahedron *27*, 3611 (1971).

[56] *F. A. Neugebauer, H. Brunner*, and *K. M. Hausser*, Tetrahedron *27*, 3623 (1971).

[57] *G. P. Schiemenz*, J. Magn. Resonance *6*, 291 (1972).

[58] *H. G. Richey, Jr.* and *F. W. von Rein*, Tetrahedron Lett. *1971*, 3781.

[59] *A. H. Lewin*, Tetrahedron Lett. *1971*, 3583.

[60] *H. Huber* and *C. Pascual*, Helv. Chim. Acta *54*, 913 (1971).

[61] *J. R. Corfield* and *S. Trippett*, Chem. Commun. *1971*, 721.

[62] *P. V. Demarco, T. K. Elzey, R. B. Lewis*, and *E. Wenkert*, J. Amer. Chem. Soc. *92*, 5734 (1970).

[63] *C. C. Hinckley, M. R. Klotz*, and *F. Patil*, J. Amer. Chem. Soc. *93*, 2417 (1971).

[64] *G. H. Wahl, jun.* and *M. R. Petersen, jun.*, Chem. Commun. *1970*, 1167.

[65] *L. H. Keith*, Tetrahedron Lett. *1971*, 3.

[66] *S. Farid, A. Ateya*, and *M. Maggio*, Chem. Commun. *1971*, 1285.

[67] *A. F. Cockerill* and *D. M. Rackham*, Tetrahedron Lett. *1970*, 5149.

[68] *A. J. Rafalski, J. Barciszewski*, and *M. Wiewiorowski*, Tetrahedron Lett. *1971*, 2829.

[69] *Z. W. Wolkowski*, Tetrahedron Lett. *1971*, 825.

[70] *A. F. Cockerill* and *D. M. Rackham*, Tetrahedron Lett. *1970*, 5153.

[71] *J. Barciszewski, A. J. Rafalski,* and *M. Wiewiorowski,* Bull. Acad. Pol. Sci, Sér. Sci. Chim. *19,* 545 (1971).

[72] *M. R. Willcott, J. F. M. Oth, J. Thio, G. Plinke,* and *G. Schröder,* Tetrahedron Lett. *1971,* 1579.

[73] *J. Paasivirta,* Suomen Kemistilehti B *44,* 131, 135 (1971).

[74] *J. Paasivirta* and *P. J. Mälkönen,* Suomen Kemistilehti B *44,* 230, 238 (1971).

[75] *L. Ernst,* Chem.-Ztg. *95,* **325** (1971).

[76] *J. Goodisman* and *R. S. Matthews,* Chem. Commun. *1972,* 127.

[77] *J. K. M. Sanders* and *D. H. Williams,* J. Amer. Chem. Soc. *93,* 641 (1971).

[78] *R. R. Fraser* and *Y. Y. Wigfield,* Chem. Commun. *1970,* 1471.

[79] *C. Beauté, Z. W. Wolkowski,* and *N. Thoai,* Tetrahedron Lett. *1971,* 817.

[80] *C. Beauté, Z. W. Wolkowski, J. P. Merda,* and *D. Lelandais,* Tetrahedron Lett. *1971,* 2473.

[81] *Z. W. Wolkowski,* Tetrahedron Lett. *1971,* 821.

[82] *R. v. Ammon, B. Kanellakopulos,* and *R. D. Fischer,* Chem. Ber. *105,* 45 (1972).

[83] *P. H. Mazzocchi, H. J. Tamburin,* and *G. R. Miller,* Tetrahedron Lett. *1971,* 1819.

[84] *R. Caple* and *S. C. Kuo,* Tetrahedron Lett. *1971,* 4413.

[85] *T. H. Siddall, III,* Chem. Commun. *1971,* 452.

[86] *S. B. Tjan* and *F. R. Visser,* Tetrahedron Lett. *1971,* 2833.

[87] *R. E. Cramer* and *K. Seff,* Chem. Commun. *1972,* 400.

[88] *M. Kishi, K. Tori,* and *T. Komeno,* Chem. Commun. *1972,* 3525.

[89] *N. S. Bhacca* and *J. D. Wander,* Chem. Commun. *1971,* 1505.

[90] *A. F. Bramwell, G. Riezebos,* and *R. D. Wells,* Tetrahedron Lett. *1971,* 2489.

[91] *H.-D. Scharf* and *M.-H. Feilen,* Tetrahedron Lett. *1971,* 2745.

[92] *S. G. Levine* and *R. E. Hicks,* Tetrahedron Lett. *1971,* 311.

[93] *M. Gielen, N. Goffin,* and *J. Topart,* J. Organometal. Chem. *32,* C38 (1971).

[94] *K. C. Yee* and *W. G. Bentrude,* Tetrahedron Lett. *1971,* 2775.

[95] *H. Kato* and *H. Kato,* Bull. Chem. Soc. Japan *44,* 1734 (1971).

[96] *J. A. Peters, J. E. Remijnse, A. van der Wiele,* and *H. van Bekkum,* Tetrahedron Lett. *1971,* 3065.

[97] *C. Beauté, S. Cornuel, D. Lelandis, N. Thoai,* and *Z. W. Wolkowski,* Tetrahedron Lett. *1972,* 1099.

[98] *T. J. Marks, J. S. Kristoff, A. Alich,* and *D. F. Shriver,* J. Organometal. Chem. *33,* C35 (1971).

[99] *L. Ernst* and *A. Mannschreck,* Tetrahedron Lett. *1971,* 3023.

[100] *I. Fleming, S. W. Hanson,* and *J. K. M. Sanders,* Tetrahedron Lett. *1971,* 3733.

[101] *Y. Kashman* and *O. Awerbouch,* Tetrahedron *27,* 5593 (1971).

[102] *H. Hart* and *G. M. Love,* Tetrahedron Lett. *1971,* 625.

[103] *A. R. Katritzky* and *A. Smith,* Tetrahedron Lett. *1971,* 1765.

[104] *J. E. Guillet, I. R. Peat,* and *W. F. Reynolds,* Tetrahedron Lett. *1971, 3493.*

[105] *F. F.-L. Ho,* Polymer Letters *9,* 491 (1971).

[106] *H. Kessler,* Angew. Chem. *82,* 237 (1970); Angew. Chem. internat. Edit. *9,* 219 (1970).

[107] *A. C. Adams* and *E. H. Larsen,* Inorg. Chem. *5,* 814 (1966).

[108] *T. R. Stengle* and *C. H. Langford,* Coord. Chem. Rev. *2,* 349 (1967).

[109] *C. Beauté, Z. W. Wolkowski,* and *N. Thoai,* Chem. Commun. *1971,* 700.

[110] *F. Lux, G. Wirth, K. W. Bagnall,* and *D. Brown,* Z. Naturforsch. *24b,* 214 (1969).

[111] *A. Fratiello, V. Kubo, R. E. Lee, S. Peak,* and *R. E. Schuster,* J. Inorg. Nucl. Chem. *32,* 3114 (1970).

[112] *A. Fratiello, V. Kubo, S. Peak, B. Sanchez,* and *R. E. Schuster,* Inorg. Chem. *10,* 744 (1971) and literature cited therein.

[113] *E. Breitmaier, G. Jung,* and *W. Voelter,* Angew. Chem. *83,* 659 (1971); Angew. Chem. internat. Edit. *10,* 673 (1971).

[114] *O. A. Gansow, M. R. Wilcott,* and *R. E. Lenkinski,* J. Amer. Chem. Soc. *93,* 4295 (1971).

[115] *B. Birdsall, J. Feeney, J. A. Glasel, R. J. P. Williams,* and *A. V. Xavier,* Chem. Commun. *1971,* 1473.

[116] *W. H. Pirkle* and *S. D. Beare,* J. Amer. Chem. Soc. *91,* 5150 (1969), and literature cited therein.

[117] *C. R. Powers* and *G. W. Everett, Jr.,* J. Amer. Chem. Soc. *91,* 3468 (1969).

[118] *R. E. Ernst, M. J. O'Connor,* and *R. H. Holm,* J. Amer. Chem. Soc. *89,* 6104 (1967); *90,* 5305 (1968).

[119] *G. M. Whiteside* and *D. W. Lewis,* J. Amer. Chem. Soc. *92,* 6979 (1970).

[120] *H. L. Goering, J. N. Eikenberry,* and *G. S. Koermer,* J. Amer. Chem. Soc. *93,* 5913 (1971).

[121] *G. M. Whitesides* and *D. W. Lewis,* J. Amer. Chem. Soc. *93,* 5914 (1971).

[122] *E. A. Berends* and *J. G. Brushmiller,* Inorg. Nucl. Chem. Lett. *6,* 847 (1970).

[123] *N. Ahmad, N. S. Bhacca, J. Selbin,* and *J. D. Wander,* J. Amer. Chem. Soc. *93,* 2564 (1971).

[124] *L. Tomić, Z. Majerski, M. Tomić,* and *D. E. Sunko,* Chem. Commun. *1971,* 719.

[125] *A. E. Crease* and *P. Legzdins,* Chem. Commun. *1972,* 268.

[126] *J. E. Maskasky, J. R. Mooney,* and *M. E. Kenney,* J. Amer. Chem. Soc. *94,* 2132 (1972).

[127] *L. Pohl,* Kontakte (Merck) *1,* 17 (1972).

[128] *A. Ahmadi,* Bericht CEA-R-4235 (Saclay) (1971).

[129] *K. Fricke,* Spectrochim. Acta *28A,* 735 (1972).

[130] *I. Morishima, K. Okada,* and *T. Yonezawa,* J. Amer. Chem. Soc. *94,* 1425 (1972).

[131] *R. Claramunt, J. Elguero,* and *R. Jacquier,* Org. Magn. Resonance *3,* 595 (1971).

[132] *W. H. Pirkle, R. L. Muntz,* and *I. C. Paul,* J. Amer. Chem. Soc. *93,* 2817 (1971).

[133] *D. F. Evans* and *M. Wyatt,* Chem. Commun. *1972,* 312.

[134] *Y. Takagi, S. Teratani,* and *J. Uzawa,* Chem. Commun. *1972,* 280.

[135] *G. V. Smith, W. A. Boyd,* and *C. C. Hinckley,* J. Amer. Chem. Soc. *93,* 6319 (1971).

[136] *C. C. Hinckley, E. A. Boyd,* and *G. V. Smith,* Tetrahedron Lett. *1972,* 879.

[137] *A. Ius, G. Vecchio,* and *G. Carrea,* Tetrahedron Lett. *1972,* 1543.

[138] *W. L. F. Armarego, T. J. Batterham,* and *J. R. Kershaw,* Org. Magn. Resonance *3,* 575 (1971).

[139] *M. R. Willcott, III, R. E. Lenkinski,* and *R. E. Davis,* J. Amer. Chem. Soc. *94,* 1742 (1972).

[140] *R. E. Davis* and *M. R. Willcott, III,* J. Amer. Chem. Soc. *94,* 1744 (1972).

[141] *I. Armitage, G. Dunsmore, L. D. Hall,* and *A. G. Marshall,* Chem. Commun. *1971,* 1281; Chem. Ind. *1972,* 79.

[142] *D. R. Kelsey,* J. Amer. Chem. Soc. *94,* 1764 (1972).

[143] *D. E. Williams,* Tetrahedron Lett. *1972,* 1345.

[144] *R. v. Ammon* and *B. Kanellakopulos,* Ber. Bunsenges. Phys. Chem., in press.

[145] *L. R. Isbrandt* and *M. T. Rogers,* Chem. Commun. *1971,* 1378.

[146] *Th. Moeller* in *K. W. Bagnall:* MTP International Review of Science, Inorg. Chem. Ser. 1, Vol. 7, p. 275, Butterworths, London 1972.

[147] *L. A. Aslanov, E. F. Korytnyi,* and *M. A. Porai-Koshits,* J. strukt. Chim. (Russ.) *12,* 661 (1971); Engl. transl. *12,* 600 (1971).

[148] *B. Kanellakopulos, E. Dornberger, R. v. Ammon,* and *R. D. Fischer,* Angew. Chem. *82,* 956 (1970); Angew. Chem. internat. Edit. *9,* 957 (1970).

[149] *V. Schurig,* Inorg. Chem. *11,* 736 (1972).

[150] *M. van Gorkom* and *G. E. Hall,* Quart. Rev. *22,* 14 (1968).

[151] *A. M. Grotens, J. Smid,* and *E. de Boer,* J. Magn. Resonance *6,* 612 (1972).

[152] *R. D. Bennett* and *R. E. Schuster,* Tetrahedron Lett. *1972,* 673.

[153] *G. J. Martin, N. Naulet, F. Lefevre,* and *M. L. Martin,* Org. Magn. Resonance *4,* 121 (1972).

[154] *H. E. Francis* and *W. F. Wagner,* Org. Magn. Resonance *4,* 189 (1972).

[155] *M. Freymann* and *R. Freymann,* C. R. Acad. Sci. *250,* 3638 (1960).

[156] *C. D. Barry, A. C. T. North, J. A. Glasel, R. J. P. Williams,* and *A. V. Xavier,* Nature *232,* 236 (1971).

[157] *B. L. Shapiro, M. D. Johnston,* and *R. L. R. Towns,* J. Amer. Chem. Soc. *94,* 4381 (1972).

[158] *J. K. M. Sanders, S. W. Hanson,* and *D. H. Williams,* J. Amer. Chem. Soc., in press.

[159] *I. M. Armitage, V. Gibb, L. D. Hall,* and *A. G. Marshall,* 2nd Int. Symp. NMR Spectroscopy, Guildford (England), June 1972.

[160] *B. E. Mann* in Spectroscopic Properties of Inorganic and Organometallic Compounds. Specialist Periodical Report, The Chemical Society, London 1972.

[161] *C. L. Honeybourne*, Tetrahedron Lett. 1095 (1972).

[162] *W. DeW. Horrocks, Jr.* and *J. P. Sipe, III*, XIV[th] Internat. Conf. Coord. Chem., Toronto, June 1972; Science, in press.

[163] *B. Bleaney, C. M. Dobson, B. A. Levine, R. B. Martin, R. J. P. Williams*, and *A. V. Xavier*, Chem. Commun., in press.

[164] *A. S. Beryland* and *L. I. Martinenko*, Vestnik Mosk. Univ. Khim. *12*, 731 (1971).

[165] *L. Tomić, Z. Majerski, M. Tomić*, and *D. E. Sunko*, Croat. Chem. Acta *43*, 267 (1971).

[166] *W. B. Smith* and *D. L. Deavenport*, J. Magn. Resonance *6*, 256 (1972).

[167] *A. M. Grotens, C. W. Hilbers, E. de Boer*, and *J. Smid*, Tetrahedron Lett. *1972*, 2067.

[168] *J. K. M. Sanders* and *D. H. Williams*, Chem. Commun. *1972*, 436.

[169] *J. Bouquant* and *J. Chuche*, Tetrahedron Lett. *1972*, 2337.

Organic Syntheses *via* Free-Radical Displacement Reactions of Organoboranes[**]

By Herbert C. Brown and M. Mark Midland[*]

In the few short years since the discovery that organoboranes undergo facile free-radical substitution, application of these reactions has become a major new area of synthetic utility. Organoboranes undergo a wide variety of free-radical reactions such as autoxidation to the alcohol or hydroperoxide, 1,4 addition to α,β-unsaturated derivatives, addition to disulfides, and oxygen-induced radical coupling. It is evident that organoboranes constitute a versatile new source of free radicals and that these reactions can be readily controlled to give very clean syntheses. The application of these reactions will be discussed.

1. Organoboranes as Excellent Sources of Free Radicals

Recognition that the organoboranes are excellent sources of free radicals and can participate in free-radical chain reactions came about through detailed mechanistic studies of the reaction of organoboranes with oxygen[1-3] and with α,β-unsaturated carbonyl compounds[4].

Originally, it was suggested that the autoxidation of a trialkylborane proceeds *via* an intermediate "borineperoxide" (*1*)[5]. More recently, it was recognized that

$$R_3\overset{\ominus}{B}-\overset{\oplus}{O}=O \qquad (1)$$

these peroxides are true alkyl peroxide derivatives, containing the structure ROOB≤. Thus, the reaction of oxygen with tri-*sec*-butylborane in dilute solution yields the diperoxide (*2*)[6]. However, the formation of these

$$sec\text{-}Bu_3B + 2O_2 \longrightarrow sec\text{-}BuB(O_2\text{-}sec\text{-}Bu)_2 \qquad (2)$$

peroxides was long considered to involve non-radical processes because many of the usual radical inhibitors, such as hydroquinone, had no apparent effect upon the reaction[7].

The oxidation of optically active 1-phenylethylboronic acid gave a racemic product and this was considered to be suggestive of a process involving radicals[1]. Indeed, it was observed that a remarkable induction period occurs in the autoxidation of this compound in the presence of added inhibitors such as copper(II) *N,N*-dibutyldithiocarbamate and galvinoxyl [2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxyl][1]. It was then discovered that galvinoxyl also effectively inhibits the autoxidation of triisobutylborane[3], the epimeric trinorbornylboranes[2] and other organoboranes[3]. These findings led to the suggestion that the autoxidation of trialkylboranes proceeds *via* a free-radical chain process[1-3].

$$\begin{aligned} R_3B + O_2 &\longrightarrow R\cdot + R_2BO_2\cdot \\ R\cdot + O_2 &\longrightarrow RO_2\cdot \\ RO_2\cdot + BR_3 &\longrightarrow RO_2BR_2 + R\cdot \end{aligned}$$

Perhaps the most unusual feature about this proposed process is the assumption that a free alkylperoxy radical is capable of rapidly attacking boron with displacement of an alkyl radical, the latter then continuing the chain. Evidence for this reaction course has accumulated rapidly. For example, when di-*tert*-butylperoxide is

[*] Prof. H. C. Brown and M. Mark Midland
R. B. Wetherill Laboratory
Purdue University
Lafayette, Indiana 47907 (USA)

[**] Based in part on Chapter XIX of a forthcoming book (Baker Lectures) by *H. C. Brown:* Boranes in Organic Chemistry. Cornell University Press, Ithaca, N.Y. (USA)

photolyzed in the presence of trimethylborane in the cavity of an ESR spectrometer the ESR spectrum of the methyl radical can be recorded[8].

$$(tert\text{-}BuO)_2 \xrightarrow{h\nu} 2\,tert\text{-}BuO\cdot$$

$$tert\text{-}BuO\cdot + B(CH_3)_3 \longrightarrow tert\text{-}BuOB(CH_3)_2 + CH_3\cdot$$

Similar results have been obtained with triethylborane[8] and tri-*n*-butylborane[9]. This reaction, in which an alkyl group is readily displaced by reaction of a free radical containing the odd electron on oxygen ($RO\cdot$)[8,9], nitrogen ($R_2N\cdot$)[12], and sulfur ($RS\cdot$)[13], appears to be of wide generality for the trialkylboranes[10,11].

The ease with which these reactions proceed may be due to the high strengths of the bonds of boron with oxygen, nitrogen, and sulfur, providing a potent driving force for the facile displacement of alkyl radicals from organoboranes. However, irrespective of the precise reason for this new facile reaction, the reaction itself opens up a major new area of application for the organoboranes in free-radical chemistry.

2. The Autoxidation of Organoboranes

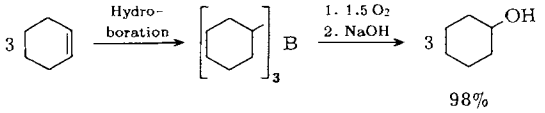
2.1. Alcohol Formation

It has long been known that organoboranes, both aliphatic and aromatic, are highly reactive toward oxygen[14]. Considerable attention has been paid to the mechanism of the autoxidation reaction[15]; but the reaction was considered not to hold promise for synthetic purposes[16,17]. Sufficient oxygen is readily absorbed to oxidize all three carbon-boron bonds, but the reaction is reported to be complex. In an unsuccessful attempt to achieve high conversion to the alcohol, long reaction times and elevated temperatures were used in the oxidation.

It is quite clear that the initial product of such oxidations is the peroxide *(3)*[6].

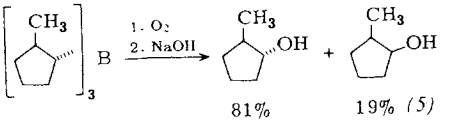
$$R_3B + O_2 \longrightarrow \underset{(3)}{R_2BO_2R}$$

It appeared possible that the low yields were due to the thermal instability of the peroxide. Consequently, gentle conditions (0 °C) were used for the introduction of the stoichiometric amount of oxygen (1.5 mol O_2 per mol R_3B) into a solution of the organoborane (0.5 M) in tetrahydrofuran (THF)[18,19]. The reaction product, possibly $RB(O_2R)OR$, was treated with aqueous alkali. Essentially quantitative yields of alcohol were obtained.

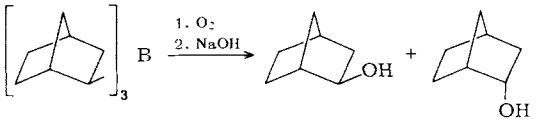


98%

A disadvantage of this procedure is that it does not possess the stereospecificity of the oxidation with alkaline hydrogen peroxide, which, for example, gives *exo*-norborneol in an isomeric purity of 99.5%. Similarly, the alcohol from 1-methylcyclopentene is essentially pure *trans*-2-methylcyclopentanol. The oxidation with oxygen produces a much larger amount of the alternate isomers *(4)* and *(5)*.



81% 19% *(5)*



86% 14% *(4)*

The formation of the alternate isomers is presumably a result of the free-radical chain reaction involved in the uptake of oxygen by the organoborane[2]. In cases where such stereochemical properties are not involved, simple oxidation with oxygen can be utilized to achieve essentially quantitative conversion of the organoborane to the corresponding alcohol. The alternative oxidation with alkaline hydrogen peroxide[20] does not involve free-radical intermediates and is very widely applicable.

2.2. Hydroperoxides

The initial product of the autoxidation of organoboranes is a peroxide *(3)*, which may either react with a second mol of oxygen to give *(6)* or undergo an intermolecular redox reaction to give *(7)*[17]. In concentrated solution (0.5 M) the redox reaction predominates at 0 °C and the peroxide content is substantially decreased.

$$\underset{(3)}{RO_2BR_2} + O_2 \longrightarrow \underset{(6)}{(RO_2)_2BR}$$

$$\underset{(3)}{RO_2BR_2} + R_3B \longrightarrow \underset{(7)}{2ROBR_2}$$

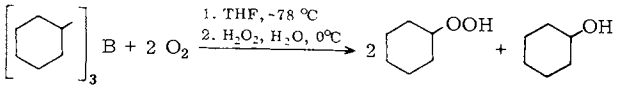
Control over formation of *(6)* and *(7)* would provide a useful route to alkyl hydroperoxides. Indeed, the intermolecular reaction has been minimized by using highly dilute (0.01 – 0.05 M) solutions. Two mols of oxygen are absorbed to form a diperoxide *(6)*. The remaining boron-carbon bond was then oxidized by the addition of an oxidizing agent such as perbenzoic acid[7]. Consequently, the autoxidation of dilute solutions of organoboranes provides a possible synthesis for alkyl hydroperoxides[21]. However, the procedure suffers from several disadvantages. It would be much more convenient if the synthesis could be realized using relatively concentrated solutions of the organoborane in THF, the preferred solvent for hydroborations.

Examination of the autoxidation of 0.5 M solutions of organoborane in THF at −78 °C using the automatic

gas generator[19] (adapted for oxygen production[18]) revealed that the reaction is initially very fast, even at this low temperature[22]. The first mol of oxygen is absorbed within 2 – 3 minutes. Organoboranes produced from disubstituted olefins having internal double bonds, such as cyclohexene, absorb the second mol of oxygen within a period of 1 hour. On the other hand, organoboranes produced from olefins with terminal double bonds, such as 1-butene, fail to absorb the second mol of oxygen at this temperature. In both cases, however, warming to 0 °C results in the rapid absorption of a second mol of oxygen. Addition of a 30% aqueous solution of hydrogen peroxide to the reaction mixture at 0 °C liberates the alkyl hydroperoxide with concurrent oxidation of the remaining boron-carbon bond. The reaction is applicable to a wide variety of structures and gives excellent results.

$$n\text{-}Bu_3B + 2\ O_2 \xrightarrow[-78\,^\circ C \rightarrow 0\,^\circ C]{THF} n\text{-}BuB(O_2Bu)_2 \xrightarrow[H_2O]{H_2O_2} 2\ n\text{-}BuOOH + n\text{-}BuOH$$

91%



95%

The above procedure provides the alkyl hydroperoxide in THF solution in a molar ratio of $2RO_2H:1ROH$. For many purposes, such mixtures of hydroperoxide may be used directly. If, however, it is desirable to separate and to isolate the pure hydroperoxide, this is readily done by treating the above solution with an excess of aqueous potassium hydroxide. The potassium salt of the hydroperoxide dissolves in the aqueous phase while the alcohol remains in the organic phase. Acidification of the aqueous phase provides the pure hydroperoxides. The low temperature autoxidation of organoboranes provides a rapid, convenient synthesis of alkyl hydroperoxides. The reaction is applicable to a wide variety of derivatives. Unlike the reaction of alkyl methanesulfonates with hydrogen peroxide[23], which produces hydroperoxides in 10—15% yield, the present procedure accommodates substrates which do not readily undergo nucleophilic substitution, such as cyclohexyl and norbornyl. The organoborane route also accommodates a wide variety of functional groups which cannot be used in the Grignard reaction[24].

3. The 1,4 Addition of Trialkylboranes

3.1. Methyl Vinyl Ketone and Acrolein

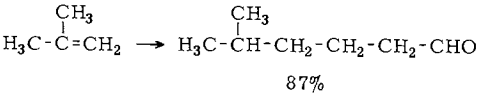
Organoboranes are much less reactive organometallic compounds than the organolithium and organomagnesium derivatives and they do not add to the carbonyl groups of aldehydes and ketones in the same manner as the latter more reactive organometallics. However, certain α,β-unsaturated carbonyl derivatives, such as methyl vinyl ketone[25] and acrolein[26], undergo an exceptionally fast 1,4-addition reaction with representative organoboranes produced *via* hydroboration.

$$R_3B + H_2C{=}CH{-}CHO \xrightarrow[25\,^\circ C]{THF} RCH_2CH{=}CH{-}OBR_2 \quad (8)$$

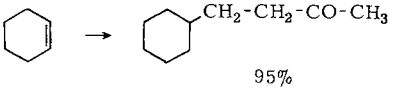
Addition of water to the reaction mixture results in the rapid hydrolysis of the intermediates *(8)* and subsequent liberation of the corresponding aldehyde or methyl ketone.

$$RCH_2{-}CH{=}CH{-}OBR_2 + H_2O \longrightarrow RCH_2{-}CH_2{-}CHO + R_2BOH$$

The reaction provides an exceedingly simple means of homologation, in which the chain is lengthened by three or more carbon atoms. Moreover, it appears to be generally applicable to a wide range of olefins structures.



87%

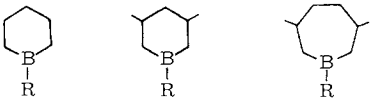


95%

Recycling of the intermediate R_2BOH on an industrial scale should offer no difficulty. However, it is inconvenient to attempt such a recycle in laboratory syntheses.

Tri-*n*-butylborane, prepared by hydroboration of 1-butene, contains 94% *n*-butyl and 6% *sec*-butyl groups; however, the product from this tri-*n*-butylborane and acrolein contains 85% of *n*-heptanal and 15% of 4-methylhexanal[26]. Clearly the *sec*-butyl groups in the trialkylborane are transferred preferentially.

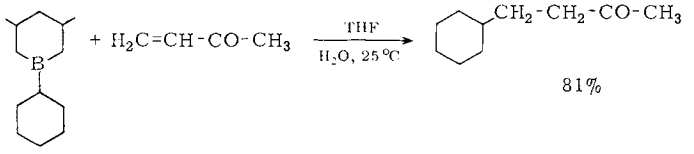
This observation suggested that *B*-alkylborinanes *(9)* or the more readily available methyl derivatives *(10)* and *(11)*, containing secondary or tertiary groups on the boron atom, might solve the difficulty.



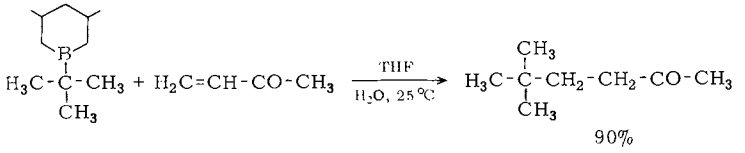
(9) *(10)* *(11)*

Convenient methods have been developed for the synthesis of the parent reagents[27].

These *B*-alkylboracycloalkanes react easily with methyl vinyl ketone and similar α,β-unsaturated carbonyl derivatives to give the desired products in excellent yields[28].



81%

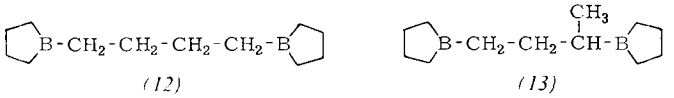


90%

3.2. Scope of the 1,4-Addition Reaction

The 1,4-addition reaction of organoboranes to methyl vinyl ketone and acrolein is capable of accommodating a wide range of structures in the alkyl group—from acyclic, to cyclic, to bicyclic. Indeed, cyclic organoboranes, which can be obtained by hydroboration of dienes, readily participate in the reaction, thus providing a simple route to the synthesis of ω-hydroxyaldehydes and -ketones[29].

For example, the product obtained by hydroboration of 1,3-butadiene contains 1,4- and 1,3-diborabutane moieties *(12)* and *(13)*[30]. Reaction with methyl vinyl



(12) *(13)*

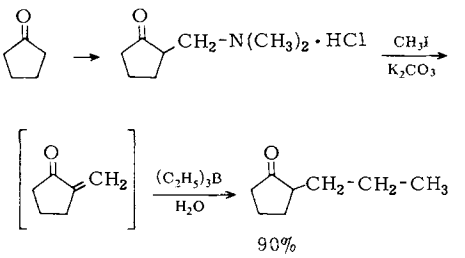
ketone in the presence of water or alcohol, followed by oxidation with alkaline hydrogen peroxide gave an 85% yield of ω-hydroxyketones containing 8-hydroxyoctan-2-one and its isomer, presumably 7-hydroxy-5-methyl-2-heptanone in a ratio of 70:30. If *(13)* is removed by thermal treatment[30], the 8-hydroxy-2-octanone is formed in a purity of 95%.

We also investigated the scope of this new synthesis with respect to the α,β-unsaturated carbonyl component. Derivatives such as acrolein and methyl vinyl ketone are often highly reactive and difficult to isolate in pure form. Organic chemists have frequently simplified the problems of working with these species by utilizing them in the form of the corresponding Mannich bases[31,32]. Accordingly, we examined the question of whether Mannich bases could be used in this synthesis.

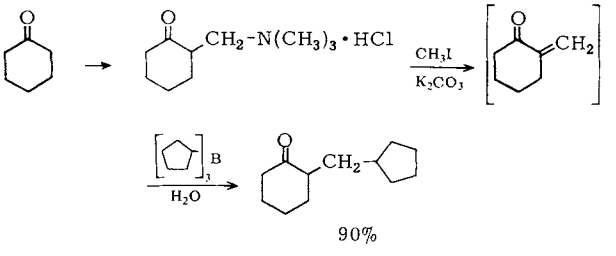
We found that Mannich bases, derived from ketones such as cyclopentanone, cyclohexanone, and norbornanone, quaternized *in situ*, react smoothly in alkaline solution with organoboranes to give the corresponding alkylated ketones[33]. A wide range of trialkylboranes can evidently be accommodated in this reaction. These reactions presumably proceed *via* the *in situ* formation of the labile α,β-unsaturated carbonyl derivatives.

Substituents in the 2-position of acrolein do not affect the reaction adversely. Thus, both 2-methylacrolein and 2-bromoacrolein react smoothly[34] (figures quoted are yields of isolated products). This appears to be the most suitable possible route to the α-bromoaldehydes.

Unexpectedly, neither crotonaldehyde nor 3-penten-2-one reacted with the organoborane under these condi-

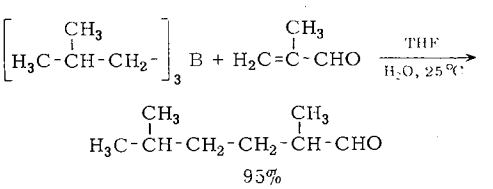


90%

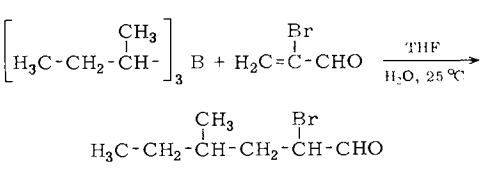


90%

tions. This was surprising. Evidently, the introduction of a methyl group in the acrolein molecule in the 1-position or the 2-position had no adverse effect on



95%

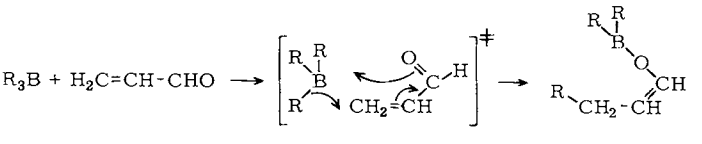


81%

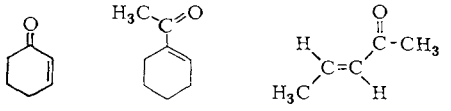
the ease of reaction. However, a methyl group in the 3-position completely blocked the reaction even under drastic conditions (24 hours at 125 °C). This was puzzling and induced us to investigate the reaction mechanism.

3.3. The 1,4 Addition as a Free-Radical Chain Reaction

The 1,4 addition of the Grignard reagent to α,β-unsaturated ketones is believed to proceed through a cyclic transition state[35]. As a working hypothesis, we originally assumed that the 1,4 addition of the organoborane likewise proceeded *via* a cyclic transitition state.



The failure of 2-cyclohexen-1-one *(14)* to react was not surprising and seemed to be consistent with the cyclic mechanism[4]. That the 1-cyclohexenyl methyl ketone *(15)* also failed to react appeared to be difficult to rationalize in terms of the proposed cyclic



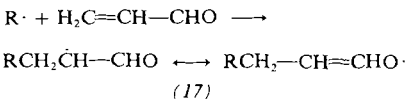
(14) *(15)* *(16)*

mechanism. However, the failure of *trans*-crotonaldehyde and the related *trans*-3-penten-2-one *(16)* to react was much more difficult to explain in terms of this mechanism.

Such enormous effects of terminal methyl groups on reactivity are often observed in free-radical polymerizations[36]. We were therefore led to consider the possibility that free-radical intermediates are involved in this reaction.

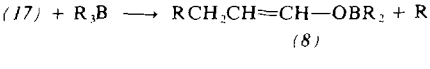
Galvinoxyl is known to be an efficient scavenger for free radicals[37] and has been successfully employed to inhibit the autoxidation of certain organoboranes[1-3]. We therefore explored its effect on the 1,4-addition and found that the presence of 5 mol % of galvinoxyl does, in fact, effectively stop the otherwise very fast reaction of trialkylboranes with acrolein and methyl vinyl ketone. It can be concluded, therefore, that the reactions must be free-radical chain reactions.

The mechanism evidently involves the addition of a radical to the carbon-carbon double bond of the carbonyl compound, whereby a radical intermediate *(17)* is formed. In the absence of a reactive organoborane, this intermediate would add to the monomer through



(17)

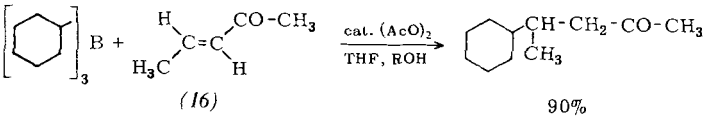
carbon to initiate a typical vinyl polymerization[38]. However, in the presence of free trialkylborane this intermediate evidently reacts through the oxygen atom to form the borinate *(8)* with its very strong boron-oxygen bond. This step thus resembles the reaction of



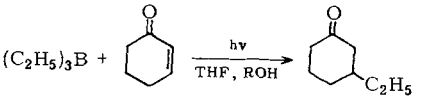
(8)

alkoxy radicals with organoboranes[8,9] as was discussed earlier.

If the inability of these terminally substituted α,β-unsaturated carbonyl compounds to undergo 1,4-addition is the result of a relatively short chain-length, it should be possible to effect the reaction by introducing an efficient free-radical initiator. We observed that the 1,4-addition reactions could be extended to these terminally substituted derivatives by both photochemical activation and the addition of diacetyl peroxide[39].



(16) 90%

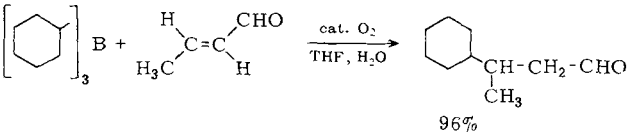


(14) 95%

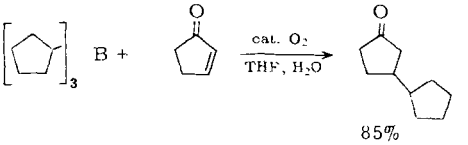
As was pointed out earlier, the addition of oxygen to organoboranes produces free radicals. It was suggested, therefore, that the addition of air to a mixture of the organoborane and the "inert" α,β-unsaturated carbonyl derivative might induce the desired 1,4-addition. This was tested. Indeed, 4-methyl-2-hexanone was formed in 70% yield when a slow stream of air was passed over a solution of triethylborane and *trans*-3-penten-2-one in aqueous THF[40].

It is essential that the air be added slowly and in controlled amounts. In experiments in which oxygen was added rapidly, oxidation of the organoborane became the dominant reaction, and only a minor amount of the 1,4-addition product was obtained. Even when oxygen is added slowly, some of the organoborane is lost through oxidation. However, this is usually so small that the loss can be considered insignificant; a small excess of the organoborane can be added to compensate for that lost through oxidation.

The reaction appears to be one of general applicability, accommodating a wide variety of organoboranes and α,β-unsaturated carbonyl compounds; the corresponding β-substituted aldehydes and ketones are formed in excellent yields.



96%



85%

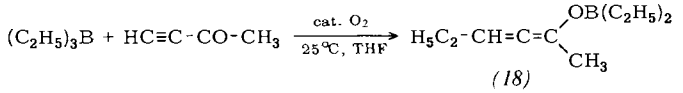
This finding suggested that the slow introduction of oxygen or air into an organoborane generates free radicals, which in turn initiate free-radical chain reactions. In suitable systems the organoborane is also active for chain propagation. Consequently, the organoboranes appeared to be very promising reagents for free-radical chain reactions, so we undertook to explore such systems.

3.4. Extension of the 1,4-Addition Reaction to New Systems

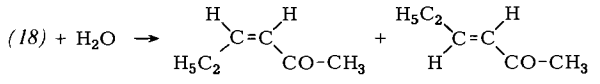
3.4.1. Acetylacetylene

No reaction takes place between triethylborane and acetylacetylene when air and light are carefully excluded

from the reaction mixture, even with an extended reaction time of 24 hours. However, 3-hexen-2-one is obtained in 79% yield in 2 hours under identical reaction conditions provided the reaction mixture is exposed to a slow stream of air[41].



(18)

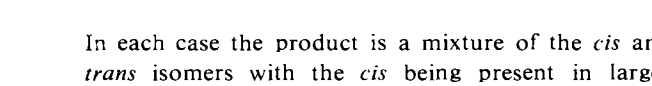


In contrast to the behavior of methyl vinyl ketone, the presence of water in the reaction mixture is required in order to achieve a good yield of the desired product. Presumably, the allene intermediate *(18)* is highly susceptible to further attack by the free-radical intermediates and this side reaction is minimized by the *in situ* hydrolysis of the borinate. Solvolysis of the intermediate may also be achieved through the use of alcohols, such as methanol and ethylene glycol. This is especially recommended in cases where anhydrous conditions should be maintained.

The conclusion that the reaction proceeds *via* a free-radical chain reaction is supported by the fact that other typical free-radical initiators may be used to induce the 1,4-addition. As an example, the reaction of triethylborane can be induced photolytically or by the thermal decomposition of azobis(isobutyronitrile) at 40 °C. The yields are comparable to those obtained when air is used for the initiation.

The reaction appears to be one of wide generality; unsaturated methyl ketones can be prepared in this way from various types of alkenes.





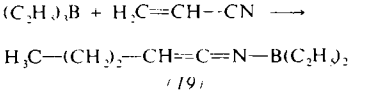
In each case the product is a mixture of the *cis* and *trans* isomers with the *cis* being present in larger amounts than the *trans*. The ratio of the isomers appears to vary with the conditions of the protonolysis stage. However, further investigations are necessary for a complete understanding of the reaction in this connection.

This oxygen-induced reaction of organoboranes with acetylacetylene produces α,β-unsaturated ketones. These have previously been shown to undergo the 1,4-addition reaction with organoboranes. Accordingly, the reaction appears capable of being controlled introduce two different groups from two different organoboranes, thus making available a wide variety of ketones.



3.4.2. Acrylonitrile

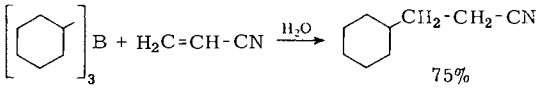
Similarly, acrylonitrile fails to react with trialkylboranes in the absence of oxygen or other free-radical initiators. In the presence of oxygen the reaction of triethylborane with acrylonitrile proceeds readily, the reagents being consumed in a 1:1 ratio[42]. However, the intermediate *(19)* evidently undergoes some other reaction



(19)

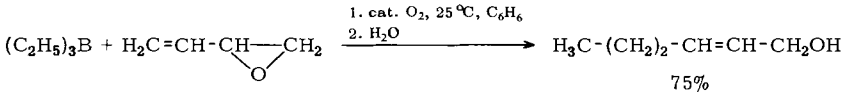
prior to hydrolysis, since valeronitrile is not present in the reaction mixture.

With secondary alkyl derivatives, such as tricyclohexylborane, the reaction proceeds in the normal manner. In this case oxygen or other initiators initiate a reaction resulting in the formation of 3-cyclohexylpropionitrile.



3.4.3. 1,3-Butadiene Monoxide

No reaction takes place between 1,3-butadiene monoxide and triethylborane in the absence of oxygen.



However, the reaction proceeds smoothly on introduction of small quantities of air[43]. With equimolar amounts of the two reactants, the yield was only 44%.

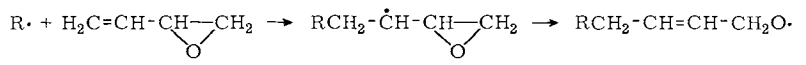
However, use of an excess of 1,3-butadiene monoxide led to improved yields. The 2-hexen-1-ol product was predominantly the *trans* isomer (89% *trans*, 11% *cis*).

Typical free-radical initiators, such as di-*tert*-butyl peroxide, azobis(isobutyronitrile), and oxygen, are also effective in promoting the reaction. Moreover, a typical free-radical scavenger, galvinoxyl, inhibits the reaction. Thus the reaction must involve a free-radical chain mechanism.

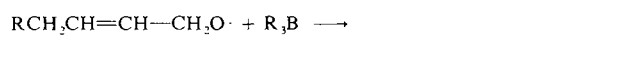
As was discussed earlier, trialkylboranes react with oxygen to generate alkyl radicals.

In the presence of 1,3-butadiene monoxide, these alkyl radicals must add to the double bond of the epoxide

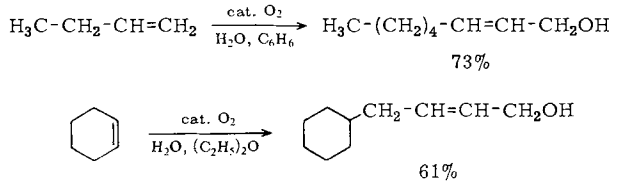
to yield an intermediate radical which rearranges to give an alkoxy free radical.



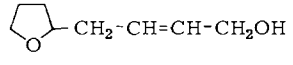
The alkoxy radical reacts with the trialkylborane to form a borinate, displacing an alkyl radical which continues the chain.



Hydrolysis of the intermediate borinate affords the 4-alkyl-2-buten-1-ol. The reaction proceeds satisfactorily with a variety of alkyl groups and reasonable yields of product are obtained.



Since trialkylboranes are generally prepared in THF solution, this has usually been the solvent of choice for reactions of organoboranes. However, in the present case, we observed the formation of considerable quantities of 4-(2′-tetrahydrofurfuryl)-2-buten-1-ol *(20)*.



(20)

Apparently the free-radical intermediates can attack the THF molecule, producing a new free-radical intermediate which can add to the 1,3-butadiene monoxide. This side reaction can be avoided in benzene; accordingly, this was the preferred solvent for the reaction of organoboranes with primary alkyl groups. For some reason, organoboranes with secondary alkyl groups give slightly higher yields in ethyl ether as the solvent, in spite of a competitive reaction with solvent analogous to that observed in THF.

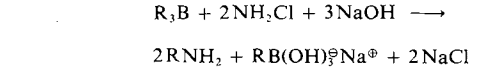
These initial results indicate that the free-radical addition of organoboranes must be quite general, far more general than was indicated by our initial explorations. Thus, our studies directed at understanding why crotonaldehyde and 3-penten-2-one failed to undergo a reaction that is readily participated in by the very similar structures acrolein and methyl vinyl ketone led to a wide extension of the original reaction.

4. Other Types of Free-Radical Reactions

An essential feature of the chemistry discussed up to this point has been the newly discovered facile reaction of alkoxy free radicals, $RO\cdot$, with organoboranes with displacement of alkyl radicals. As was pointed out earlier, this reaction also occurs readily with the related free radicals, $R_2N\cdot$ and $RS\cdot$. This suggests that a large number of chain reactions of organoboranes involving $R_2N\cdot$ and $RS\cdot$ intermediates should exist; these would be analogous to the many chain reactions we have been reviewing involving $RO\cdot$. In fact, recognition of this possibility resulted in the resolution of a long-standing problem.

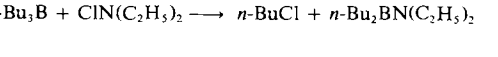
4.1. Reaction of Boranes with *N*-Chlorodimethylamine

It had previously been observed that chloramine reacts with organoboranes in the presence of base to produce the corresponding amine[44].

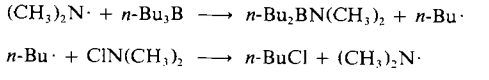


Although this reaction utilizes only two of the three groups of the organoboranes, it provides a very convenient stereospecific route to certain amines.

Sharefkin and *Banks* tried to extend the reaction to the synthesis of alkyldiethylamines, especially *n*-butyldiethylamine[45]. However, the reaction took another course: *n*-butyl chloride was formed.



It has now been shown that this last reaction is a free-radical chain reaction, proceeding *via* the $(CH_3)_2N\cdot$ radical[46]. Addition of galvinoxyl inhibits the free-



radical reaction and the reaction then follows the polar pathway, leading to formation of the tertiary amine.

Unfortunately the reaction, in its present state of development, does not yet appear to be of any use for synthetic purposes. Nevertheless, it looks highly promising and is being further explored.

4.2. Reaction of Boranes with Organic Disulfides

Trialkylboranes either do not react, or react very slowly, with disulfides such as phenyl disulfide or methyl disulfide. However, under the influence of light or with passage of a slow stream of air into a mixture of the

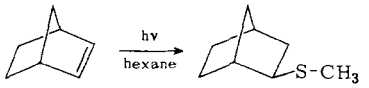
organoborane and disulfide, a facile reaction is induced that appears to be broady applicable, and provides the

$$R_3B + H_5C_6{-}S{-}S{-}C_6H_5 \xrightarrow[\text{or air}]{h\nu} R{-}S{-}C_6H_5 + R_2B{-}S{-}C_6H_5$$

$$R_3B + 2\,H_3C{-}S{-}S{-}CH_3 \xrightarrow[\text{or air}]{h\nu} 2\,R{-}S{-}CH_3 + RB(S{-}CH_3)_2$$

corresponding sulfide in excellent yield[47].

$$H_3C{-}(CH_2)_5{-}CH{=}CH_2 \xrightarrow[\text{hexane}]{h\nu} H_3C{-}(CH_2)_7{-}S{-}CH_3 \quad 95\%$$



95%

The reaction is strongly inhibited by iodine and consequently must involve a free-radical chain reaction proceeding *via* methylthio radicals. An interesting feature is the conclusion that free radicals must attack

$$R_3B + O_2 \longrightarrow R_2BO_2\cdot + R\cdot$$
$$R\cdot + R'SSR' \longrightarrow RSR' + R'S\cdot$$
$$R'S\cdot + R_3B \longrightarrow R'SBR_2 + R\cdot$$
$$R'S\cdot + R'SBR_2 \longrightarrow (R'S)_2BR + R\cdot$$

one of the sulfur atoms in the disulfide linkage to form the corresponding sulfide with liberation of an organothio radical. Such reactions of sulfides have been long accepted[48].

4.3. The Oxygen-Induced Reaction of Alkyl Iodides with Organoboranes

4.3.1. Alkyl Iodide Formation

As was pointed out earlier, the rate of oxygen absorption by solutions of organoboranes can be conveniently followed with the aid of the automatic gas generator. We used this technique to establish the rate of oxygen uptake by representative organoboranes and then began to investigate the effect of various added materials. Added iodine caused a complete inhibition of oxygen absorption; this phenomenon was subjected to a detailed study[49,50].

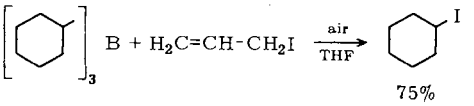
An examination of the effect of typical organic iodides on the rate of reaction of trialkylboranes with oxygen revealed that the rate is not significantly altered (unless significant amounts of iodine are liberated), but the products are very different. With tri-*n*-butylborane, *n*-butyliodide was formed[51].

The products suggest that the *n*-Bu· formed in the initiation step of autoxidation can react either with the organic iodide present or with oxygen in the usual way.

$$n\text{-Bu}\cdot + RI \longrightarrow n\text{-BuI} + R\cdot$$
$$n\text{-Bu}\cdot + O_2 \longrightarrow n\text{-BuO}_2\cdot$$

These considerations suggested that it might be possible, by controlling the rate and quantity of oxygen introduced, to control the course of the reaction to produce alkyl iodide preferentially. Indeed, we discovered that by introducing air into a reaction mixture containing equimolar amounts of R_3B and allyl iodide it was possible to obtain essentially quantitative yields of the alkyl

$$(C_2H_5)_3B + H_2C{=}CH{-}CH_2I \xrightarrow[THF]{air} C_2H_5I \quad 100\%$$



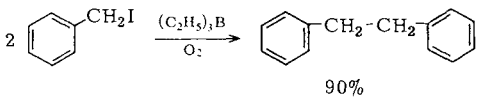
iodide. Consequently, the reaction may be used as an alternative to the base-induced iodination of trialkylboranes for the preparation of alkyl iodides[52]. It should be especially valuable for alkyl groups which are sensitive to alkaline solutions.

4.3.2. Coupling

In the reactions which have been discussed earlier (other than oxidation), only a catalytic amount of oxygen has been required to induce the desired reaction. However, in the present reaction involving organic halides, approximately one mol of oxygen is required per mol of alkyl iodide formed. Hence the reaction is not a chain reaction.

The stable radicals produced after halogen abstraction, such as allyl and benzyl, do not continue the chain, but undergo coupling. Initially, the molar quantity of biallyl formed is one-half that of the alkyl iodide produced in the reaction. However, in the final stages of the reaction the amount of biallyl formed fails to increase significantly, even though additional alkyl iodide is formed. A possible explanation for this is that in the final stages of the reaction the autoxidation of the residual organoborane (proceeding *via* ethyl radicals) fails to compete effectively with the allyl radicals for the oxygen dissolved in the solution.

To obtain high yields of the coupled product, the reaction of the allyl radical (and related radicals) with oxygen must be minimized. This is readily achieved by using an excess of organoborane. The readily available triethylborane was adopted as the reagent and was used in 100% excess to obtained the desired coupled product.



$$2\ H_2C{=}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{-}CH_2I \xrightarrow[O_2]{(C_2H_5)_3B} H_2C{=}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{=}CH_2 \quad 90\%$$

The reaction was very clean; no detectable amount of coupling with ethyl radicals was observed. Evidently the ethyl radicals abstract iodine or react with oxygen

rapidly and do not couple. On the other hand, mixed coupling products could be obtained from mixed allylic and benzylic iodides. The coupling gave a nearly statistical distribution of products. If one desired to couple an expensive or rare iodide with a more available iodide, an excess of the latter can be used to increase the conversion of the more valuable material. Thus 4-phenyl-1-butene was obtained in 72% yield when a 4-fold excess of allyl iodide was used along with benzyl iodide.

The free-radical coupling of olefins may be readily achieved by hydroboration followed by treatment of the organoborane with alkaline silver nitrate[53, 54]. The air-induced coupling of allylic and benzylic iodides now provides a method of coupling alkyl groups under mild conditions—a feature which hydroboration cannot offer. Both methods may accommodate a wide variety of functional groups.

5. Conclusion

The reaction of oxygen with organoboranes was first studied in 1862[55], yet it was not until 1967 that it was finally recognized that the reaction must involve a facile free-radical chain process[1]. The 1,4-addition reaction of organoboranes with methyl vinyl ketone[25] and acrolein[26] was first reported in 1967. Recognition that these reactions also proceeded *via* free-radical chain reactions was reported in 1970[4]. We are presently only in the initial stages of our studies of such free-radical reactions; however, the present state of our knowledge of these systems indicates that we can anticipate a large increase in the number and kinds of free-radical reactions involving organoboranes.

Received: July 7, 1971 [A 890 IE]
German version: Angew. Chem. *84*, 702 (1972)

[1] *A. G. Davies* and *B. P. Roberts*, J. Chem. Soc. *B 1967*, 17.

[2] *A. G. Davies* and *B. P. Roberts*, J. Chem. Soc. *B 1969*, 311.

[3] *P. G. Allies* and *P. B. Brindley*, J. Chem. Soc. *B 1969*, 1126.

[4] *G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase*, and *M. Itoh*, J. Amer. Chem. Soc. *92*, 710 (1970).

[5] *J. R. Johnson* and *M. G. Van Campen*, J. Amer. Chem. Soc. *60*, 121 (1938).

[6] *A. G. Davies* and *D. G. Hare*, J. Chem. Soc. *1959*, 438.

[7] *M. H. Abraham* and *A. G. Davies*, J. Chem. Soc. *1959*, 429.

[8] *P. J. Krusic* and *J. K. Kochi*, J. Amer. Chem. Soc. *91*, 3942 (1969).

[9] *A. G. Davies* and *B. P. Roberts*, J. Chem. Soc. *D 1969*, 699.

[10] *A. G. Davies* and *B. P. Roberts*, Nature Phys. Sci. *229*, 221 (1971).

[11] *K. U. Ingold* and *B. P. Roberts:* Free Radical Substitution Reactions. Interscience, New York 1971, p. 46.

[12] *A. G. Davies, S. C. W. Hook*, and *B. P. Roberts*, J. Organometal. Chem. *22*, C37 (1970).

[13] *A. G. Davies*, private communication, May 1, 1970.

[14] Triarylboranes having large sterically demanding groups, *e. g.* trimesitylborane, are stable to oxygen and can be handled in air without special precautions. *H. C. Brown* and *V. H. Dodson*, J. Amer. Chem. Soc. *79*, 2302 (1957).

[15] *A. G. Davies, K. U. Ingold, B. P. Roberts*, and *R. Tudor*, J. Chem. Soc. *B 1971*, 698.

[16] *S. B. Mirviss*, J. Amer. Chem. Soc. *83*, 3051 (1961).

[17] *S. B. Mirviss*, J. Org. Chem. *32*, 1713 (1967).

[18] *H. C. Brown, M. M. Midland*, and *G. W. Kabalka*, J. Amer. Chem. Soc. *93*, 1024 (1971).

[19] We used the small automatic hydrogenator, *C. A. Brown* and *H. C. Brown*, J. Amer. Chem. Soc. *84*, 2829 (1962), modified to generate oxygen [18] so that the rate and amount of oxygen absorbed could be accurately followed.

[20] *H. C. Brown* and *G. Zweifel*, J. Amer. Chem. Soc. *83*, 2544 (1961).

[21] *G. Wilke* and *P. Heimbach*, Liebigs Ann. Chem. *652*, 7 (1962).

[22] *H. C. Brown* and *M. M. Midland*, J. Amer. Chem. Soc. *93*, 4078 (1971).

[23] *H. R. Williams* and *H. S. Mosher*, J. Amer. Chem. Soc. *76*, 2984, 2987 (1954).

[24] *C. Walling* and *S. A. Buckler*, J. Amer. Chem. Soc. *77*, 6032 (1955).

[25] *A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogić*, and *M. W. Rathke*, J. Amer. Chem. Soc. *89*, 5708 (1967).

[26] *H. C. Brown, M. M. Rogić, M. W. Rathke*, and *G. W. Kabalka*, J. Amer. Chem. Soc. *89*, 5709 (1967).

[27] *H. C. Brown* and *E. Negishi*, J. Organometal. Chem. *28*, C1 (1971).

[28] *H. C. Brown* and *E. Negishi*, J. Amer. Chem. Soc. *93*, 3777 (1971).

[29] *A. Suzuki, S. Nozawa, M. Itoh, H. C. Brown, E. Negishi*, and *S. K. Gupta*, J. Chem. Soc. *D 1969*, 1009.

[30] *H. C. Brown, E. Negishi*, and *S. K. Gupta*, J. Amer. Chem. Soc. *92*, 2460 (1970).

[31] *F. F. Blicke*, Org. Reactions *1*, 303 (1942).

[32] *J. H. Brewster* and *E. L. Eliel*, Org. Reactions *7*, 99 (1953).

[33] *H. C. Brown, M. W. Rathke, G. W. Kabalka*, and *M. M. Rogić*, J. Amer. Chem. Soc. *90*, 4166 (1968).

[34] *H. C. Brown, G. W. Kabalka, M. W. Rathke*, and *M. M. Rogić*, J. Amer. Chem. Soc. *90*, 4165 (1968).

[35] *R. E. Lutz* and *W. G. Revely*, J. Amer. Chem. Soc. *63*, 3184 (1941).

[36] *P. J. Flory:* Principles of Polymer Chemistry, Cornell University Press, Ithaca, 1953, p. 55.

[37] *P. D. Bartlett* and *T. Funahashi*, J. Amer. Chem. Soc. *84*, 2596 (1962).

[38] *F. J. Welch*, J. Polymer Sci. *61*, 243 (1962).

[39] *H. C. Brown* and *G. W. Kabalka*, J. Amer. Chem. Soc. *92*, 712 (1970).

[40] *H. C. Brown* and *G. W. Kabalka*, J. Amer. Chem. Soc. *92*, 714 (1970).

[41] *A. Suzuki, S. Nozawa, M. Itoh, H. C. Brown, G. W. Kabalka*, and *G. W. Holland*, J. Amer. Chem. Soc. *92*, 3503 (1970).

[42] Research in progress with Dr. *G. W. Holland*.

[43] *A. Suzuki, N. Miyaura, M. Itoh, H. C. Brown, G. W. Holland*, and *E. Negishi*, J. Amer. Chem. Soc. *93*, 2792 (1971).

[44] *H. C. Brown, W. R. Heydkamp, E. Breuer*, and *W. S. Murphy*, J. Amer. Chem. Soc. *86*, 3565 (1964).

[45] *J. G. Sharefkin* and *H. D. Banks*, J. Org. Chem. *30*, 4313 (1965).

[46] *A. G. Davies, S. C. W. Hook*, and *B. P. Roberts*, J. Organometal. Chem. *23*, C11 (1970).

[47] *H. C. Brown* and *M. M. Midland*, J. Amer. Chem. Soc. *93*, 3291 (1971).

[48] *W. A. Pryor* and *T. L. Pickering*, J. Amer. Chem. Soc. *84*, 2705 (1962).

[49] *M. M. Midland* and *H. C. Brown*, J. Amer. Chem. Soc. *93*, 1506 (1971).

[50] *H. C. Brown* and *M. M. Midland*, J. Chem. Soc. *D 1971*, 699.

[51] *A. Suzuki, S. Nozawa, M. Harada, M. Itoh, H. C. Brown*, and *M. M. Midland*, J. Amer. Chem. Soc. *93*, 1508 (1971).

[52] *H. C. Brown, M. W. Rathke*, and *M. M. Rogić*, J. Amer. Chem. Soc. *90*, 5038 (1968).

[53] *H. C. Brown* and *C. H. Snyder*, J. Amer. Chem. Soc. *83*, 1001 (1961).

[54] *H. C. Brown, C. Verbrugge*, and *C. H. Snyder*, J. Amer. Chem. Soc. *83*, 1002 (1961).

[55] *E. Frankland*, J. Chem. Soc. *15*, 363 (1962).

Enzymatic Hydroxylations with Molecular Oxygen

By Volker Ullrich[*]

For thermodynamic reasons, biological hydroxylations cannot usually proceed according to the β-oxidation scheme, but are possible only with the aid of molecular oxygen by a route requiring a large amount of energy. The corresponding enzymes, known as "mixed function oxygenases" or more appropriately "monooxygenases", require two reduction equivalents for the activation of oxygen. The cytochrome P-450-dependent monooxygenases are taken as examples for the discussion of the chemistry of the enzymatic catalysis. The central problem of the activation of oxygen has not yet been solved, but an "oxenoid" mechanism can be deduced from model investigations.

1. The Problem of the Activation of Oxygen

Molecular oxygen owes its existence to photosynthesis, and may therefore be regarded as a bioelement. Its formation in biological systems in this manner and its universal occurrence often lead us to forget that only a metastable equilibrium exists between organic material and oxygen. Once the necessary activation energy has been supplied, organic compounds undergo very rapid oxidation, with simultaneous reduction of oxygen. The free energy change of these "combustion reactions" is considerable, and is exceeded only by that of reactions with molecular fluorine[1].

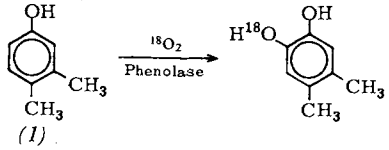
These two characteristics of oxygen, *i.e.* inertia on the one hand and high oxidation potential on the other, are responsible for its unique importance to the energetics of vital processes. It is therefore not surprising that many investigations aimed at the elucidation of the complex chemistry of the oxygen molecule arose from interest in its biological reactions.

To explain the readiness with which oxygen reacts under physiological conditions, it was essential to postulate some "activation of oxygen". This was proposed at an early stage in the publications of *Traube*[2], *Engler*[3], and *Bach*[4], and its experimental foundation was laid by the investigations of *Otto Warburg*. *Warburg*'s model experiments in conjunction with the investigations on the photochemical action spectrum of cytochrome oxidase proved the importance of the bivalent iron ion to the binding of oxygen[5]. If one bears in mind the more recent discovery that the paramagnetic structure of oxygen has a very stable electron configuration, which can be partly disrupted by bonding to iron[6,7], the oxygen "activation" concept introduced by *Warburg* can be justified for all biological oxidations involving molecular oxygen.

It was only in 1955 that proof was found that *Warburg*'s ideas on the activation of oxygen could be applied much more directly to a special group of enzymatic reactions of oxygen. With the aid of the heavy oxygen isotope $^{18}O_2$, *Mason et al.*[8] were able to demonstrate the direct incorporation of molecular oxygen into 3,4-dimethylphenol (*1*), a substrate of phenolase.

[*] Prof. Dr. V. Ullrich
Physiologisch-Chemisches Institut
der Universität des Saarlandes
665 Homburg/Saar (Germany)

In contrast with the principle of biological oxidation, according to which oxygen merely functions as an electron acceptor, the substrate in these reactions undergoes



(*1*)

oxygenation *via* direct attack by oxygen. The cleavage of a CH bond with hydroxylation of the carbon undoubtedly requires enzymatic activation of the oxygen molecule, so that a fresh discussion of this problem was necessary.

2. General Properties of Monooxygenases

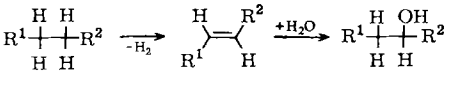
2.1. Definition and Nomenclature

In enzymatic hydroxylations with molecular oxygen, one oxygen atom is introduced into the substrate, while the other is reduced to water. The overall equation for the reaction was first formulated by *Mason*[9]:

$$RH + DoH_2 + {}^{18}O_2 \rightarrow R^{18}OH + Do + H_2{}^{16}O$$

RH = substrate
DoH_2 = hydrogen donor

The hydrogen donor in many reactions is reduced nicotinamide adenine dinucleotide phosphate ($NADPH_2$) or reduced nicotinamide adenine dinucleotide ($NADH_2$). However, tetrahydropteridines, reduced flavins, or ascorbic acid can also provide the two electrons (cf. Table 1). It seems paradoxical at first that oxidation proceeds only in the presence of and with consumption of reduction equivalents, which are thus lost to the cell for the production of energy. One could therefore ask why hydroxylation does not take place by the much more economical dehydrogenation of the substrate with subsequent addition of water.



In this way, *e.g.* malic acid is formed from succinic acid *via* fumaric acid in the citric acid cycle, and the

hydrogen formed in this hydroxylation can yield 2 ATP *via* the respiratory chain.

Hydroxylations with xanthine oxidase[10] and with a nicotine hydroxylase[11] proceed similarly. Thermodynamic considerations show that for aliphatic or aromatic compounds without polarizing groups, energy factors rule out this path, leaving hydroxylation with oxygen as the only alternative.

The fact that hydroxylations can occur in principle by the two routes described makes a more specific nomenclature necessary. Owing to the "mixed" function of the oxygen as an oxidizing and oxygenating agent, *Mason* proposed the term "mixed function oxidase", whereas *Hayaishi*[12] later suggested the designation "monooxygenase". This suggestion by *Hayaishi* places more emphasis on the oxygenating function of these enzymes and allows a more systematic distinction from the "dioxygenases", which introduce both atoms of molecular oxygen into the substrate[13].

The official nomenclature of the Enzyme Commission treats the enzymes as "hydroxylases" under the number 1.14. The systematic name is based on the designation "oxygen oxidoreductase"; in addition to the substrate, it specifies the electron donor, and the word "hydroxylating" is added; *e. g.* 1.14.1.2. L-kynurenine, reduced-NADP: oxygen oxidoreductase (hydroxylating). The nomenclature used in the present article will be based on the term monooxygenase, so that the enzyme mentioned above will receive the simpler name "L-kynurenine 3-monooxygenase". There is no need to name the electron donor, since this is generally not very specific.

2.2. Significance in Metabolism

To provide aliphatic or aromatic CH bonds with functional groups, the chemist has available a series of reactions, such as halogenations, sulfonation, or nitration followed by reduction with amination. In metabolism, the synthesis and degradation of substrates always requires the presence of functional groups, on which the enzymatic reactions take place. If these are lacking, as in many lipophilic compounds, the introduction of hydroxyl groups *via* the monooxygenases is the only route available for the formation of derivatives. This need arises *e. g.* in steroid biosyntheses, in which the highly active hormones are formed from cholesterol by introduction of hydroxyl groups. Monooxygenations are also common in amino acid metabolism, *e. g.* in the synthesis of tyrosine, hydroxyproline, hydroxykynurenine, or dopamine. Monooxygenations are of the greatest importance in the degradation and excretion of lipophilic compounds. Substances of this type can leave the body only after they have been made water-soluble by hydroxylation. The monooxygenases for foreign substances in the liver have been claiming the attention of pharmacologists and physicians for about ten years. Hormonal regulation by steroids requires the continuous inactivation of these compounds, which is also performed in the liver by monooxygenases.

The importance of monooxygenases to the adaptive microorganisms has only recently been recognized. Bacteria and yeasts can grow even on nonphysiological carbon sources, such as aromatic or aliphatic hydrocarbons. This process requires the specific induction of monooxygenases, which prepare the way for the degradation of these inert substrates by one or more hydroxylations to enable the metabolites to enter the normal metabolic pathways. Since the activities of the monooxygenases are usually very low, the hydroxylations are nearly always the rate-determining step of the degradation reactions. To ensure fast breakdown of the organic compounds and hence rapid cell growth, such adapted microorganisms contain very high concentrations of monooxygenase proteins. The conversion of petroleum into animal feeds is possible in this way, and has already been achieved[14].

Bacterial strains that contain highly specific steroid monooxygenases, and can therefore be used for the synthesis of hydroxylated steroid hormones, which are difficult to obtain by chemical routes, are of commercial interest[15].

2.3. Survey of the Principal Monooxygenases

The above-mentioned adaptive properties of microorganisms allow the induction of monooxygenases for practically any organic compound. Only monooxygenases that are important in the mammalian metabolism and that have been investigated sufficiently will therefore be mentioned in the review (Table 1).

2.4. Problems of the Mode of Action of Monooxygenases

To exercise its catalytic function, any monooxygenase requires not only the substrate but also molecular oxygen and an electron donor as cosubstrates. The simultaneous presence of these three components in the monooxygenation offers many possibilities of combination, all of which have been discussed in detail[9].

A feature common to all monooxygenases is the activation of the oxygen molecule, which occurs with the uptake of two electrons. The principle underlying this activation of oxygen can be discerned only in broad outline from the existing results on the enzymatic reactions and their models. In their other properties, however, the monooxygenases exhibit far-reaching differences. The following three points are largely decisive for the characterization of these enzymes.

2.4.1. The Substrate Specificity

The specificity of an enzymatic reaction is determined by the bonding of the substrate to the "active site" of the protein. The affinity of the substrate for the enzyme is determined by the nature and number of the interaction forces. At least three bonding sites must be present for stereospecific binding of the substrate molecule in the protein[48]. This condition must be satisfied *e. g.* for the stereospecific hydroxylations of steroids or amino acids.

With some monooxygenases, the formation of the enzyme-substrate complex can be followed by direct optical measurements. In this case, the affinity of the

Table 1. Survey of the principal mammalian monooxygenases.

Enzyme	Electron donor	Occurrence [a]	Remarks	Ref.
Steroid monooxygenases				
Squalene 2,3-monooxygenase (epoxidizing) (EC 1.14.1.3)	$NADPH_2$	ER of the liver	Epoxide is the precursor of lanosterol	[16, 17]
11β-Monooxygenase (EC 1.14.1.6)	$NADPH_2$	Mitochondria of the adrenal cortex	Consists of reductase containing FAD, non-heme iron protein, and cytochrome P-450, reconstitutable	[18—20]
C-21 monooxygenase (EC 1.14.1.8)	$NADPH_2$	ER of the adrenal cortex	Contains cytochrome P-450	[21, 22]
Cholesterol 20-monooxygenase (EC 1.14.1.9)	$NADPH_2$	Mitochondria of the adrenal cortex, testes, ovary, placenta	Contains cytochrome P-450, precursor for side-chain removal	[23, 24]
2β-, 6α,6β-, 7α,7β,1α,1β-, 15α,16α-, 18α-monooxygenases	$NADPH_2$	ER of the liver	Participates in the breakdown of steroids	[25—28]
Amino acid monooxygenases				
L-Kynurenine 3-monooxygenase (EC 1.14.1.2)	$NADPH_2$, NADH	Liver mitochondria (outer membrane)	Contains FAD	[29, 30]
Dopamine β-monooxygenase (EC 1.14.2.1)	Ascorbate	Adrenal medulla	Contains 2Cu	[31, 32]
4-Hydroxyphenylpyruvate 1-monooxygenase (EC 1.14.2.2)	Aldehyde formed as intermediate	Liver cytoplasm	Sensitive to oxidation. Side chain migrates into *ortho* position	[33, 34]
Phenylalanine 4-monooxygenase (EC 1.14.3.1)	Tetrahydrobiopterin	Liver cytoplasm		[35, 36]
Proline 4-monooxygenase	Ascorbate	Collagen-synthesizing tissue	Contains Fe^{2+}, hydroxylates proline only in the peptide	[37, 38]
Various				
Heme α-monooxygenase	$NADPH_2$	ER of the liver and spleen	Contains cytochrome P-450, products are biliverdin and CO. Inducible by hemin	[39]
Fatty acid ω-monooxygenase	$NADPH_2$	ER of the liver and kidney	Contains cytochrome P-450. Inducible by laurate	[40 - 42]
Xenobiotic monooxygenases				
Aryl 4-monooxygenase	$NADPH_2$		Probably contains cytochrome P-450 and flavoprotein. Inducible by polycyclic hydrocarbons; nonspecific	[43, 44]
Alkane monooxygenase	$NADPH_2$ ($NADH_2$)	ER of the liver	Contains cytochrome P-450 and flavoprotein. Inducible by barbiturates. Nonspecific, prefers ω-1-position and tertiary CH bonds	[41, 45—47]

[a] ER = endoplasmic reticulum.

enzyme for the substrate can be described by the substrate concentration required to convert half of the enzyme into the enzyme-substrate complex (spectral dissociation constant, "K_s").

2.4.2. The "Terminal Oxidase"

This is the name given to the component of the monooxygenase system that binds the oxygen and activates it with the aid of the two electrons. The binding of oxygen is possible on the basis of its character as an excellent electron acceptor. The terminal oxidases are therefore always electron donors. Particularly stable bonding of the oxygen to the active site of the terminal oxidase arises if back-bonding also occurs between the p_π orbital of the oxygen and the d orbitals of heavy metal ions[49]. Iron(II) and copper(I) complexes are therefore the most common terminal oxidases. However, organic compounds such as reduced flavin systems can also activate oxygen. Monooxygenases of this type are found mainly among the bacterial enzymes[50 - 52].

2.4.3. The Electron Transport

The terminal oxidase is a redox system, which converts the oxygen into an active form by transfer of two electrons.

After the hydroxylation of the substrate, the terminal oxidase remains in its oxidized form, and must be converted back into the reduced, oxygen-binding form

for the next cycle. This reduction is possible in principle with any electron donor that has a sufficiently negative potential. It can be seen from Table 1 that ascorbic acid and tetrahydropteridines play the part of the electron donor for some monooxygenases, but reduced pyridine nucleotides are necessary for the majority.

In this case, the transport of electrons to the oxygen is a complicating factor, since the pyridine nucleotide can give up its reaction equivalents only by hydride ion transfer in a two-electron step[53], whereas oxygen can be reduced only in one-electron steps. $NADPH_2$- or $NADH_2$-dependent monooxygenases therefore also contain redox components such as flavin and iron-sulfur proteins, which allow the two-electron transfer to be split up into one-electron steps. These pyridine nucleotide-dependent monooxygenases form multienzyme complexes similar to those that occur in the respiratory chain and are often bound to biological membranes. It should be mentioned that these reduction systems are not always very specific for the acceptor, and can frequently even be interchanged in related systems.

A monooxygenase is therefore characterized, not by the electron transport system, but primarily by the nature of its terminal oxidase. The monooxygenases should therefore be classified as iron-containing, copper-containing, or flavin-containing enzymes. The monooxygenases containing iron in the form of cytochrome P-450 as the oxygen-activating component have been the most intensively studied so far. The mode of action of these enzymes will be discussed in the following sections as an example of the action of monooxygenases in general.

3. Cytochrome P-450-Dependent Monooxygenases

As was shown by *Warburg*'s experiments, iron ions are the most important cofactors in the metabolism of oxygen. A particularly important place is occupied by the porphyrin complexes of iron, in which the nitrogen atoms of the four pyrrole rings fix one plane of the octahedral coordination sphere of the iron ion. The fifth and sixth coordination sites are thus separated by this plane, so that ligand exchange is impossible. This allows the stereospecific fixation of the oxygen molecule by all enzymes with iron-porphyrin complexes as prosthetic groups. The bonding of oxygen occurs on the sixth coordination site, while the fifth coordination site is used for the bonding to the protein.

In 1958 *Klingenberg*[54] and *Garfinkel*[55] discovered, in the microsome fraction of rat livers, a cytochrome whose reduced state formed a carbon monoxide compound having an absorption maximum at 450 nm. The position of this band was unusual, since all known carbon monoxide compounds of iron-porphyrin complexes absorb at much shorter wavelengths (at about 420 nm). This new cytochrome was also found in the microsome fraction of the adrenal cortex. It was known from experiments by *Ryan* and *Engel*[21] that the same fraction was able to hydroxylate steroids on C-21, and that the hydroxylation was inhibited by carbon monoxide. On the basis of the observation of the photodissociation of the iron(II)-carbon monoxide complexes, and using *Warburg*'s classic experimental arrangement for the photochemical action spectrum, *Estabrook et al.*[56] showed that this cytochrome participates in the C-21 hydroxylation as the terminal oxidase (Fig. 1).

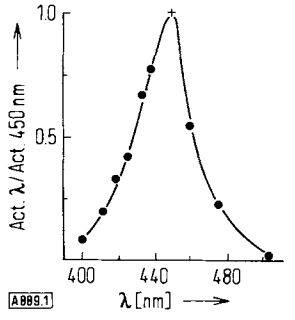


Fig. 1. Photochemical action spectrum of the steroid C-21 monooxygenase in the presence of carbon monoxide [56].

Because of the unusual absorption band of its CO compound, the heme protein was given the temporary name "cytochrome P-450"; however, this has not yet been replaced by any more systematic name.

The cytochrome was found in subsequent years not only in mammals but also in insects[57], yeast[58,59], and bacteria[60-62].

This detection was made possible through the methods developed by *Chance*[63] for absorption measurements in turbid solutions. Every attempt at protein-chemical purification of the particulate cell fraction had led to rapid destruction of the cytochrome. The active cytochrome was converted into an inactive form, whose CO compound absorbed at 420 instead of 450 nm, and which was therefore named "cytochrome P-420"[64,65].

In nearly every case it was possible to assign a function in a hydroxylation to the cytochrome P-450 found in the various tissues and cells, so that it may justifiably be regarded as the preferred prosthetic group of monooxygenases.

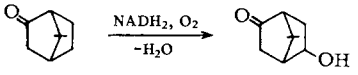
In the investigation of the C-21 hydroxylation in the microsome fraction of the adrenal cortex, *Cooper et al.*[22] observed a change in the spectrum of the cytochrome P-450 when substrates of the C-21 monooxygenase were added. The same observation in rat-liver microsomes on addition of hexobarbital was interpreted by *Schenkman et al.*[66] as resulting from the formation of an enzyme-substrate complex. Further elucidation of the mode of action of the enzyme in these microsome fractions was hindered by the strong attachment of the monooxygenase system to the membrane.

The first successful enrichment and purification of a structure-bound monooxygenase system was achieved by *Omura et al.*[19] in the case of the steroid 11β-monooxygenase from mitochondria of the adrenal cortex (see Table 1). Three protein components, which together restore the full activity of the enzyme, were isolated from detergent-treated suspensions. These were an NADPH-oxidizing flavoprotein[67], an iron-sulfur protein[68], and cytochrome P-450[69]. Reconstitution experiments showed that the iron-sulfur protein was reduced

by the flavoprotein, which in turn transferred the electrons to the cytochrome P-450. Further protein-chemical purification of the cytochrome was again found to be difficult in this system, since only "pseudo-solubilization" could be achieved in the presence of the detergent. Important clues to the course of the cytochrome P-450 catalysis were nevertheless obtainable from spectroscopic studies on the membrane-bound cytochrome of the various tissues. However, clarification of many unanswered questions became possible only after the discovery of a soluble cytochrome P-450-dependent monooxygenase system from bacteria.

3.1. The Camphor 5-Monooxygenase from *Pseudomonas putida*

In 1968, *Katagiri et al.*[61,70] reported the occurrence of cytochrome P-450 in the (+)-camphor monooxygenase from *Pseudomonas putida*, which had been studied by *Gunsalus*'s research group[71,72]. This enzyme is present in high concentrations in the cells of a strain of *Pseudomonas putida* grown on camphor, and is responsible for the first hydroxylating step in the degradation of camphor *(2)*.



(2)

The stoichiometry of the hydroxylation requires 1 mol of $NADH_2$ and 1 mol of oxygen per mol of 5-hydroxycamphor[72,73]. The entire monooxygenase system, like the 11β-monooxygenase system, consisted of a flavoprotein, a non-heme iron protein, and cytochrome P-450. However, the cytochrome was completely soluble, and was therefore obtainable in the pure state[74]. It was thus possible to carry out detailed studies on the unusual spectral properties of the cytochrome in the absolute spectra (Fig. 2).

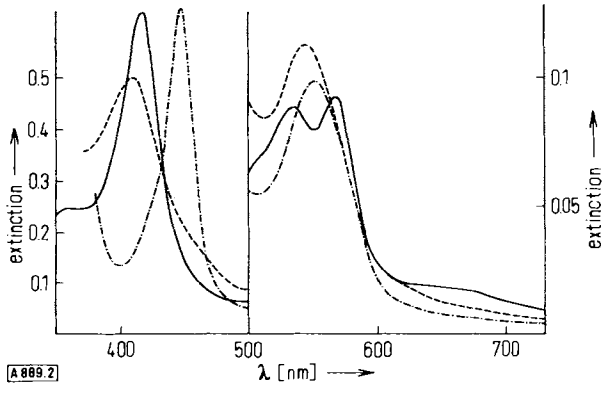


Fig. 2. Absolute spectrum of the cytochrome P-450 from *Ps. putida* [73]. (——) oxidized cytochrome, (– – –) reduced cytochrome, (–·–·–) reduced cytochrome + carbon monoxide.

In the presence of oxygen, the cytochrome occurs only in its oxidized form with trivalent iron, in which it has a Soret band at 417 nm with a pronounced α band at 578 nm and the β band at 535 nm. Under anaerobic conditions, it can be reduced by sodium dithionite or, after addition of the flavoprotein and of the iron-sulfur protein, by $NADH_2$. This leads to unusual broadening of the Soret band, with displacement to shorter wavelengths (maximum at 410 nm). In the visible region only one band at 540 nm appears. This iron(II) form can add on carbon monoxide, and it then has the typical maximum at 448 nm. This reaction competes with the addition of oxygen, and so inhibits the hydroxylation of camphor[75].

In the presence of D-(+)-camphor one finds the change observed previously for other cytochrome P-450 preparations in the spectrum of the oxidized cytochrome on addition of the corresponding substrates (Fig. 3).

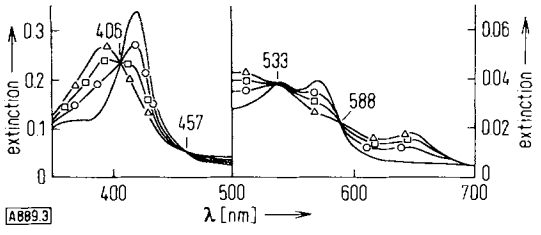


Fig. 3. Titration of cytochrome P-450 from *Ps. putida* with camphor [73]. Concentrations: cytochrome P-450 3.3 μmol/l, camphor (——) 0, (– ○ – ○ –) 2 μmol/l, (– □ – □ –) 6 μmol/l, (– △ △ –) 20.5 μmol/l.

Increasing concentrations of (+)-camphor lead to the development of a new absorption band at 388 nm. At the same time, the α and β bands disappear, and a new long-wave absorption appears at 646 nm. The camphor concentrations required for complete conversion correspond to the saturation concentrations for the hydroxylation reaction[73]. Only a few derivatives of camphor have a similar effect, and these act only in much higher concentrations. All the results point to the formation of an enzyme-substrate complex. Considerable stabilization of the cytochrome is achieved by the binding of the substrate, so that it was even possible to crystallize the enzyme-substrate complex[74].

The development of the long-wave absorption is characteristic of "high-spin" iron-porphyrin complexes[76], so that the probable reason for this spectral change is the transition from a "low-spin" form to a "high-spin" complex of the trivalent cytochrome. This assumption has been confirmed with the aid of electron spin resonance (EPR)[73,77] and by measurement of the magnetic susceptibility[73]. The anisotropic EPR spectrum of oxidized cytochrome P-450 is typical of "low-spin" hemin compounds, but with the characteristic that the g values lie close together. In the presence of (+)-camphor, the signal largely disappears, and a new absorption appears at $g = 7.9$; however, this new signal can be observed only at about 7 °K (Fig. 4).

The measurement of the magnetic susceptibility shows that this transition is accompanied by an increase in the number of unpaired electrons, which corresponds to the conversion of a heme with one unpaired electron into a state with five unpaired electrons[73].

According to preliminary results, the spin transition is also linked with a change in potential. The free cytochrome has a strongly negative normal potential at pH = 7.0 (E'_0) of about −380 mV, whereas after the

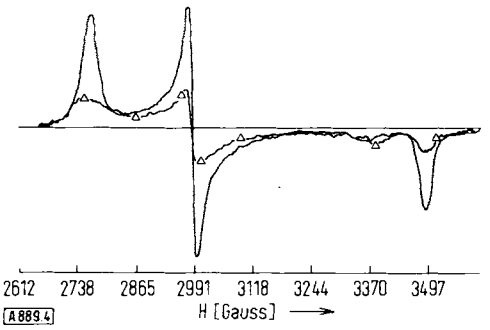


Fig. 4. EPR spectrum of cytochrome P-450 from *Ps. putida* with (–△–△–) 5 μmol/l and (——) without camphor [73]. Cytochrome P-450: 68 μmol/l, temperature: −170 °C.

binding of camphor, the "high-spin" complex has a corresponding potential of about −170 mV[78]. This change in redox potential presumably plays a significant part in the hydroxylation mechanism (Section 3.3).

The activation of oxygen begins with the addition of the oxygen molecule to the reduced form of cytochrome P-450. Since the cytochrome is a one-electron acceptor and donor[73,79], the first step should be the transfer of an electron to the oxygen and the formation of an "oxy form" of the cytochrome:

$$Fe^{2\oplus} + O_2 \rightleftharpoons Fe^{2\oplus}O_2 \rightleftharpoons Fe^{3\oplus}O_2^{\ominus}$$

An oxygen adduct of this type can be observed if the reduced form of the cytochrome is rapidly mixed with oxygen and the spectrum recorded immediately (Fig. 5)[80,81].

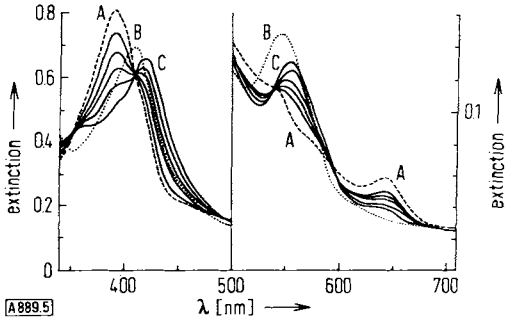


Fig. 5. Autocatalytic decomposition of "oxy"-cytochrome P-450 from *Ps. putida* at 5 °C [81]. A (– – –) cytochrome P-450-camphor complex, B (·····) reduced cytochrome P-450, C (——) reduced cytochrome P-450 aerated with oxygen. The spectra were recorded in the course of 45 min.

The "oxy"-cytochrome P-450 becomes a very stable compound with a half-life of 10—20 minutes if the subsequent further reduction is prevented. The only possible decomposition reaction is a disproportionation with formation of hydrogen peroxide and the "high-spin" form[80]:

$$2Fe^{3\oplus}O_2^{\ominus} \xrightarrow{+2H^{\oplus}} 2Fe^{3\oplus} + O_2 + H_2O_2$$

The absorption maxima of the oxygenated compound are situated at 418, 555, and 580 nm. At the temperature of liquid nitrogen, it gives no ESR spectrum, so that this form, like oxyhemoglobin, is probably diamagnetic. The actual "active oxygen" should be formed only on reduction of the oxy complex with a second electron. This process has not yet been investigated, but is the most interesting step in the course of the enzyme reaction. Possible structures for the expected "active oxygen" are discussed in Section 4 on the basis of model investigations.

3.2. The Microsomal Monooxygenases of the Liver

The "microsome" fraction of the liver consists predominantly of the fragments of the endoplasmic reticulum. It has been known since about 1950[83] that these cell organelles are responsible for the breakdown of steroids, drugs, and foreign substances ("xenobiotics")[82]. The monooxygenase system contained in this microsome fraction hydroxylates numerous organic lipophilic compounds, which become water-soluble as a result of the introduction of the hydroxyl group, and can thus be eliminated from the organism *via* the kidneys. The characteristic feature of the microsomal hydroxylations is the extensive nonspecificity of the enzyme system responsible. This enables the organism to metabolize and excrete even entirely new synthesized compounds, and hence to avoid intoxication.

It was shown by the above-mentioned method of the photochemical action spectrum that the monooxygenation of codeine, 4-methylaminoantipyrine, acetanilide, and testosterone is catalyzed by the microsomal cytochrome P-450[84]. However, the preferred substrates are the aliphatic hydrocarbons[46,47,85–87], for which the action spectrum of a typical representative, *i.e.* cyclohexane, is shown in Figure 6[45].

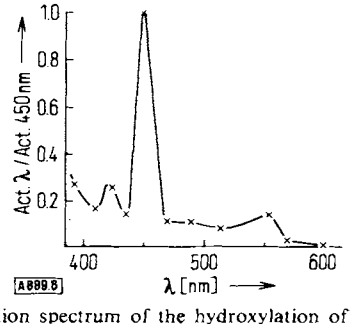


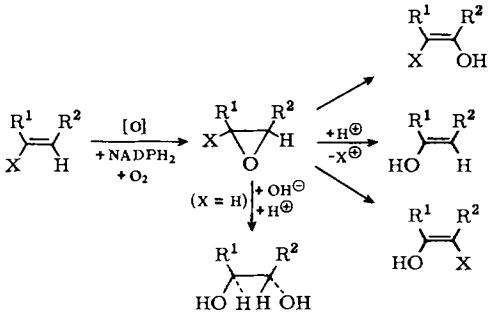
Fig. 6. Photochemical action spectrum of the hydroxylation of cyclohexane with rat-liver microsomes in the presence of carbon monoxide [45].

The influence of the substrate on the spectral properties of the oxidized cytochrome cannot be investigated with the aid of absolute spectra, but only by recording the difference spectra, owing to the turbidity of the microsome solutions. As in the case of the camphor monooxygenase, the half-maximum saturation concentration ("K_s") for the bonding of the substrate to the cytochrome corresponds to the Michaelis-Menten constant (K_M) for the hydroxylation of cyclohexane to cyclohexanol[86]; this again points to the formation of an enzyme-substrate complex. As in the case of bacterial cytochrome P-450, the spectral change is associated with the

transition from the "low-spin" to the "high-spin" form of cytochrome P-450[88]. The fact that a molecule like cyclohexane, with no functional groups, can be bonded to the cytochrome shows that strong lipophilic interactions must occur between the substrate and the active center. Owing to the nonspecificity of these bonding forces, it was reasonable to assume that hydrocarbons related to cyclohexane would also be bound and transformed by the same cytochrome. It has been shown that this is probably so for the C_4 to C_7 alkanes[46, 87].

Another consequence of the nonspecific hydrophobic bonding is the large number of hydroxylation products, among which nearly all the possible isomeric alcohols have been detected[87] (Table 2). The attack by the active oxygen takes place preferentially on the tertiary CH bonds, followed by the secondary and primary CH bonds. For the hydrocarbons mentioned, the proportions in which these bonds are attacked are roughly 150:25:1, and thus correspond to the ratios for a very selective substitution reaction.

indicated in the following scheme are available for the monooxygenation of the sp^2-hybridized carbon atom.



An important question that now arises is whether the same cytochrome P-450 is involved in all monooxygenations catalyzed by the microsome fraction. A number of observations indicate that there are in fact several species of cytochrome P-450, each having a certain

Table 2. Product distribution in monooxygenations in rat-liver microsomes.

Substrate	Products (% relative yield)	Remarks	Ref.
Cyclohexane	Cyclohexanol (100)	Inducible by barbiturates	[86]
n-Butane	2-Butanol (< 100)	Inducible by barbiturates	[87]
Isobutane	2-methyl-2-propanol (< 100)	Inducible by barbiturates	[87]
2-Methylbutane	(2-Methyl-1-butanol + 3-methyl-1-butanol), 3-methyl-2-butanol, 2-methyl-2-butanol (6:20:74)	Inducible by barbiturates	[87]
Methylcyclohexane	1-, 2-, 3-, 4-Methylcyclohexanols, hexahydrobenzyl alcohol (25:8:43:23:1)	Inducible by barbiturates	[87]
Toluene	Benzyl alcohol ≫ cresols (*o*-:*m*-:*p*-cresol = 59:13:28)	ω-Hydroxylation inducible by barbiturates	[88–90]
Anisole	Phenol, 2-, 4-hydroxyanisoles (60:7:33)	*O*-Dealkylation *via* hypothetical α-hydroxylated intermediate	[90]

A very similar result is obtained in the hydroxylation of monosubstituted and disubstituted aromatic hydrocarbons (Table 2). In this case, the hydroxylation clearly follows the rules of electrophilic aromatic substitution, and must therefore proceed *via* an addition of the active oxygen to the π-electron system. This assumption is confirmed by the fact that isolated double bonds are converted into epoxides. In polycyclic hydrocarbons whose π bonds exhibit partial double-bond character, the addition leads to epoxides as intermediates[91, 92]. However, these are very rapidly hydrolyzed both enzymatically and spontaneously to *trans*-dihydrodiols.

The possibility that the hydroxylation of simple aromatic hydrocarbons might also proceed *via* arene oxides was suggested by the observed migration of substituents to the neighboring ring carbon atom, which is referred to in the literature as the "NIH shift"[93]. The hydroxylation of the aromatic carbon atom is accompanied by the displacement not only of chlorine and bromine, but also of tritium, deuterium, and hydrogen into the *ortho* position, often to a large extent[94, 95]. This effect is observed even for isolated double bonds[96], and it must therefore be assumed that the reaction possibilities

group specificity. Important evidence on this point is provided by pharmacological studies on the induction of the monooxygenase system of the liver[97, 98]. Pretreatment of experimental animals with drugs or other foreign substances leads to an increase in the concentrations of cytochrome P-450 and of its reductase in the microsome fraction, which causes an increase in the specific monooxygenase activity, often by a factor of four to eight, and which is the cause of acquired tolerance to drugs.

It was found in these induction experiments, however, that depending on the nature of the compound administered, different increases occur for the various substrates. Barbiturates, for example, increase the monooxygenase activity toward the predominantly aliphatic substrates, whereas pretreatment with polycyclic hydrocarbons greatly increases the activity for the hydroxylation of aromatic compounds. Differences in the spectral properties of the cytochromes[99, 100] and in their inhibition behavior[47, 101, 102] have also been reported.

Small differences in substrate and product specificity exist even within these two groups[103], so that instead

of the total nonspecificity formerly assumed for microsomal monooxygenases, it is now necessary to postulate a group specificity.

3.3. The Course of the Cytochrome P-450-Catalyzed Monooxygenation

Insofar as a general picture of the reactions on cytochrome P-450 is now available, the course of these reactions is independent of the source of the cytochrome. The sequence of the individual reaction steps follows logically from the results obtained so far; it is summarized in Figure 7.

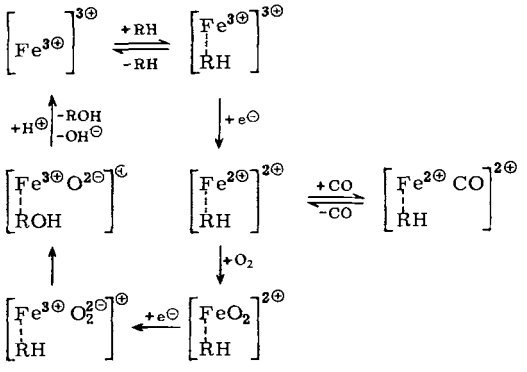


Fig. 7. Reaction scheme for the mode of action of cytochrome P-450-dependent monooxygenases.

As in any enzymatic catalysis, the first step is the formation of an enzyme-substrate complex. The associated change in the conformation of the enzyme allows the spin change, and so leads to the spectral shift observed. This process proceeds at a high rate. For example, the second order rate constant for the formation of the camphor-cytochrome P-450 complex at 8 °C is $3.7 \times 10^6 \,\mathrm{l\,mol^{-1}\,s^{-1}}$[104]. The equilibrium constant in the presence of potassium ions has the following value[73]:

$$K = \frac{[\mathrm{E \cdot Camphor}]}{[\mathrm{E}]\,[\mathrm{Camphor}]} = 0.47 \times 10^6 \,\mathrm{l\,mol^{-1}}$$

In addition to the dipole interactions between the substrate and the protein, the main bonding forces are the apolar bonds, which are largely responsible for the increase in entropy on transfer of the lipophilic substrate from the aqueous phase into the hydrophobic environment of the active center. The substrate can often be completely displaced from the active center by addition of organic solvents[105].

The precise location of the substrate will be obtainable only from the X-ray structure analysis of the crystallized cytochrome P-450-camphor complex[74]. Inhibition experiments with metyrapone [2-methyl-1,2-bis-(3-pyridyl)-1-propanone][106] have shown that the bonding site of the substrate must lie in the immediate vicinity of the oxygen bonding site, *i.e.* of the iron ion. The metyrapone molecule is bonded stoichiometrically *via* a pyridine nitrogen to the iron, and at the same time competitively inhibits the bonding of camphor. In the reduced state, this compound also inhibits the addition of carbon monoxide, so that the sixth coordination site, as the oxygen bonding site, must be occupied[106]. The particular properties of cytochrome P-450 can be satisfactorily explained by the ligand on the fifth coordination site, which is probably the $S^{\ominus}$ group of a cysteine[107]. The main evidence, apart from the reactivation of cytochrome P-420 to cytochrome P-450 by cysteine[108], is the unusual EPR spectrum, which has been very closely simulated in a model from myoglobin and alkylthiols (Fig. 8)[109].



Fig. 8. EPR spectrum of rat-liver microsomes (bottom) and of the metmyoglobin-butanethiol complex (top) at −170 °C [109a].

As a "soft" ligand[110], the sulfur could be responsible for the strongly negative potential of the cytochrome.

The details of the spin reversal on bonding of the substrate are not yet clear. It is assumed[73,77,111] that the substrate displaces a histidine residue from the sixth coordination site, with the result that the formation of the "high-spin" complex becomes possible. In this case, the entire process of the bonding of the substrate could proceed as indicated in the hypothetical Figure 9.

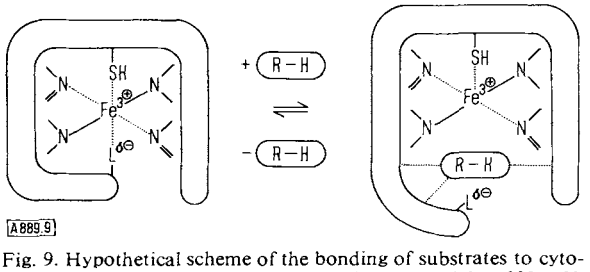


Fig. 9. Hypothetical scheme of the bonding of substrates to cytochrome P-450. Left: "low-spin" complex, potential −380 mV, Soret band at 418 nm; right: "high-spin" complex, potential approx. −170 mV, Soret band at 390 nm.

The next step in the reaction must be transfer of an electron to the cytochrome. It can be shown for the microsomal cytochrome P-450 that the cytochrome-

substrate complex is reduced one order of magnitude more rapidly than the free cytochrome[112]. The electron transport is thus coupled with the presence of the substrate in the active center, and mere oxidation of the hydrogen donor is avoided. This reduction step proceeds relatively slowly; it is usually the rate-determining step in the monooxygenase-catalyzed reactions[112,113]. The oxygen molecule then adds to the reduced enzyme-substrate complex to give the oxy form, from which it can be displaced again by carbon monoxide.

The actual active form of the oxygen is produced from the oxy complex by the transfer of a further electron. This follows first from the stoichiometry of the monooxygenases and from the model reactions that will be discussed in Section 4. Experimental evidence may be seen in *Cooper*'s observations[114], which show that the cytochrome P-450 of the 11β-hydroxylase is unable to hydroxylate deoxycorticosterone after stoichiometric reduction followed by addition of oxygen. The 11β-hydroxylation of the substrate occurs only upon addition of reduced iron-sulfur protein (adrenodoxine).

No measurements have yet been reported for the rate of this second reduction step. The observation that the oxy form of the cytochrome can be detected in microsomes in the steady state of the hydroxylation[115,116] suggests a relatively slow reduction, which cannot, however, be slower than the first electron transfer.

The structure of the active oxygen on the cytochrome P-450 is still completely unknown; a peroxide complex is indicated only formally in Figure 7. The actual monooxygenation of the substrate on transfer of an oxygen atom probably occurs rapidly. It is usually not rate-determining, as is shown by the absence of an isotope effect in the hydroxylation of cyclohexane in microsomes[86].

After the uptake of a proton, the second oxygen atom, which has been reduced to the oxidation stage of water, can dissociate from the cytochrome P-450, so releasing the latter for bonding of the next substrate molecule.

A special situation arises when a compound can be bonded like a substrate, but has no position that can be hydroxylated. This case arises in particular for the microsomal cytochrome P-450, whose substrates are bound to cytochrome P-450 merely because of their lipid-solubility. For example, perfluorinated hydrocarbons can form the enzyme-substrate complex just as easily as the corresponding alkanes, but cannot be hydroxylated because of the stability of the CF bond[117]. In this case, the active oxygen is further reduced to water; the system is thus "uncoupled". This phenomenon is frequently found in the less specific monooxygenase systems.

4. Model Investigations on the Activation of Oxygen by Monooxygenases

As in many enzymatic reactions, the direct investigation of the transition state of monooxygenases is not yet possible. In such cases, one may turn to the study of model reactions, but it is then necessary to face the problems that arise in the application of results obtained from models to enzymatic reactions. In the monooxygenase models, because of the numerous reactions of oxygen, the agreement of the enzyme reactions with the model reactions must be checked repeatedly.

Any proposed model must satisfy the stoichiometry of the monooxygenation of two electrons per mole of oxygen and hydroxylated product. It is always difficult to check this stoichiometry in model hydroxylations, since coupling of the reduction and activation of oxygen with the hydroxylation of the substrate can be brought about only by the enzyme through conformational changes in the protein. In all the models known at present, the further reduction of the active oxygen to water accompanies and may even predominate over the hydroxylation.

Because of the high specificity of the reactions, the distribution of the products in the enzymatic catalysis generally provides little information about the transition state. In the microsomal monooxygenases of the liver, we are dealing with a largely unspecific enzyme system, by which, as shown in Table 2, aliphatic compounds undergo selective hydroxylation and aromatic compounds electrophilic hydroxylation. A further characteristic is the epoxide formation and the migration of the aromatic substituent into the *ortho* position, which thus largely characterize the chemical properties of the "active oxygen". Similar attacks on CH bonds and additions to π-electron systems have also been reported for carbenes or carbenoids[118]. It therefore seems reasonable to postulate an "oxenoid" structure for the active oxygen[119,120], the attacking oxygen thus being defined as an electrophilic particle with six valence electrons[121].

4.1. Oxenoid Reactions

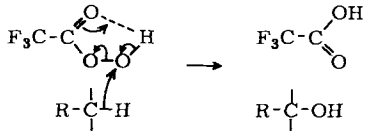
The stoichiometry of the monooxygenase reactions suggests that the active oxygen is in the oxidation state of peroxide or of the oxygen atom. Hydrogen peroxide itself is too weak an oxidizing agent to be responsible for the observed hydroxylations. With increasing polarization of the O—O bond by substitution, however, its oxidation potential also increases. Perbenzoic and peracetic acids are still relatively weak oxidizing agents,

Table 3. Hydroxylations with trifluoroperacetic acid.

Compound	Products (% relative yield)	Ref.
2-Methylbutane	(2-methyl-1-butanol + 3-methyl-1-butanol), 3-methyl-butanol, 2-methyl-2-butanol (1.7:5.8:92.5)	[124]
Methylcyclohexane	1-, 2-, 3-, 4-methylcyclohexanol, hexahydrobenzyl alcohol (88.7:3.4:3.6:4.2:0.2)	[124]
[4-D]-Toluene	4-methylphenol, [2-D]-4-methylphenol (32:68)	[125]
Acetanilide	2-, 3-, 4-hydroxyacetanilide (43:1:56)	[44]
4-Bromoacetanilide	2-, 3-hydroxy-4-bromoacetanilide, 4-hydroxy-3-bromoacetanilide, 4-hydroxyacetanilide (41:5:45:9)	[44]

though they already allow epoxide formation[122]. Trichloroperacetic acid is much stronger, and the strongest polarizing action is achieved with the trifluoromethyl group[123]. Table 3 shows the products obtained on oxidation of some compounds with trifluoroperacetic acid.

The essential characteristics of the enzymatic reactions, *i.e.* selectivity, electrophilicity, and substituent migration, are also found in the oxidations with trifluoroperacetic acid, which are best interpreted by the assumption of a concerted substitution mechanism[23,125,126].



This is in agreement with the observed isotope effect of 2.9 in the hydroxylation of cyclohexane and perdeuteriocyclohexane[86]. Aromatic compounds exhibit no isotope effect in their hydroxylation, since the rate-determining step is the rearomatization of the intermediate product[86]. No evidence of the occurrence of a hydroxyl cation (OH^+) has been found from isotope experiments[125,127].

4.2. Model Hydroxylations with Molecular Oxygen

Though an oxenoid reaction course is very probable for the monooxygenases, it is not known at present how such a peroxide could be formed from molecular oxygen and whether the reaction of an acid in an almost anhydrous medium can be compared with an enzyme reaction in aqueous media.

The first hydroxylase model with molecular oxygen was proposed by *Udenfriend et al.*[128,129]. It consisted of the iron(II)-ethylenediaminetetraacetic acid complex and ascorbic acid, and it catalyzed the electrophilic hydroxylation of aromatic compounds with incorporation of molecular oxygen at pH 7. *Breslow* and *Lukens*[130] found, however, that this system is only a modified Fenton reagent, which yields OH radicals *via* hydrogen peroxide formed as an intermediate. These radicals do not form epoxides and alcohols, and exhibit no substituent migration; they must therefore be ruled out as a model for the active oxygen[120].

The "Udenfriend system" was greatly simplified in subsequent investigations by the replacement of ascorbic acid by other reducing agents and of the iron complex by other autoxidizable metal complexes of iron(II), copper(I), titanium(III), vanadium(III), and tin(II). In addition to the OH radicals, however, these hydroxylation systems also clearly contain a further form of active oxygen, which is much more reactive and also attacks aliphatic compounds with hydroxylation. This new hydroxylation reaction was most easily observed in the reduction of oxygen with tin(II) phosphate complexes, since hydrogen peroxide formed as an intermediate here was immediately reduced to water before OH radicals could be formed[131]. The oxygen of the hydroxyl group introduced was derived exclusively from the gas phase, and the stoichiometry also satisfied the condition of the enzymatic reactions[131]:

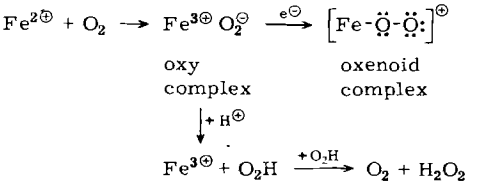
$$Sn^{2\oplus} + {}^{18}O_2 + RH \xrightarrow{H^{\oplus}} Sn^{4\oplus} + R^{18}OH + OH^{\ominus}$$

However, the attack by the unknown active form of oxygen took place nonselectively and almost randomly on all the CH bonds present[131,132].

This increased reactivity in comparison with that of the postulated "oxenoid" complex of the monooxygenases could be due to weaker stabilization of the active oxygen on the tin(IV) ion. To assimilate the model further to the enzymatic reactions, iron(II) chelates containing the thiol ligands characteristic of cytochrome P-450 were investigated. Because of the poor water-solubility of the organic chelating agents, it was necessary to work in an organic phase.

A hydroxylating system with new properties was found in the iron(II)-2-mercaptobenzoic acid complex, with acetone as the solvent. With reduction of molecular oxygen, this system not only hydroxylates aromatic compounds in good yields by an electrophilic mechanism, but also selectively hydroxylates aliphatic compounds[124]. However, epoxides are not formed, and the characteristic substituent migration cannot be detected. It is therefore not yet certain how far this system can serve as a model for hydroxylation.

However, the use of organic solvents may be essential to the further development of the model reactions, since they undoubtedly correspond more closely than aqueous solutions to the conditions in the active center of the monooxygenase. Further investigation of the chemistry and thermodynamics of the reduction of oxygen by metal complexes in nonaqueous solutions is still necessary. It is conceivable, however, that the protonation of the O_2^- intermediate, which decreases the yields in the model reactions at present, can be suppressed by avoidance of the aqueous phase.



5. Outlook

For the sake of clarity, it has been necessary to confine this review to the illustrative discussion of the cytochrome P-450-dependent monooxygenases. However, some of the enzymes containing copper[31,32] or flavin[50-52] have also been intensively studied and described in reviews[8,13,15,52,95,121,133,134]. The oxenoid mechanism appears to be common to all monooxygenases. The necessary coupling of the reduction of oxygen and the monooxygenation is evidently always achieved by the substrate-induced change in the conformation of the terminal oxidase.

Since the spin reversal on substrate bonding can be readily followed for cytochrome P-450 by optical

methods and by the electron spin resonance, this cytochrome should be a suitable model for the study of enzyme-substrate complexes. Cytochrome P-450 also offers good prospects for the direct investigation of the activation of oxygen in the transition state, though no suitable measuring methods are available at present. All the model reactions used so far for this purpose have the disadvantage that the reduction of oxygen with homogeneous catalysis does not stop at the stage of the active peroxide, but proceeds further, mainly with formation of water.

It is even possible that the enzymatic monoxygenations may be able to serve in future as models for chemical hydroxylation processes. Further study of the monooxygenases would also seem worthwhile from this point of view, since the specific introduction of hydroxyl groups into organic compounds is undoubtedly an important aspect of preparative chemistry, and is even of technical interest because of the cheap reactants, oxygen and electrical power.

I am deeply grateful to the colleagues mentioned in connection with my own results for their collaboration, as well as to the Deutsche Forschungsgemeinschaft (SFB 38) and the Stiftung Volkswagenwerk for their financial support. A great deal of valuable advice and assistance has resulted from collaboration with Prof. Dr. R. W. Estabrook, Prof. Dr. D. Y. Cooper, and Dr. J. A. Peterson. I am particularly grateful to Prof. Dr. Hj. Staudinger for many joint investigations and for his support of my work over the years.

Received: May 26, 1971 [A 889 IE]
German version: Angew. Chem. *84*, 689 (1971)
Translated by Express Translation Service, London

[1] *P. George* in *T. King, H. S. Mason*, and *M. Morrison:* Oxidases and Related Redox Systems. Wiley, New York 1965.

[2] *M. Traube*, Ber. dtsch. chem. Ges. *15*, 666 (1882).

[3] *C. Engler* and *W. Wild*, Ber. dtsch. chem. Ges. *30*, 1669 (1897).

[4] *A. Bach*, Chem.-Ztg. *398*, 436 (1897).

[5] *O. Warburg:* Schwermetalle als Wirkungsgruppen von Fermenten. 2nd Edit., Cantor, Freiburg 1949.

[6] *M. Zerner, M. Gouterman*, and *H. Kobayashi*, Theor. Chim. Acta 6, 303 (1966).

[7] *J. B. Wittenberg, B. A. Wittenberg, J. Peisach*, and *W. E. Blumberg*, Proc. Nat. Acad. Sci. USA *67*, 1846 (1970).

[8] *H. S. Mason, W. Fowlks*, and *E. Peterson*, J. Amer. Chem. Soc. *77*, 2914 (1955).

[9] *H. S. Mason*, Advan. Enzymol. *19*, 79 (1957).

[10] *A. White, P. Handler*, and *E. L. Smith:* Principles of Biochemistry. McGraw-Hill, New York 1968, p. 378.

[11] *A. L. Hunt, D. E. Hughes*, and *J. M. Lowenstein*, Biochem. J. *69*, 170 (1958).

[12] *O. Hayaishi*, Proceedings of the Plenary Sessions, Vol. 33, p. 31. Sixth Int. Congr. Biochemistry, New York City, 1964, J. U. B.

[13] *O. Hayaishi* in *O. Hayaishi:* Oxygenases. Academic Press, New York 1962.

[14] *J. Someya, T. Murakami, N. Tagaya, N. Futai*, and *Y. Sonoda*, J. Ferment. Technol. *48*, 291 (1970).

[15] *R. Abraham, E. Balke, K. Krisch, S. Leonhäuser, K. Leybold, K. A. Sack*, and *Hj. Staudinger* in *Hoppe-Seyler-Thierfelder:* Handbuch der physiologisch- und pathologisch-chemischen Analyse. 10th Edit., Vol. VI/A, Springer, Berlin 1964, p. 917.

[16] *J. Willett, K. Sharpless, K. Lord, E. van Tamelen*, and *R. Clayton*, J. Biol. Chem. *242*, 4182 (1967).

[17] *T. Scallen, W. Dean*, and *M. Schuster*, J. Biol. Chem. *243*, 5202 (1968).

[18] *M. L. Sweat* and *M. D. Lipscomb*, J. Amer. Chem. Soc. *77*, 5185 (1955).

[19] *T. Omura, E. Sanders, R. W. Estabrook, D. Y. Cooper*, and *O. Rosenthal*, Arch. Biochem. Biophys. *117*, 660 (1966).

[20] *W. Cammer, D. Y. Cooper*, and *R. W. Estabrook* in *K. W. McKerns:* Functions of the Adrenal Cortex. Appleton-Century-Crofts, New York 1968.

[21] *K. J. Ryan* and *L. L. Engel*, J. Biol. Chem. *225*, 103 (1957).

[22] *D. Y. Cooper, S. Narasimhulu, O. Rosenthal*, and *R. W. Estabrook* in *K. W. McKerns:* Function of the Adrenal Cortex. Appleton-Century-Crofts, New York 1968.

[23] *E. R. Simpson* and *G. S. Boyd*, Biochem. Biophys. Res. Commun. *24*, 10 (1966).

[24] *E. R. Simpson* and *G. S. Boyd*, Biochem. Biophys. Res. Commun. *28*, 945 (1967).

[25] *A. H. Conney* and *A. Klutch*, J. Biol. Chem. *238*, 1611 (1963).

[26] *B. P. Lisboa* and *J.-A. Gustafsson*, Eur. J. Biochem. *6*, 419 (1968).

[27] *K. Leybold* and *Hj. Staudinger*, Biochem. Z. *331*, 399 (1959).

[28] *R. Abraham* and *Hj. Staudinger*, Hoppe-Seylers Z. Physiol. Chem. *346*, 198 (966).

[29] *H. Okamoto* and *O. Hayaishi*, Biochem. Biophys. Res. Commun. *29*, 394 (1967).

[30] *U. Horn, V. Ullrich*, and *Hj. Staudinger*, Hoppe-Seylers Z. Physiol. Chem. *351*, 1580 (1970).

[31] *S. Friedman* and *S. Kaufman*, J. Biol. Chem. *240*, 763 (1965).

[32] *M. Goldstein, T. H. Joh*, and *T. O. Garvey*, Biochemistry *7*, 2724 (1968).

[33] *B. N. La Du* and *V. G. Zannoni*, Nature *177*, 574 (1956).

[34] *B. N. La D* and *V. G. Zannoni*, J. Biol. Chem. *217*, 777 (1955).

[35] *S. Kaufman*, J. Biol. Chem. *234*, 2677 (1959).

[36] *S. Kaufman* in *O. Hayaishi:* Oxygenases. Academic Press, New York 1962, p. 129.

[37] *S. Udenfriend*, Science *152*, 1335 (1966).

[38] *B. Peterkowsky* and *S. Udenfriend*, Proc. Nat. Acad. Sci. USA *53*, 335 (1963).

[39] *R. Tenhunen, H. S. Marver*, and *R. Schmidt*, J. Biol. Chem. *244*, 6388 (1969).

[40] *B. Preiss* and *K. Bloch*, J. Biol. Chem. *239*, 85 (1964).

[41] *M. L. Das, S. Orrenius*, and *L. Ernster*, Eur. J. Biochem. *4*, 519 (1968).

[42] *A. Y. H. Lu* and *M. J. Coon*, J. Biol. Chem. *239*, 1331 (1968).

[43] *C. Mitoma, H. S. Posner, H. C. Reitz*, and *S. Udenfriend*, Arch. Biochem. Biophys. *61*, 431 (1956).

[44] *V. Ullrich, J. Wolf, E. Amadori*, and *Hj. Staudinger*, Hoppe-Seylers Z. Physiol. Chem. *349*, 85 (1968).

[45] *H. Diehl, S. Capalna*, and *V. Ullrich*, FEBS-Lett. *4*, 99 (1969).

[46] *U. Frommer, V. Ullrich*, and *Hj. Staudinger*, Hoppe-Seylers Z. Physiol. Chem. *351*, 903 (1970).

[47] *K. Ichihara, E. Kusunose*, and *M. Kusunose*, Biochem. Biophys. Acta *176*, 713 (1969).

[48] *H. R. Mahler* and *E. H. Cordes:* Biological Chemistry. Harper & Row, New York 1967, p. 316.

[49] *E. Bayer* and *P. Schretzmann*, Structure and Bonding *2*, 181 (1967).

[50] *M. Katagiri, S. Takemori, K. Suzuki*, and *H. Yasuda*, J. Biol. Chem. *241*, 5675 (1966).

[51] *K. Hosokawa* and *R. Y. Stanier*, J. Biol. Chem. *241*, 2453 (1966).

[52] *O. Hayaishi*, Annu. Rev. Biochem. *38*, 21 (1969).

[53] *H. Sund, H. Diekmann*, and *K. Wallenfels*, Advan. Enzymol. *26*, 115 (1964).

[54] *M. Klingenberg*, Arch. Biochem. Biophys. *75*, 376 (1958).

[55] *D. Garfinkel*, Arch. Biochem. Biophys. *77*, 493 (1958).

[56] *R. W. Estabrook, D. Y. Cooper*, and *O. Rosenthal*, Biochem. Z. *338*, 741 (1963).

[57] *S. E. Lewis, C. F. Wilkinson*, and *J. W. Ray*, Biochem. Pharmacol. *16*, 1195 (1967).

[58] *A. Lindenmayer* and *L. Smith*, Biochim. Biophys. Acta *93*, 445 (1964).

[59] *J.-M. Lebeault, E. T. Lode*, and *M. J. Coon*, Biochem. Biophys. Res. Commun. *42*, 413 (1971).

[60] *C. A. Appleby*, Biochim. Biophys. Acta *172*, 71 (969).

[61] *M. Katagiri, B. N. Ganguli*, and *I. C. Gunsalus*, Fed. Proc. *27*, 525 (1968).

[62] *G. Gardini* and *P. Jurtshuk*, J. Biol. Chem. *245*, 2789 (1970).

[63] *B. Chance* in *S. P. Colowick* and *N. O. Kaplan:* Methods in Enzymology. Academic Press, New York 1957, Vol. 4, p. 273.

[64] *T. Omura* and *R. Sato*, J. Biol. Chem. *239*, 2370 (1964).

[65] *T. Omura* and *R. Sato*, J. Biol. Chem. *239*, 2379 (1964).

[66] *J. B. Schenkman, H. Remmer*, and *R. W. Estabrook*, Mol. Pharmacol. *3*, 113 (1967).

[67] *E. Sanders, R. W. Estabrook, D. Y. Cooper*, and *O. Rosenthal*, Arch. Biochem. Biophys. *117*, 660 (1966).

[68] *T. Kimura* and *K. Suzuki*, J. Biol. Chem. *242*, 485 (1967).

[69] *D. Y. Cooper, S. Narasimhulu, A. Slade, W. Raich, O. Foroff*, and *O. Rosenthal*, Life Sci. *4*, 2109 (1965).

[70] *M. Katagiri, B. N. Ganguli*, and *I. C. Gunsalus*, J. Biol. Chem. *243*, 3543 (1968).

[71] *J. Hedegaard* and *I. C. Gunsalus*, J. Biol. Chem. *240*, 4038 (1965).

[72] *H. E. Conrad, K. Lieb*, and *I. C. Gunsalus*, J. Biol. Chem. *240*, 4029 (1965).

[73] *J. A. Peterson*, Arch. Biochem. Biophys. *144*, 678 (1971).

[74] *C.-A. Yu* and *I. C. Gunsalus*, Biochem. Biophys. Res. Commun. *40*, 1431 (1970).

[75] *J. A. Peterson*, unpublished.

[76] *A. S. Brill* and *R. J. P. Williams*, Biochem. J. *78*, 246 (1961).

[77] *J. Peisach* and *W. E. Blumberg*, Proc. Nat. Acad. Sci. USA *67*, 172 (1970).

[78] *J. A. Peterson*, personal communication.

[79] *V. Ullrich, B. Cohen, D. Y. Cooper*, and *R. W. Estabrook* in *K. Okunuki, M. D. Kamen*, and *I. Sekuzu:* Structure and Function of Cytochromes. University Park Press, Baltimore, Md. 1968, p. 649.

[80] *I. C. Gunsalus:* Wenner-Gren Symposium on Structure and Function of Oxidation Reduction Enzymes. Stockholm, August 1970.

[81] *Y. Ishimura, V. Ullrich*, and *J. A. Peterson*, Biochem. Biophys. Res. Commun. *42*, 140 (1971).

[82] *A. S. Mason, J. C. North*, and *M. Vanneste*, Fed. Proc. *24*, 1172 (1965).

[83] *B. B. Brodie, J. Axelrod, Y. R. Cooper, L. Gaudette, B. N. La Du, C. Mitoma*, and *S. Udenfriend*, Science *121*, 603 (195).

[84] *D. Y. Cooper, S. Levin, S. Narasimhul , O. Rosenthal*, and *R. W. Estabrook*, Science *147*, 400 (1965).

[85] *M. P. Mitchell* and *G. Hübscher*, Biochem. J. *103*, 23 P (1967).

[86] *V. Ullrich*, Hoppe-Seylers Z. Physiol. Chem. *350*, 357 (969).

[87] *U. Frommer, V. Ullrich*, and *Hj. Staudinger*, Hoppe-Seylers Z. Physiol. Chem. *351*, 913 (1970).

[88] *M. Waterman, V. Ullrich*, and *R. W. Estabrook*, unpublished.

[89] *V. Ullrich*, Z. Naturforsch. *24b*, 699 (1969).

[90] *V. Ullrich*, unpublished.

[91] *D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg*, and *S. Udenfriend*, Biochemistry *9*, 147 (1970).

[92] *B. M. Bloom* and *G. M. Shull*, J. Amer. Chem. Soc. *77*, 5767 (1955).

[93] *G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop*, and *S. Udenfriend*, Science *158*, 1524 (1967).

[94] *J. W. Daly, G. Guroff, D. M. Jerina, S. Udenfriend*, and *B. Witkop*, Hoppe-Seylers Z. Physiol. Chem. *349*, 1000 (1968).

[95] *L. Nover*, Pharmazie *7*, 361 (1969).

[96] *K. H. Byington* and *K. C. Leibman*, Mol. Pharmacol. *1*, 247 (1965).

[97] *H. Remmer*, Arch. Exp. Pathol. Pharmakol. *235*, 279 (1959).

[98] *A. H. Conney* and *J. J. Burns*, Nature *184*, 363 (1959).

[99] *A. P. Alvares, G. Schilling, W. Levin*, and *R. Kuntzman*, Biochem. Biophys. Res. Commun. *29*, 521 (1967).

[100] *A. Hildebrandt, H. Remmer*, and *R. W. Estabrook*, Biochem. Biophys. Res. Commun. *30*, 607 (1968).

[101] *Y. Imai* and *R. Sato*, Biochem. Biophys. Res. Commun. *25*, 80 (1966).

[102] *K. Ichihara, E. Kusunose*, and *M. Kusunose*, Biochim. Biophys. Acta *176*, 704 (1969).

[103] *W. Bohn, V. Ullrich*, and *Hj. Staudinger*, Naunyn-Schmiedebergs Arch. Pharmakol. *270*, 41 (1971).

[104] *J. A. Peterson* and *B. Griffin*, Fed. Proc. *30*, 1143 (1971).

[105] *V. Ullrich, J. A. Peterson*, and *M. Waterman*, to be published.

[106] *J. A. Peterson, V. Ullrich*, and *A. Hildebrandt*, Arch. Biochem. Biophys. *145*, 531 (1971).

[107] *H. A. O. Hill, A. Röder*, and *R. J. P. Williams*, Structure and Bonding *8*, 123 (1970).

[108] *I. C. Gunsalus*, Symposium on Cytochrome P-450. Philadelphia, March 970.

[109] *C. R. E. Jefcoate* and *F. C. Gaylor*, Biochemistry *8*, 3464 (1969).

[109a] *H. H. Ruf* and *V. Ullrich*, unpublished.

[110] *Ch. K. Jørgensen*, Z. Naturwiss.-Med. Grundlagenforsch. *2*, 248 (1965).

[111] *Y. Ichikawa, B. Hagihara, K. Mori*, and *T. Yamano* in *K. Bloch* and *O. Hayaishi:* Biological and Chemical Aspects of Oxygenases. Maruzen, Tokyo 1966, p. 211.

[112] *H. Diehl, J. Schädelin*, and *V. Ullrich*, Hoppe-Seylers Z. Physiol. Chem. *351*, 1359 (1970).

[113] *P. L. Gigon, T. E. Gram*, and *J. R. Gillette*, Biochem. Biophys. Res. Commun. *31*, 558 (1968).

[114] *D. Y. Cooper*, Int. Symposium on Microsomes and Drug Oxidations. Tübingen, July 1969.

[115] *R. W. Estabrook, A. Hildebrandt*, and *V. Ullrich*, Hoppe-Seylers Z. Physiol. Chem. *349*, 1605 (1968).

[116] *R. W. Estabrook, A. G. Hildebrandt, J. Baron, K. J. Netter*, and *K. Leibman*, Biochem. Biophys. Res. Commun. *42*, 132 (1971).

[117] *V. Ullrich* and *H. Diehl*, Eur. J. Biochem. *20*, 509 (1971).

[118] *W. Kirmse:* Carbene, Carbenoide und Carbenanaloge. Verlag Chemie, Weinheim 1969.

[119] *G. A. Hamilton*, J. Amer. Chem. Soc. *86*, 339 (1964).

[120] *V. Ullrich* and *Hj. Staudinger* in *K. Bloch* and *O. Hayaishi:* Biological and Chemical Aspects of Oxygenases. Maruzen, Tokyo 1966, p. 235.

[121] *S. K. Erickson, J. Schädelin, U. Schmeling, H.-H. Schott, V. Ullrich*, and *Hj. Staudinger* in *S. Patai:* The Chemistry of the Hydroxyl Group. Interscience, New York 1971, p. 755.

[122] *N. Prileschajew*, Ber. dtsch. chem. Ges. *42*, 4811 (1969).

[123] *K. M. Ibne-Rasa* and *J. O. Edwards*, J. Amer. Chem. Soc. *84*, 763 (1962).

[124] *U. Frommer* and *V. Ullrich*, Z. Naturforsch. *26B*, 322 (1971).

[125] *D. M. Jerina, J. W. Daly*, and *B. Witkop*, Biochemistry *10*, 366 (1971).

[126] *P. O. Bartlett*, Rec. Chem. Progr. *11*, 47 (1950).

[127] *A. G. Davies:* Organic Peroxides. Butterworths, London 1961, p. 128.

[128] *S. Udenfriend, G. T. Clark, J. Axelrod*, and *B. B. Brodie*, J. Biol. Chem. *208*, 731 (1954).

[129] *B. B. Brodie, J. Axelrod, P. A. Shore*, and *S. Udenfriend*, J. Biol. Chem. *208*, 741 (1954).

[130] *R. Breslow* and *L. N. Lukens*, J. Biol. Chem. *235*, 292 (1960).

[131] *V. Ullrich* and *Hj. Staudinger*, Z. Naturforsch. *24b*, 583 (1969).

[132] *V. Ullrich* and *Hj. Staudinger* in *B. Hess* and *Hj. Staudinger:* Biochemie des Sauerstoffs. Springer, Berlin 1969, p. 229.

[133] *S. Kaufman*, Pharmacol. Rev. *18*, 61 (1966).

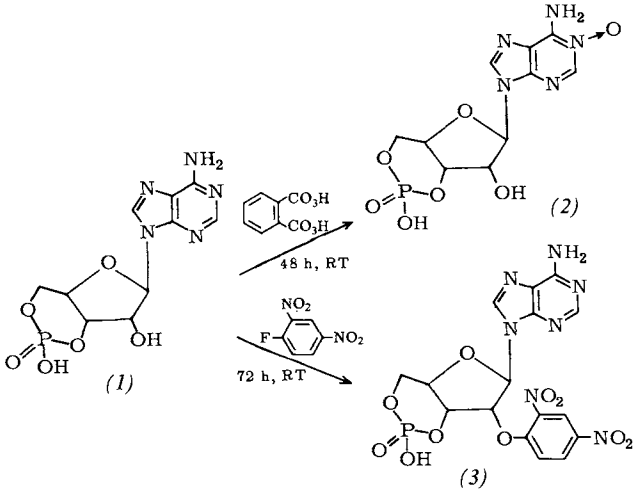
[134] *O. Hayaishi, Y. Ishimura, T. Nakazawa*, and *M. Nozaki* in *B. Hess* and *Hj. Staudinger:* Biochemie des Sauerstoffs. Springer, Berlin 1969, p. 196.

New Analogs of Adenosine-3′,5′-cyclophosphate

By *Bernd Jastorff* and *Wolfgang Freist*[*]

During the past few years adenosine-3′,5′-cyclophosphate (c-AMP) has become recognized as being one of the most important low-molecular weight regulation molecules in all stages of evolution[1]. Numerous derivatives of c-AMP have recently been synthesized[2] in order to obtain substances having specific biological activity and to elucidate the molecular interaction with the receptor. Here we report the synthesis of derivatives modified in the N-1, C-2, and C-2′ positions.

For modification of the N-1 and C-2′ positions, we used adenosine-3′,5′-cyclophosphoric acid *(1)* as starting material.

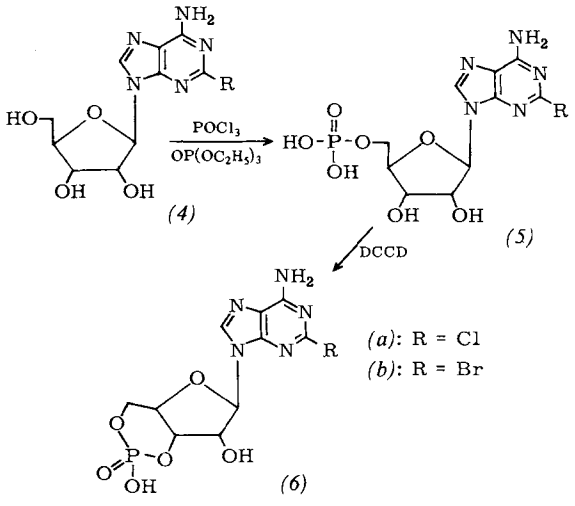


Oxidation (48 h, room temperature) of adenosine-3′,5′-cyclophosphoric acid *(1)* with monoperphthalic acid[3] in phosphate buffer (pH = 7)[4] affords the 1-*N*-oxide *(2)* in 78% yield (paper chromatographic isolation).

The dinitrophenyl ether *(3)* was prepared by reaction (72 h, room temperature) of the tri-*n*-butylammonium salt of *(1)* with four equivalents of 2,4-dinitrofluorobenzene in DMF/diisopropylethylamine (Hünig base) (40:1) and isolated by preparative layer chromatography (yield 66%).

The C-2 substituted derivatives *(6)* cannot be obtained directly from c-AMP; they were prepared by phosphorylation of the 2-halonucleosides *(4)*[5] with $POCl_3$ in triethyl phosphate[6] [yields: *(5a)*, 68%; *(5b)*, 61%] and subsequent cyclization of the 5′-phosphate *(5)* with dicyclohexylcarbodiimide in anhydrous pyridine: DMSO[7] [yields: *(6a)*, 72%; *(6b)*, 55%].

Preliminary biological investigations of the c-AMP analogs synthesized showed that all compounds are cleaved by bovine-heart cyclophosphodiesterase (E. C. 3.1.4.1). In the case of *(2)* the rate of cleavage is only slightly, in *(3)* about 50%, and in *(6a)* and *(6b)* considerably reduced. Reaction of c-AMP with the enzyme was inhibited 12% *(2)*, 50% *(3)*, 55% *(6a)*, and 77% *(6b)* by equimolar amounts of the analogs. At a concentration of 10^{-5} M all analogs activate the protein-kinase of bovine muscle to about the same degree as c-AMP itself. The combination of reduced rate of cleavage



by the phosphodiesterase and undiminished power of activation of the kinase could lead to enhanced physiological action in intact cells.

Received: May 2, 1972 [Z 656 IE]
German version: Angew. Chem. *84*, 711 (1972)

[1] *J. P. Jost* and *H. V. Rickenberg*, Annu. Rev. Biochem. *40*, 741 (1971).

[2] *A. Murayama*, *B. Jastorff*, *F. Cramer*, and *H. Hettler*, J. Org. Chem. *36*, 3029 (1971); *G. Michal*, *V. Nelböck*, and *G. Weimann*, Z. Anal. Chem. *252*, 189 (1970); *G. H. Jones*, *H. P. Albrecht*, *N. P. Damodaran*, and *J. G. Moffatt*, J. Amer. Chem. Soc. *92*, 5510 (1970); *K. Muneyama*, *R. J. Bauer*, *D. A. Shuman*, *R. K. Robins*, and *L. N. Simon*, Biochemistry *10*, 2390 (1971).

[3] *G. B. Payne*, J. Org. Chem. *24*, 1354 (1959).

[4] *F. Cramer* and *K. Randerath*, Angew. Chem. *70*, 571 (1958).

[5] *J. A. Montgomery* and *K. Hewson*, J. Heterocycl. Chem. *1*, 213 (1964).

[6] *M. Yoshikawa*, *T. Kato*, and *T. Takenishi*, Tetrahedron Lett. *50*, 5065 (1967).

[7] *R. H. Symons*, Biochem. Biophys. Res. Commun. *38*, 807 (1970).

A Novel Carrier for the Solid Phase Synthesis of Oligomers[1][**]

By *Hubert Köster* and *Stephan Geussenhainer*[*]

The principal drawbacks exhibited by most of the carriers previously used for solid phase synthesis by the Merrifield method[2] are porosity and swelling[3]. In the synthesis of oligonucleotides further difficulties are presented by the polarity of the phosphodiester bond during reactions in the cavities of the apolar carrier substance[4]. These disadvantages ought to be overcome if non-swellable and non-porous carriers are used. The

[*] Dr. B. Jastorff and Dr. W. Freist
Max-Planck-Institut für experimentelle Medizin,
Abteilung Chemie
34 Göttingen, Hermann-Rein-Strasse 3 (Germany)

[*] Dr. H. Köster and Dipl.-Chem. S. Geussenhainer
Institut für Organische Chemie
und Biochemie der Universität
2 Hamburg 13, Papendamm 6 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

reactions can take place only on the outer surfaces. The requirement of a sufficiently large surface area necessitates the preparation of very small beads of carrier substance. We were able to prepare a polymer having the desired properties from styrene and 20% divinylbenzene. It consisted of beads having diameters between one and two μm and smaller, and a specific surface area of 8.1 m^2/g. No swelling or porosity was discernable under the conditions used in our studies.

The material can be benzoylated by a Friedel-Crafts reaction. The benzophenone groupings react with *p*-bromoanisole in a Grignard reaction to give *p*-methoxytriphenylmethanol, which is converted into the chloride on reaction with HCl gas in acetic anhydride. Bonding of the nucleotide material takes place *via* the 5'-OH group. As is to be expected on the grounds of specific area, the order of magnitude of the loading is: 6.6 μmol of 3'-*O*-acetyldeoxythymidine and 6.1 μmol of 3'-*O*-acetyldeoxythymidylyl-3',5'-deoxythymidine per gram of carrier substance. These loadings are almost equivalent, whereas in the case of the macroporous bead polymers and emulsion-polymers-used previously a ratio of about 10:1 was observed[5,6]. Cleavage of the nucleotide material from the carrier takes place within 10 minutes in acetic acid at 70°C. Cleavage of the 3'-*O*-acetyl group takes place quantitatively within 2 h in dimethylformamide/pyridine/1 M sodium methoxide (5:4:1, v/v) at room temperature.

Preparation of the polymer:

A two-necked 2 l flask was used for the polymerization (diameter of flask: 12 cm; neck sizes: NS-29 and NS-14.5; distance of top edge of the NS-29 neck from bottom of flask: 26 cm). The NS-29 neck was used for incorporation of a "Tornado-Emulsion" stirrer (manufactured by Emmendinger Maschinenbau) and the NS-14.5 neck for a delivery tube whose drawn-out tip lay directly beneath the stirrer vanes.—A 0.5% aqueous solution of polyvinyl alcohol (1 liter; Schuchardt) was fed into the polymerization flask and the apparatus purged with nitrogen. The stirrer was set at 20000 rpm and the mixture of monomers [divinylbenzene (78 mmol), styrene/ethylstyrene (312 mmol), and azoisobutyronitrile (4.68 mmol) introduced slowly into the flask. The temperature of the reaction mixture increased to 50°C within an hour due to the frictional heat of the stirrer, and commencement of polymerization was readily noticed by the cloud point. The temperature rapidly increased to 65—68°C because of the heat of reaction. This temperature was maintained for a further 3 h, and polymerization was terminated after an additional 3 h at 75°C. The mixture was then passed through a fine sieve (6400 meshes/cm^2) and centrifuged at 2000 rpm. The centrifugate was discarded and the sediment was slurried and centrifuged several times in hot water and then twice in methanol. After drying, the sediment was subjected to several hours' Soxhlet extraction with benzene and finally dried under high vacuum: Yield of polymer 36.5 g (78.3%).

Received: May 23, 1972 [Z 657 IE]
German version: Angew. Chem. *84*, 712 (1972)

[1] Polymer-supported oligonucleotide synthesis, Part IX.—Part VIII: *H. Köster*, Tetrahedron Lett. *1972*, 1535.

[2] *R. B. Merrifield*, J. Amer. Chem. Soc. *85*, 2249 (1963).

[3] *E. Wünsch*, Angew. Chem. *83*, 773 (1971); Angew. Chem. internat. Edit. *10*, 786 (1971).

[4] *F. Cramer* and *H. Köster*, Angew. Chem. *80*, 488 (1968); Angew. Chem. internat. Edit. *7*, 473 (1968).

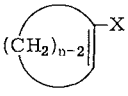
[5] *H. Köster*, Dissertation, Braunschweig 196 .

[6] *S. Geussenhainer*, Diplomarbeit, Hamburg 1972.

Solvolysis of 1-Cyclobutenyl Nonafluorobutanesulfonate[1][**]

By *L. R. Subramanian* and *Michael Hanack*[*]

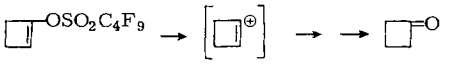
Cyclic vinyl trifluoromethanesulfonates (triflates) and cyclic vinyl nonafluorobutanesulfonates (nonaflates) of structure *(1)*, $n = 5$ to 8, undergo solvolysis in solvents of varying ionizing strength to give the corresponding



(1a), X = $-OSO_2CF_3$
(1b), X = $-OSO_2C_4F_9$

ketones[2]. From the very slowly reacting 1-cyclopentenyl triflate (or nonaflate) onwards, increasing rates of solvolysis were measured as the ring size was increased[2,3]. The maximum rate of solvolysis was found in the case of cyclononenyl- *(1a)*, $n = 9$, and of cis-cyclodecenyltriflate *(1a)*, $n = 10$[1]. The dependence of the reaction rate on the ring size is further experimental proof of the intermediary formation of vinyl cations as well as of their preference to assume linear geometry[2,3].

A still lower rate of solvolysis was to be expected for 1-cyclobutenyl nonaflate *(2)*, the lowest homolog of the cyclic vinyl fluoroalkylsulfonates known so far, than for 1-cyclopentenyl nonaflate *(1b)*, $n = 5$, if a highly strained 1-cyclobutenyl cation *(3)* occurs as intermediate.



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

All attempts to prepare 1-cyclobutenyl triflate *(1a)*, $n = 4$, were without success, presumably because of its high volatility. However, we were able to synthesize 1-cyclobutenyl nonaflate *(2)* by reaction of cyclobutanone with nonafluorobutanesulfonic acid anhydride[3] in the presence of tributylamine at 0°C (yield (15%)). *(2)* was purified by column chromatography (silica gel; petroleum ether, b.p. 40—60°C). IR spectrum (capillary): 1643 ($\nu_{C=C}$); 1445, 1225, 1150 cm^{-1} (ν_{-SO-O-}); NMR spectrum (CCl_4): $\tau = 4.58$ (broad s, 1 H, vinyl proton), 7.02 (m, 2H, next to Nf), 7.7 (m, 2H).

1-Cyclobutenyl nonaflate *(2)* (1 mmol) was solvolyzed for two days at 100°C in 50% aqueous ethanol buffered with triethylamine (2 mmol). Cyclobutanone *(4)* was the only reaction product formed.

Table 1. Rates of solvolysis of cyclobutenyl nonaflate *(2)* [a].

Compound	Temp. (°C)	k_1 (sec^{-1})	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$
50-proz. Ethanol	51.2	$(2.57 \pm 0.02) \times 10^{-5}$	23.6	−7.2
	74.8	$(3.27 \pm 0.08) \times 10^{-4}$		
80-proz. Ethanol	74.8	$(3.23 \pm 0.04) \times 10^{-5}$		

[a] Determined by the continuous method [4].

[*] Dr. L. R. Subramanian and Prof. Dr. M. Hanack
Institut für Organische Chemie der Universität
66 Saarbrücken (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie. L. R. S. thanks the Alexander-von-Humboldt Foundation for a grant.

Table 1 shows the rates of solvolysis of cyclobutenyl nonaflate *(2)* in ethanol/water mixtures of various ionizing strengths; Table 2 shows the rates of solvolysis of *(2)* in comparison with those of other vinyl nonaflates. Although the highly strained vinyl cation *(3)*

Table 2. Rates of solvolysis of cyclic Vinyl nonaflates in 50% Ethanol at 100 °C [a].

Nonaflate	k (sec^{-1})	k_{rel}
Cyclobutenyl-	3.5×10^{-3}	73400
Cyclopentenyl-	4.7×10^{-8}	1
Cyclohexenyl-	9.4×10^{-7}	20
Cyclooctenyl-	10.5×10^{-3}	222500

[a] Extrapolated from measurements at other Temperatures [3].

ought to be formed from *(2)*, the latter has a comparatively very high rate of solvolysis. It reacts much more rapidly than cyclopentyl nonaflate and at about the same rate as cyclooctenyl nonaflate, for which the linear geometry of the vinyl cation is readily attainable.

In order to exclude a possible addition-elimination mechanism[5] in the solvolysis of 1-cyclobutenyl nonaflate, the reaction rate constant of *(2)* was measured within a pH range of 3.2 to 9.2. As shown in Table 3, the rate of solvolysis is almost independent of pH[6].

Table 3. Rates of solvolysis of *(2)* as a function of pH in 50% Ethanol at 52.2 °C [a].

pH	$k_1 \times 10^5$ (sec^{-1}) [b]
3.2	2.66
4.2	2.55
5.2	2.69
6.2	2.57
7.2	2.74
8.2	2.86
9.2	2.83

[a] Determined by the continuous method [4].
[b] Mean error: 1.7%.

Further evidence for the formation of a vinyl cation in the solvolysis of *(2)* is provided by the fact that the rate of solvolysis increases with increasing ionizing strength of the solvent (Table 1). The calculated *m*-value (Winstein-Grunwald) of 0.61 is in good agreement with values expected for S_N1 reactions of vinyl derivative [5, 7].

The high rate of solvolysis of cyclobutenyl nonaflate *(2)* is indicative of a stabilization of the intermediary vinyl cation. We have already suggested the formation of a stabilized 1-cyclobutenyl cation in the rearrangement of homopropargyl compounds to cyclobutanones and cyclopropyl ketones[5, 8]. CNDO calculations for the cyclobutenyl cation *(3)* have shown[9] that a bridged form *(5)* ought to be more stable than *(3)*. The high reactivity of *(2)* thus points to the formation of a non-classical vinyl cation *(5)* in which the conditions are particularly suitable for orbital overlapping[9].


(5)

Received: June 12, 1972 [Z 659 IE]
German version: Angew. Chem. *84*, 714 (1972)

[1] Vinyl cations, Part 7.—Part 6: *E. Lamparter* and *M. Hanack*, Chem. Ber., in press.

[2] *W. D. Pfeifer, C. A. Bahn, P. v. R. Schleyer, S. Bocher, C. E. Harding, K. Hummel, M. Hanack*, and *P. J. Stang*, J. Amer. Chem. Soc. *91*, 1513 (1971).

[3] *L. R. Subramanian* and *M. Hanack*, Chem. Ber. *105*, 1465 (1972).

[4] *H. J. Schneider, H. Schneider-Bernlöhr*, and *M. Hanack*, Liebigs Ann. Chem. *722*, 234 (1969).

[5] *M. Hanack*, Accounts Chem. Res. *3*, 209 (1970).

[6] *Z. Rappoport, T. Bäßler*, and *M. Hanack*, J. Amer. Chem. Soc. *92*, 4985 (1970); *C. A. Grob* and *H. R. Pfaendler*, Helv. Chim. Acta *54*, 2060 (1971).

[7] *Z. Rappoport* and *A. Gal*, J. Org. Chem. *37*, 1174 (1972).

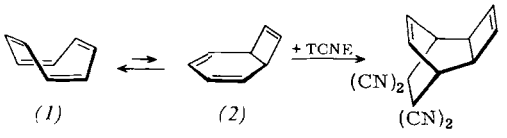
[8] *M. Hanack, V. Vött*, and *H. Ehrhardt*, Tetrahedron Lett. *1968*, 4617; *M. Hanack, S. Bocher, I. Herterich, K. Hummel*, and *V. Vött*, Liebigs Ann. Chem. *733*, 5 (1970).

[9] *H. Fischer, K. Hummel*, and *M. Hanack*, Tetrahedron Lett. *1969*, 2169.

1,4-Cycloaddition of Azodicarboxylic Phenylimide [4-Phenyl-1,2,4-triazoline-3,5-dione] to Cyclooctatetraene and Its Halogen Derivatives

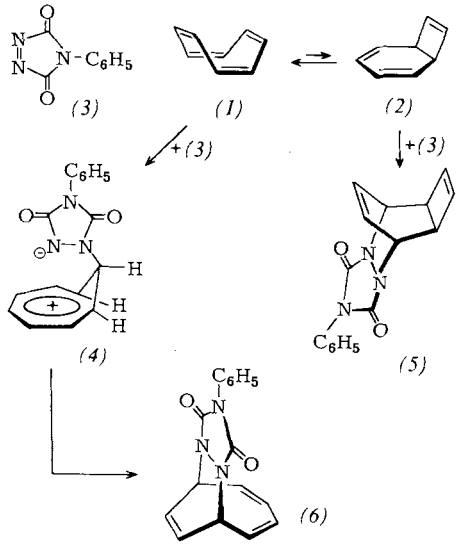
By *Rolf Huisgen, Will Elmar Konz*, and *Ulrich Schnegg*[*]

The boat conformation *(1)* of cyclooctatetraene results in maximal hindrance to conjugation of the localized double bonds and thus does not provide a planar 1,3-diene system suitable for the Diels-Alder reaction. It is not only formally that the Diels-Alder adducts with dienophiles[1] are derived from bicyclo[4.2.0]octatriene *(2)*, for kinetic study of the reactions with tetracyanoethylene and other highly active dienophiles has shown that the cycloaddition is preceded by the valence tautomerization *(1)* → *(2)*, which affords the necessary quasiplanar diene system[2, 3].



(1) *(2)*

Azodicarboxylic phenylimide [4-phenyl-1,2,4-triazoline-3,5-dione] *(3)* combines with *(1)* to give not only the "normal" adduct *(5)*[4], but also the direct 1,4-



(3) *(1)* *(2)* *(4)* *(5)* *(6)*

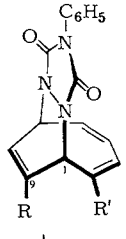
[*] Prof. Dr. Rolf Huisgen, Dr. W. E. Konz, and Dipl.-Chem. U. Schnegg
Institut für Organische Chemie der Universität
8 München 2, Karlstrasse 23 (Germany)

adduct *(6)* of cyclooctatetraene[5, 6]. The activation energy of the valence isomerization *(1)* → *(2)* amounting to 27.4 kcal/mol[3] must be provided for the formation of *(5)*. However, a smaller temperature coefficient is to be expected for the 1,4-cycloaddition; both the multicenter Diels-Alder reaction and the two-step reaction by way of a zwitterion should show large negative activation entropies. If the reaction of *(3)* with itself[7] is suppressed in dilute solution, the temperature dependence of the composition of the mixed adducts (determined by NMR spectroscopy) accords with expectation (Table 1). The formation of *(5)* is suppressed at 20 °C; that the yield of *(5)* + *(6)* decreases from 100 to 20 °C is explained by the fact that an increasing percentage of the sensitive *(3)* suffers decomposition during the long reaction times required at low temperatures.

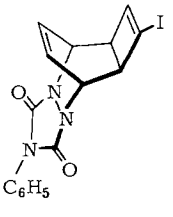
Table 1. Yields of the cycloadducts *(5)* and *(6)* on reaction of cyclooctatetraene (0.04 M) with azodicarboxylic phenylimide (0.01 M) in dioxane.

Temp. (°C)	Reaction time	Yield (%) *(5)*	*(6)*	*(5)*/*(6)*
100	15 min	32	31	1.0
60	3 h	13	41	0.32
40	2 days	6	37	0.16
20	14 days	0	37	0.00

The activity of *(3)* exceeds that of tetracyanoethylene not only as dienophile[4] but also as electrophile. We presume therefore that the cycloaddition of *(3)* to *(1)* proceeds *via* the homotropylium zwitterion *(4)*. Halogenation of *(1)*[8, 9], 1,4-addition of *N*-chlorosulfonyl isocyanate[10], and formation of the cyclic sulfone by $SO_2 \cdot SbF_5$[11] also occur by way of the homotropylium zwitterion.



	R	R'
(7)	H	I
(8)	I	H



(9)

Whereas fluoro-[12] and chlorocyclooctatetraene[13], on reaction with *(3)*, afford only adducts of type *(5)*, both types of adduct are obtained from bromocyclooctatetraene[13]. The latter situation is also the case for iodocyclooctatetraene[14], which with 1.2 M *(3)* in ethyl acetate at 20 °C gives 7.4% of *(7)* and 4.2% of *(8)* in 4 weeks, but at 80 °C gives 5.0% of *(7)*, 3.5% of *(8)*, and 13% of *(9)* in 2 hours; the main product is 1,2-hydrazinebis(dicarboxylic phenylimide), which arises from 2 molecules of *(3)*[7]. The adducts *(7)* to *(9)* were separated by thin-layer chromatography and their structures were determined by double resonance NMR spectroscopy.

Received: June 2, 1972 [Z 660a IE]
German version: Angew. Chem. *84*, 765 (1972)

[1] *W. Reppe, O. Schlichting, K. Klager*, and *T. Toepel*, Liebigs Ann. Chem. *560*, 1 (1948).

[2] *R. Huisgen* and *F. Mietzsch*, Angew. Chem. *76*, 36 (1964); Angew. Chem. internat. Edit. *3*, 83 (1964).

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

[4] *R. C. Cookson, S. S. H. Gilani*, and *I. D. R. Stevens*, J. Chem. Soc. C *1967*, 1905.

[5] *A. B. Evnin, R. D. Miller*, and *G. R. Evanega*, Tetrahedron Lett. *1968*, 5863.

[6] Experiments by *W. E. Konz*, München 1968.

[7] *E. Brunn, E. Funke, H. Gotthardt*, and *R. Huisgen*, Chem. Ber. *104*, 1562 (1971).

[8] *R. Huisgen, G. Boche*, and *H. Huber*, J. Amer. Chem. Soc. *89*, 3345 (1967).

[9] *R. Huisgen* and *J. Gasteiger*, J. Amer. Chem. Soc., in press.

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

[11] *J. Gasteiger* and *R. Huisgen*, J. Amer. Chem. Soc., in press.

[12] *G. Schröder, G. Kirsch, J. F. M. Oth, R. Huisgen, W. E. Konz*, and *U. Schnegg*, Chem. Ber. *104*, 2405 (1971).

[13] *R. Huisgen, W. E. Konz*, and *G. E. Gream*, J. Amer. Chem. Soc. *92*, 4105 (1970).

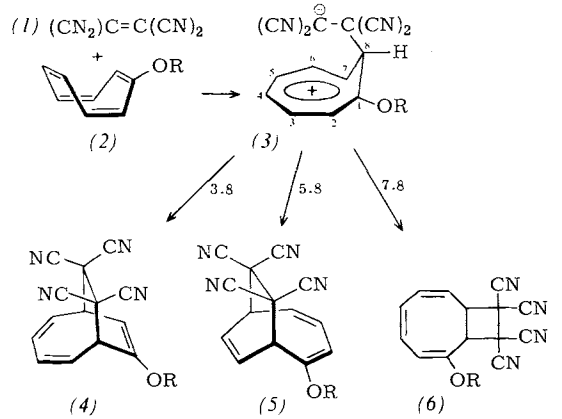
[14] Preparation: *J. Gasteiger, G. E. Gream, R. Huisgen, W. E. Konz*, and *U. Schnegg*, Chem. Ber. *104*, 2412 (1971).

1,4-Cycloaddition of Tetracyanoethylene to Methoxy- and Phenoxy-cyclooctatetraene

By *Johann Gasteiger* and *Rolf Huisgen*[*]

An increase in dienophile activity by 6 powers of ten is observed for Diels-Alder reactions in the series maleic anhydride, tetracyanoethylene *(1)*, and azodicarboxylic phenylimide[1], this order also being that of increasing electrophilicity.

With maleic anhydride or *(1)*, cyclooctatetraene reacts exclusively through the quasiplanar diene system of the valence tautomer bicyclo[4.2.0]octatriene[2]. With the azodicarboxylic imide, however, this is accompanied by direct 1,4-addition, presumably through the homotropylium intermediate[3]. If the electron density of the cyclooctatetraene is increased by a methoxyl or phenoxyl substituent, then tetracyanoethylene, but not maleic anhydride, also undergoes 1,4-addition to the four-fold unsaturated, eight-membered ring. The homotropylium intermediate *(3)* is additionally stabilized by the ether group.



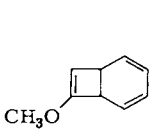
(a), R = CH_3 18% 78%
(b), R = C_6H_5 17% 74%

Reaction of methoxycyclooctatetraene *(2a)*[4] with *(1)* in benzene for 15 hours at 20 °C yields a cycloadduct

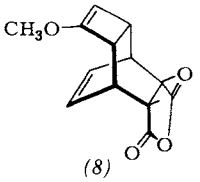
[*] Dr. J. Gasteiger and Prof. R. Huisgen
Institut für Organische Chemie der Universität
8 München 2, Karlstrasse 23 (Germany)

mixture that according to NMR analysis contains *(4a)* and *(5a)* in the ratio 1:4; fractional crystallization leads to the yields shown in the formula scheme. Treatment of phenoxycyclooctatetraene *(2b)*[4] with *(1)* for 40 hours gives an analogous result, but in this case the main product is *(6b)* containing a four-membered ring.

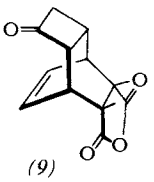
All the adducts were analyzed by NMR spectroscopy; double resonance measurements at 100 MHz and spin tickling provided all the τ- and *J*-values and made it possible to assign them unambiguously. Iteration of the spectra calculated by the LAME computer program[5] led to simulation of the experimental spectra and precise values for the parameters.



(7)

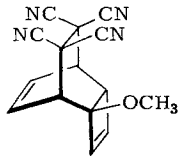


(8)

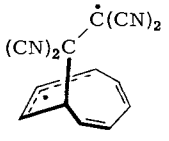


(9)

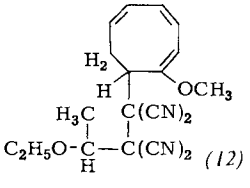
Maleic anhydride reacts with *(2a)* only by way of the valence tautomer *(7)*: after 40 hours in benzene at 70°C 99% of *(8)* can be isolated, this being hydrolyzed even in moist ethyl acetate to *(9)*, which was previously obtained from cyclooctatrienone and maleic anhydride[6].



(10)



(11)



(12)

Irradiation of the adduct *(5a)* in ether by a mercury high-pressure lamp in a glass vessel furnishes 37% of methoxycyclooctatetraene *(2a)*, 44% of the tricyclic adduct isomer *(10)*, and 6.5% of the compound *(12)* in which the adduct has formally taken up a molecule of diethyl ether. The structures *(10)* and *(12)* were likewise elucidated by 100 MHz NMR spectra with decoupling experiments.

The photolysis of *(5a)* to *(2a)* is symmetry-allowed as cycloreversion [6 + 2] from S_1; fission of *(11)* could also lead to *(2a)*. The disrotatory cyclization of the 1,3-diene systems in *(5a)* to the cyclobutene ring in *(10)* is allowed from the S_1 state. The ether adduct *(12)* could be formed through the biradical *(11)*.

Received: June 2, 1972 [Z 660b IE]
German version: Angew. Chem. *84*, 766 (1972)

[1] *J. Sauer, H. Wiest,* and *A. Mielert,* Chem. Ber. *97*, 3183 (1964); *J. Sauer* and *B. Schröder, ibid. 100*, 678 (1967).

[2] *R. Huisgen* and *F. Mietzsch,* Angew. Chem. *76*, 36 (1964); Angew. Chem. internat. Edit. *3*, 83 (1964).

[3] *R. Huisgen, W. Konz,* and *U. Schnegg,* Angew. Chem. *84*, 765 (1972); Angew. Chem. internat. Edit. *11*, 715 (1972).

[4] *J. Gasteiger, G. E. Gream, R. Huisgen, W. E. Konz,* and *U. Schnegg,* Chem. Ber. *104*, 2412 (1971).

[5] *C. W. Haigh,* Annu. Rep. NMR Spectrosc. *4*, 311 (1971).

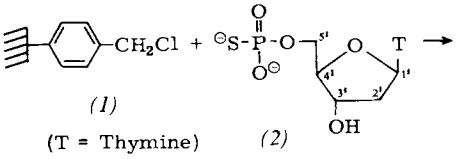
[6] *A. C. Cope, S. F. Schaeren,* and *E. R. Trumbull,* J. Amer. Chem. Soc. *76*, 1096 (1954).

Synthesis of Oligodeoxynucleotides with 5′-Terminal Phosphate Groups

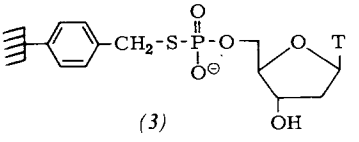
By *Hans Sommer* and *Friedrich Cramer*[*]

In most oligonucleotide syntheses[1] on polymeric carriers a nucleoside is first attached to the carrier by its 5′-OH group. Removal of the synthesized oligonucleotide regenerates a free 5′-OH group, which must be phosphorylated for further block condensation of the product[2]. This additional step can be avoided if a nucleotide is attached to the carrier by the 5′-phosphate group. Two methods of this type have already been described[3].

We have found a new and simple method of synthesizing oligonucleotides containing 5′-phosphate groups. The carrier used is a 5% crosslinked macroporous chloromethylpolystyrene *(1)*[**] (chloromethylation of the polystyrene effected by *Merrifield*'s method[4]), containing 0.75 mmol of chloromethyl groups per gram of polymer. It is treated in dimethylformamide for 24 h at 60°C with a 1.3-fold excess of sodium thymidine 5′-phosphorothioate *(2)*[5], affording *(3)* by *S*-alkylation[6]. The amount of loading with *(2)* depends on



(1) (T = Thymine) *(2)*



(3)

the reaction time, the temperature, and the relative amounts of the reactants; it ranges from 0.083 to 0.41 mmol per gram of polymer, the optimum for oligonucleotide syntheses being 0.175 to 0.27. Unchanged chloromethyl groups are etherified by 2 N Na methoxide in anhydrous pyridine (1:6) in 1 h at room temperature.

Stepwise formation of the oligonucleotide chain is achieved by linking the free 3′-OH group with a 3- to 5-fold excess of protected 3′-*O*-acetyldeoxynucleoside 5′-phosphate in anhydrous pyridine during 6 to 8 h at room temperature in presence of 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) as condensing agent (2.5-fold excess with respect to the phosphate component). After removal of the 3′-*O*-acetyl group by 2 N Na methoxide in anhydrous pyridine (1:9) during 25 min at room temperature the next condensation step can be undertaken.

Removal of the oligonucleotide from the polymer is effected by iodine (10 mg/ml) in pyridine/water (3:1) during 20 h at room temperature, the protecting groups being retained during this process. The following oligodeoxynucleotides were prepared by this method and were characterized by paper chromatography and enzy-

[*] Dr. H. Sommer and Prof. Dr. F. Cramer
Max-Planck-Institut für experimentelle Medizin, Abt. Chemie
34 Göttingen, Hermann-Rein-Strasse 3 (Germany)

[**] Commercial polymer from Bio-Rad Laboratories, Richmond, Calif., gave poorer yields.

matic degradation with phosphodiesterase (the yields refer to the last condensation step)[7]:

$(pdT)_2$ 39% $(pdT)_3$ 25% $(pdT)_4$ (19%) $(pdT)_5$ 21%
$pdTpdan^4C$ 23% $pdTpdan^4CpdT$ 18%
$pdTpdbz^6A$ 21% $pdTpdbz^6ApdT$ 25%

Received: June 2, 1972 [Z 661 IE]
German version: Angew. Chem. *84*, 710 (1972)

[1] *H.* [1] *H. Hayatsu* and *H. G. Khorana*, J. Amer. Chem. Soc. *88*, 3182 (1966); *F. Cramer* and *H. Köster*, Angew. Chem. *80*, 488 (1968); Angew. Chem. internat. Edit. *7*, 473 (1968); *L. R. Melby* and *D. R. Strobach*, J. Org. Chem. *34*, 421 (1969); *R. L. Letsinger* and *V. Mahadevan*, J. Amer. Chem. Soc. *88*, 5319 (1966); *K. F. Yip* and K. C. Tsou, J. Amer. Chem. Soc. *93*, 3272 (1971); *T. Kusama* and *H. Hayatsu*, Chem. Pharm. Bull. *18*, 319 (1970).

[2] *A. Kumar* and *H. G. Khorana*, J. Amer. Chem. Soc. *9* , 2743 (1969).

[3] *G. M. Blackburn*, *M. J. Brown*, and *M. R. Harris*, J. Chem. Soc. C *1967*, 2438; *W. Freist* and *F. Cramer*, Angew. Chem. *82*, 358 (1970); Angew. Chem. internat. Edit. *9*, 368 (1970).

[4] *R. B. Merrifield*, Biochemistry *3*, 1385 (1964).

[5] As modified by *A. W. Murray* and *M. R. Atkinson*, Biochemistry *7*, 4023 (1968).

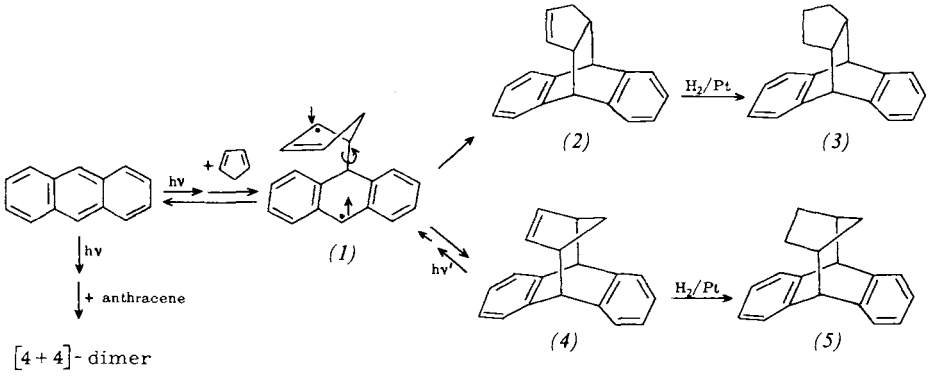
[6] *A. F. Cook*, *M. J. Holman*, and *A. L. Nussbaum*, J. Amer. Chem. Soc. *91*, 6479 (1969); *A. F. Cook*, J. Amer. Chem. Soc. *92*, 190 (1970).

[7] Abbreviations according to IUPAC-IUB, Eur. J. Biochem. *15*, 203 (1970); pdT = thymidine 5'-phosphate; $pdan^4C = N^4$-anisoyldeoxycytidine 5'-phosphate; $pdbz^6A = N^6$-benzoyldeoxyadenosine 5'-phosphate.

[2 + 4]- and [4 + 4]-Photoaddition of Cyclopentadiene to Anthracene[**]

By *Gerd Kaupp*[*]

The question whether photochemical four-center additions occur by concerted or multistep processes is important for the quantum balance and in particular is of preparative interest[1-3]. We report here about competing [2 + 4]- and [4 + 4]-photoadditions of cyclopentadiene to electronically excited anthracene[2].



On selective irradiation of anthracene (5 successive portions of 1.0 g each) in cyclopentadiene (500 ml) [0 ± 5 °C; N_2; $\lambda > 330$ nm; Hanovia 450 watt Hg high-pressure lamp, $Cu(NO_3)_2$ filter solution] to complete reaction (*ca.* 5 × 1 h), subsequent recovery of cyclopentadiene and evaporation in a high vacuum (5×10^{-4} torr, 40 °C), 1.24 g (25%) of the known anthracene dimer[4] was isolated by filtration. The ether-soluble portion of the residue consists, according to NMR analysis, of 42% of *(2)* and 58% of *(4)*. The two isomers can be separated by repeated fractional crystallization from acetonitrile or by preparative layer chromatography (SiO_2, CCl_4) and can be identified by their spectral properties[5].

The asymmetry of *(2)* (m.p. 153—154 °C) accounts for its complicated NMR spectrum [60 MHz, $CDCl_3$: $\tau = 2.6$ to 3.1 (8 H/m), 4.7 (2 H/degenerate AB with central s, $\Delta\nu_{1/2} = 1.8$), 5.75 (1 H/AB, $J = 3.0$, $\Delta\nu_{1/2} = 1.1$), 5.9 (1 H/BA, $\Delta\nu_{1/2} = 1.4$), 6.6 to 6.95 (1 H/m), 7.0 to 8.4 ppm (3 H/overlapping m)].

On the other hand, the symmetry plane present in *(4)* (m.p. 117 °C) can be recognized in its NMR spectrum [$CDCl_3$: $\tau = 2.7$ to 3.05 (4 H/AA'BB'), 2.8 to 3.15 (4 H/AA'BB'), 4.3 to 4.45 (2 H/AA'XX'), 6.05 (2 H/AB, $J = 9.0$, $\Delta\nu_{1/2} = 1.5$), 7.2 (2 H/BA, $J = 9.0$, numerous couplings), 8.3 (1 H/tAB, $J = 11.4$, 4.4), 8.75 ppm (1 H/BA, $\Delta\nu_{1/2} = 3.2$)].

Further differences between the isomers which may be hydrogenated catalytically to *(3)* (m.p. 131—132 °C) and *(5)* (m.p. 159 °C)[5], respectively, occur in the positions of the UV maxima [CH_3CN; *(2)*: $\lambda_{max}(\varepsilon) = 252$ sh (720), 259sh (920), 265.5 (1440), 272.5 (1860); *(4)*: 267sh (1050), 273.5 (1740), 281nm (2550)], the fluorescence behavior [cyclohexane; *(2)*: $\lambda_{max}^{corr.} = 286$ nm, $\Phi_{Fl} = 0.38$; *(4)*: 293, $\Phi_{Fl} = 0.03$], and the efficiency of the photocycloreversion.

On irradiation (272 nm, CH_3CN; $c_0 = 5 \times 10^{-4}$ mol/liter), the intensely fluorescing hydrocarbon *(2)* affords less than 1.5% of anthracene along with unidentified other products. However, *(4)* is photolyzed largely uniformly to anthracene and cyclopentadiene (yield of anthracene 79—80%; quantum yield of anthracene formation, $\Phi = 0.26$; $c_0 = 5 \times 0^{-4}$ mol/liter; CH_3CN; 20 °C) and *(2)* (see formula scheme).

This behavior can be utilized to simplify the isolation of *(2)*, namely by (almost) selective irradiation (CH_3CN, mercury high-pressure lamp, Pyrex filter) of the longer-wave absorbing component *(4)* of *(2)*/*(4)* mixtures, whereafter 80% of dimeric anthracene [based on *(4)*] can be filtered off and an increase in the yield of *(2)* achieved [from 150 mg of pure *(4)*, 28 mg of *(2)* (the result of a photochemical 1 → 3 shift) can be isolated by chromatography].

The ratio 5:7 of [2 + 4]- to [4 + 4]-photoaddition on selective irradiation of anthracene in cyclopentadiene (quantum yield of anthracene consumption amounts to 0.065: $c < 3 \times 10^{-4}$ mol/liter, 365 nm, 18.5 °C, N_2)[6] is understandable in terms of the experimentally proved two-step mechanism of photochemical four-center reactions[1] assuming that the intermediate product *(1)* has a long enough life-time for (partial) rotation around

[*] Dr. G. Kaupp
Chemisches Laboratorium der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

the first σ-bond formed before stabilization to give the end products or starting materials. Experiments to date provide no indication whether the σ-complex *(1)* is formed from a single definite π-complex (exciplex). Molecular models and the quantum yield—the latter relatively small in comparison with dimerization of anthracene ($\Phi_{max} = 0.3$[4])—indicate, on the contrary, steric hindrance to a sandwich-like approach. The reduced fluorescence yield of anthracene in cyclopentadiene ($\Phi_{cyclohexane}/\Phi_{cyclopentadiene} = 1.8$) should then be largely the result of σ-interaction. This is indicated also by the relatively large quantum yield for the photochemical formation of anthracene from *(4)* (see formula scheme and [1]).

Unlike the observations reported above, the addition of 1,3-cyclohexadiene to anthracene appears to lead exclusively to the [4+4]-adduct (homolog of *(4)*)[7]. The results reported in the present communication, as well as previous measurements on cyclovinylogous model systems[1], strongly suggest that 1,3-cyclohexadiene is added nonconcertedly in two discrete steps. This is indicated also by the considerable geometrical change occurring in the four-center reaction, even if *chemical deactivation* begins with the postulated exciplex intermediate[7,8]. This suggests that chemical quenching of fluorescence[1] can be ruled out on the evidence of photochemical quantum yields only in cases where it is possible to make quantitative predictions about all the deactivation processes of exciplexes and intermediates of type *(1)* (see, however, p. 288 in [8]).

Received: June 8, 1972 [Z 662a IE]
German version: Angew. Chem. *84*, 718 (1972)

[1] *G. Kaupp*, Angew. Chem. *84*, 259 (1972); Angew. Chem. internat. Edit. *11*, 313 (1972); Angew. Chem. *83*, 361 (1971); Angew. Chem. internat. Edit. *10*, 340 (1971); Chimia *25*, 230 (1971).

[2] Lecture at VÖCh-GDCh joint meeting (May 17—20, 1972) at Vienna; *G. Kaupp*, Allgem. Prakt. Chemie *23*, 80 (1972).

[3] *G. Kaupp* and *K. Krieger*, Angew. Chem. *84*, 719 (1972); Angew. Chem. internat. Edit. *11*, 719 (1972).

[4] *E. J. Bowen*, Advan. Photochem. *1*, 23 (1963).

[5] All the new compounds were characterized analytically and spectroscopically.

[6] Under comparable conditions anthracene is consumed in undiluted 1,3-cyclohexadiene with a quantum yield of $\Phi = 0.16$.

[7] *N. C. Yang* and *J. Libman*, J. Amer. Chem. Soc. *95*, 1405 (1972).

[8] *L. M. Stephenson* and *G. S. Hammond*, Angew. Chem. *81*, 279 (1969); Angew. Chem. internat. Edit. *8*, 261 (1969).

Photoprocesses of Phenyl-Substituted Tetrahydropentalenes[**]

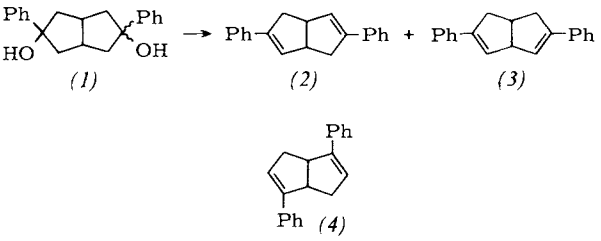
By *Gerd Kaupp* and *Klaus Krieger*[*]

The experimental evidence for the two-step course of photochemical four-center reactions[1] made it desirable to seek intramolecular [$_\pi 2 + _\pi 2$]-photocycloadditions to substrates that contain *non-parallel, fixed double bonds*[2]. We report here on the irradiation of the phenyl-substituted tetrahydropentalenes *(2)*, *(3)*, and *(4)*[3].

[*] Dr. G. Kaupp
Chemisches Laboratorium der Universität
78 Freiburg, Albertstrasse 21 (Germany)
and
K. Krieger
Hegel-Gymnasium
7 Stuttgart-Vaihingen, Krehlstrasse 65 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Contrary to previous assumptions[4], dehydration of the diol *(1)*[4] by oxalic acid at 115°C affords the two dienes *(2)* and *(3)* approximately in the ratio



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

(4)

1:1 (NMR analysis). On recrystallization from CH_3OH they are isolated as 1:1 mixed crystals (long needles, m.p. 109 to 115°C [4]: 104°C) and can be separated by chromatography (Al_2O_3, activity 1; cyclohexane), which involves large losses of *(3)*[5].

A decided improvement in the isolation of *(3)* is achieved by irradiation (CH_3CN, N_2, 0 ± 5°C, Hg high-pressure lamp, Pyrex filter) of the 1:1 mixture of *(2)* and *(3)* to nearly complete reaction of *(3)* [formation of *(6)*, see formula scheme], addition of benzoyl peroxide (molar ratio = 1:1) and further irradiation [radical polymerization of *(2)*], heating for 30 min in CCl_4 to regenerate *(3)*, and chromatography (SiO_2/CH_2Cl_2) for 0.5 h, whereupon 40 to 50% of the *(3)* originally present is obtained.

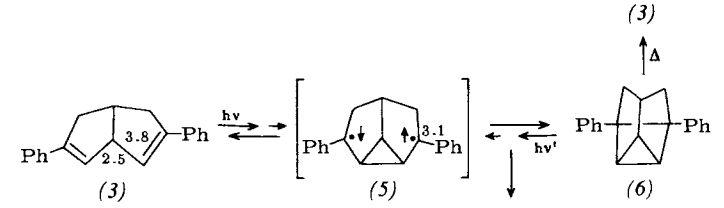
The structures of the isomers *(2)* (m.p. 118—119°C) and *(3)* (m.p. 121—122°C)[6] can be assigned from the NMR spectra because of the magnetic equivalence of the bridge protons in *(2)* [$CDCl_3$, $\tau = 2.45$ to 2.9 (10 H/m), 3.9 to 4.1 (2 H/m), 6.15 to 6.5 (2 H/m), 6.7 to 7.6 ppm (4 H/m)], the difference for *(3)* [$CDCl_3$, $\tau = 2.35$ to 2.9 (10 H/m), 3.75 to 3.9 (2 H/m), 5.75 to 6.1 (1 H/m), 6.55 to 7.65 ppm (5 H/m)], and comparison with *(4)*[7] [$CDCl_3$, $\tau = 2.4$ to 2.85 (10 H/m), 3.9 to 4.1 (2 H/m), 5.75 to 6.15 (2 H/m), 6.75 to 7.85 ppm (4 H/m)]. The UV spectra of *(2)* [$\lambda_{max}(\varepsilon) = 253$ (30000), 258 (32000)] and *(4)* [252 (29500), 257 nm (30000)] in CH_3CN are almost superposable and have long-wave fine structure; but for *(3)* [$\lambda_{max}(\varepsilon) = 269$ (28500)] also short-wave shoulders can be resolved (spectral band width 0.5 nm), and the onset of absorption (at *ca.* 310 nm) is red-shifted by about 10 nm in comparison with *(2)* and *(4)*.

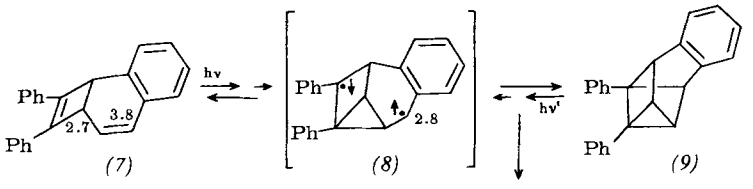
On irradiation (250 to 292 nm, CH_3CN, N_2, 20 and −190°C in ether/alcohol glasses), *(2)* and *(4)*, whose double bonds are separated by about 3.5 Å (measurement on molecular models), do not undergo intramolecular formation of tetracycles. They give intense fluorescence spectra with fine structure [cyclohexane, N_2, 20°C; *(2)*: $\lambda_{max}^{corr.}$ (Φ_{Fl}) = 300 sh, 310, 317 sh, 332 sh (0.088); *(4)*: 297, 310, 318 sh, 335 sh nm (0.090)].

However, no fluorescence ($\Phi < 10^{-4}$) can be detected for *(3)* although photochemical formation of *(6)* occurs rather slowly [NMR ($CDCl_3$, 20°C): $\tau = 2.5$ to 3.35 (10 H/m with central s, $\Delta\nu_{1/2} = 2.0$), 7.15 to 8.4 ppm (8 H/m)]. The quantum yield, measured photokinetically[1] [CH_3CN, N_2 or O_2, 20°C, 289 nm, bandpass 4.8 nm, $c_0 = (1 \text{ to } 2) \times 10^{-4}$ mol/liter] amounts to 0.025 and the isosbestic points are at 233 and 221 nm.

The failure of *(3)* to fluoresce [in contrast to *(2)* and *(4)*] is interpreted by almost quantitative transformation of electronically excited diene *(3)* into the short-lived intermediate *(5)* (chemical quenching of fluores-

cence) considering the relatively minor geometrical change (molecular models; cf.[1]). Primarily because of the rather large separation of the radical centers in *(5)*, there is a greater likelihood of cleavage of the three-membered ring to give *(3)* than of formation





of the tetracycle *(6)*. It is, therefore, not surprising that *crystalline (3)* (pure or in KBr, $\lambda > 270$ nm) does not form any *(6)* but instead polymerizes and is photostable (no phosphorescence) at -190 °C (methylcyclohexane/*n*-pentane glass, 250—292 nm), whereas the light-induced reverse reaction [*(6)* → *(3)*, 250 nm] occurs very rapidly and largely uniformly at -190 °C.

The interconversion *(7)* ⇄ *(9)*[8] substantiates this interpretation, according to which formation of the tetracycle from *(5)* is hindered by an activation barrier of geometrical origin. For geometrical reasons (molecular models) the formation of *(8)* should be more difficult than of *(5)*. Conversely, the final four-membered ring closure to give *(9)* should be more favored than that leading to *(6)*. In fact, during irradiation of *(7)* there is concurrent intense fluorescence of the stilbene chromophore (313 nm, cyclohexane, $\lambda_{max}^{corr.} = 390$ nm, $\Phi_{Fl} = 0.012$). Nevertheless, *(9)* is formed in appreciably higher quantum yield than *(6)*: $\Phi_{(7)\rightarrow(9)} = 0.16$ to 0.17 (CH_3CN or C_2H_5Br, N_2 or O_2, 20 °C, 313 or 334 nm; isosbestic points in CH_3CN at 243 and 248 nm). Again the intramolecular cycloaddition can be frozen out at -190 °C (ether/alcohol glass) and in this case can be effected also from the crystalline state at room temperature.

The photoreversion *(9)* → *(7)* (250 nm) occurs with an initial quantum yield $\Phi \leq 0.2$ (CH_3CN, N_2, 20 °C). As with *(6)*, luminescence was observed only after formation of appreciable amounts of by-products and the photoreaction becomes more uniform at -190 °C. It is conceivable that excitation of *(6)* and *(9)* affords other intermediate photoproducts besides *(5)* and *(8)*, respectively.

The experimental results do not require postulation of either a triplet mechanism or of a photochemical transition state with unequally advanced bond formation at four reaction centers.

Received: June 6, 1972 [Z 662b IE]
German version: Angew. Chem. *84*, 719 (1972)

[1] *G. Kaupp*, Angew. Chem. *84*, 718 (1972), ref. [1]; Angew. Chem. internat. Edit. *11*, 718 (1972).

[2] Some, usually sensitized, reactions of this type are known: *S. Moon* and *C. R. Ganz*, Tetrahedron Lett. *1968*, 6275; cf. *J. R. Scheffer* and *M. L. Lungle*, *ibid. 1969*, 845; *R. Criegee* and *R. Askani*, Angew. Chem. *80*, 531 (1968); Angew. Chem. internat. Edit. *7*, 537 (1968); *M. Jones*, J. Amer. Chem. Soc. *89*, 4236 (1967). Also some 1,3,6-trienes can react correspondingly: *W. R. Roth* and *B. Peltzer*, Angew. Chem. *76*, 378 (1964); Angew. Chem. internat. Edit. *3*, 440 (1964); Liebigs Ann. Chem. *685*, 56 (1965); *W. Eberbach* and *H. Prinzbach*, Helv. Chim. Acta *50*, 2490 (1967); *G. Kaupp* and *H. Prinzbach*, Liebigs Ann. Chem. *725*, 52 (1969).

[3] *G. Kaupp*, Lecture at Mulhouse on November 26, 1971, to the Société Chimique de France.

[4] *W. Treibs* and *S. Hauptmann*, Liebigs Ann. Chem. *622*, 74 (1958).

[5] *K. Krieger*, Entrance Thesis for the Scientific Examination for Admission to a teaching post at High Schools, Universität Freiburg, 1971.

[6] All the compounds were characterized analytically and spectroscopically.

[7] *S. Wawzonek*, J. Amer. Chem. Soc. *65*, 839 (1943).

[8] *P. J. Collin* and *W. H. F. Sasse*, Aust. J. Chem. *24*, 2325 (1971), where further references are given. We thank Dr. *Sasse* for samples of *(7)* and (9).

4-(Dialkylamino)quinolines and 3,3-Disubstituted 4(3*H*)-Quinolones from 4*H*-3,1-Benzoxazinones and Ynamines

By *Gerhard Höfle*, *Oswald Hollitzer*, and *Wolfgang Steglich*[*]

The 2-(trifluoromethyl)-4*H*-3,1-benzoxazinones *(1a)* to *(1d)* react with *N*,*N*-diethyl-1-propynylamine *(2)* in ether even at -20 °C with vigorous evolution of CO_2 and formation of 4-(diethylamino)quinolines *(3)* within a few minutes. In acetonitrile or 2-propanol appreciable amounts of 3,3-disubstituted 4(3*H*)-quinolones *(4)* are also formed.

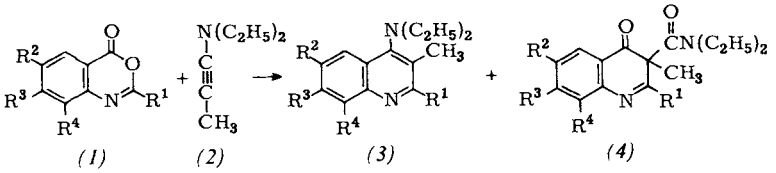
Replacing the CF_3 groups by H, CH_3, or C_6H_5 reduces the reactivity. Whereas *(1e)*[2] still reacts exothermally, for *(1f)* and *(1g)* heating or standing for a considerable time is necessary[4]. Unlike the reactions of the CF_3 compounds *(1a)* to *(1d)*, these always lead, even in apolar solvents such as ether and benzene, to mixtures of *(3)* and *(4)*. From *(1g)*, 1-benzoyl-4(1*H*)quinolone *(5)* is isolated as third product. The separation of

[*] Dr. G. Höfle, Dipl.-Chem. O. Hollitzer, and Prof. Dr. W. Steglich
Organisch-Chemisches Institut der Technischen Universität
1 Berlin 12, Strasse des 17. Juni 135 (Germany)

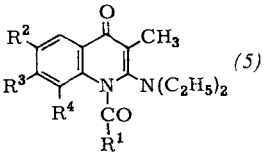
(3), (4), and (5) was achieved by different methods. Thus (4c) and (4d) are easily separated from (3c) and (3d) respectively by their lower solubility in ether/light petroleum. In case of (3f)/(4f) the stronger base (3f) was extracted with aqueous citric acid from ether. (3g), (4g), (5g) were separated by chromatography on alumina.

positions of the substituents on the pyridine nucleus were proved by synthesis of (3f) from 4-chloro-2,3-dimethylquinoline and diethylamine.

The amides (4) are of interest as the first representatives of the 4(3*H*)-quinolone series. On acid hydrolysis they afford 4(1*H*)-quinolones and when heated at 150 to



(1) (2) (3) (4)



(5)

The structures of the compounds (3) accord with their spectroscopic data[7]. With the 2-(trifluoromethyl) derivatives the appearance of H,F homoallylic coupling of 1.8 Hz with the 3-methyl group is noteworthy. The

200 °C they rearrange with C → O acyl migration to the carbamates (6) [(6c), m.p. 156 °C; IR (CCl_4), 1745 cm^{-1}; NMR ($CDCl_3$), δ(quin.-3-CH_3 = 2.46 ppm, quartet, J = 2.0 Hz].

Table 1. Product distribution on reaction of 4*H*-3,1-benzoxazinones (1) with the ynamine (2) [a].

Starting cpd. [b]	R	R^2	R^3	R^4	Reaction medium	Time	Temp. (°C)	Ratio of yields (3)	(4)	(5)
(1a)	CF_3	H	H	H	CCl_4; ether; *tert*-butyl alcohol	10 min	0	100		
					2-Propanol			75	25	
					Acetonitrile			60	40	
(1b)	CF_3	H	Cl	H	Ether	10 min	0	93	7	
(1c)	CF_3	Cl	H	Cl	Ether	10 min	0	95	5	
					Acetonitrile			60	40	
(1d)	CF_3	Br	H	Br	Ether	10 min	0	95	5	
					Acetonitrile			55	45	
(1e)	H	H	H	H	THF	20 h	25	85	15	
(1f)	CH_3	H	H	H	Benzene	20 h	80	75	25	
(1g)	C_6H_5	H	H	H	Toluene	80 h	110	35	30	35
					Acetonitrile	160 h	25		20	80

[a] Determined from the NMR spectrum of the reaction mixture.
[b] (1b), (1c), and (1d) were prepared, analogously to (1a) [1], from the anthranilic acids and trifluoroacetic anhydride.

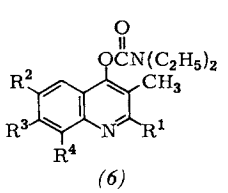
Table 2. Yields and properties of the isolated compounds (3), (4), and (5) [a].

Cpd.	Yield (%)	B.p. (°C/torr)	M.p. (°C)	IR (cm^{-1}) $\nu_{C=O, C=N}$	^{1}H-NMR ($CDCl_3$) of the CH_3 group on C-3; δ(ppm) relative to TMS = [b]
(3a)	94	123—124/0.7			2.50
(3b)	85		73—74		2.48
(3c)	94	117/0.02	213—215 [c]		2.48
(3d)	82		216—218 [c]		2.50
(3e) [6]	77	98/0.2			2.30
(3f)	71	107/0.1	53—55		2.37
(3g)	11		191—193 [c]		2.35
(4c)	35		145—146	1705, 1680, 1630, (CCl_4)	1.65
(4d)	39		145—146	1690, 1655, 1620 ($CHCl_3$)	1.70
(4f)	5		88—89	1680, 1640, 1610, 1590 (KBr)	1.60
(4g)	25		132—133	1685, 1645, 1610, 1560 (CCl_4)	1.88
(5g)	30		136—137	1730, 1625, 1605, 1565 (CCl_4)	2.05

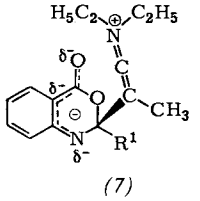
[a] All the compounds gave correct elemental analyses.
[b] Singlet; for (3a) to (3d) a multiplet, J = 1.8 Hz.
[c] Perchlorate.

The structure of *(5g)* follows from the spectroscopic data [IR, see Table 2; UV (ethanol), $\lambda_{max}(\varepsilon) = 334$ nm (12500), 325 (13800), 240 (27400)] and from acid hydrolysis to 2-(diethylamino)-3-methyl-4(1*H*)quinolone[6].

The dipolar species *(7)*, arising by nucleophilic attack of the ynamine on the C=N double bond of *(1)*[8], can be considered as intermediate leading to *(3)*. However, it is not possible to decide without ^{18}O labeling experiments, whether *(4)* and *(5)* are formed *via* attack on the C=N or the C=O group[9] of the azaanhydride system.



(6)



(7)

Our methods of preparing *(3)* extend the synthesis of 4-(dialkylamino)-2-(*sec*-alkyl)quinolines by reaction of ynamines with ketene imines as recently reported by *Ghosez* and *de Perez*[7].

4-(Diethylamino)-3-methyl-2-(trifluoromethyl)-quinoline (3a):

(2) (1.7 ml) in CCl_4 (5 ml) is added dropwise to a stirred, ice-cold solution of *(1a)* (2.15 g) in CCl_4 (10 ml). Vigorous evolution of CO_2 occurs during this addition. After 10 min the solvent and excess of *(2)* are removed in a vacuum and the residue is distilled in oil-pump vacuum. Yield: 2.65 g (94%).

6,8-Dichloro-3-[(diethylamino)carbonyl]-3-methyl-2-(trifluoromethyl)-4(3H)-quinolone (4c):

(2) (1.7 ml) in acetonitrile (2 ml) is added dropwise to *(1c)* (2.85 g) in acetonitrile (5 ml) with ice-cooling and vigorous stirring. After 10 min the solvent is removed at oil-pump vacuum and the remaining oil (3.7 g) crystallizes on addition of ether (5 ml) and light petroleum (40 ml). Filtration and two washings with ether/light petroleum (3:10) affords 1.35 g, and the mother liquor affords a further 40 mg. Total yield: 1.39 g (35%). A sample was recrystallized from CCl_4/light petroleum for analysis.

Received: June 8, 1972 [Z 663 IE]
German version: Angew. Chem. *84*, 716 (1972)

[1] *L. A. Errede*, US-Pat. 3357977, Minnesota Mining and Manufg. Co.; Chem. Abstr. *68*, 40326 (1968).

[2] *(1e)*, m.p. 43—45 °C, prepared according to [3], contains *(1f)*. Pure *(1e)*, m.p. 77—78 °C, is obtained by cyclization of *N*-formylanthranilic acid by DCC.

[3] *D. T. Zentmyer* and *E. C. Wagner*, J. Org. Chem. *14*, 967 (1949).

[4] Reaction of the ynamine with the liberated CO_2, especially in acetonitrile, leads to *N,N,N',N'*-tetraethyl-2,4-dimethyl-2,3-pentadieno-1,5-diamide as by-product [5], so that in this case an excess of *(2)* is required.

[5] *J. Ficini* and *J. Pouliquen*, J. Amer. Chem. Soc. *93*, 3295 (1971).

[6] *M. E. Kuehne* and *P. J. Sheeran*, J. Org. Chem. *33*, 4406 (1968).

[7] *L. Ghosez* and *C. de Perez*, Angew. Chem. *83*, 171 (1971); Angew. Chem. internat. Edit. *10*, 184 (1971).

[8] Ring opening with attack on the C=N double bond was observed by *H. Behringer* and *H. J. Fischer*, Chem. Ber. *94*, 1572 (1961), on reaction of 4*H*-3,1-benzoxazinones with HN_3.

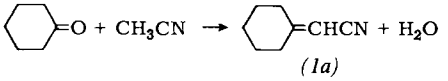
[9] *W. Steglich*, *G. Höfle*, *W. König*, and *F. Weygand*, Chem. Ber. *101*, 308 (1968).

Reaction of Acetonitrile with Cyclohexanone

By *H. J. Arpe* and *I. Leupold*[*]

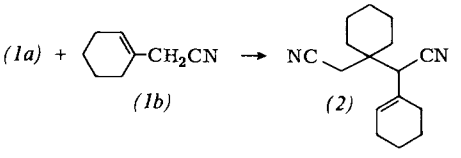
Acetonitrile reacts with ketones in liquid ammonia in the presence of stoichiometric amounts of alkali metal amide to give β-hydroxynitriles[1–3]. We have investigated the catalysis of this reaction for the case of acetonitrile and cyclohexanone.

Cyclohexylideneacetonitrile *(1a)* can be prepared in 70% yield by azeotropic distillation from H_2O at about 80 °C if the alkali metal alcoholate of a high-boiling alcohol, *e.g. n*-octanol, is used as catalyst.



(1a)

With alkali ethoxide the reaction comes to a standstill after 5—10% conversion since the ethanol formed in the hydrolysis of the alcoholate distills off. The basicity of the remaining alkali hydroxide is insufficient for abstraction of H^+ from the acetonitrile. 1-Cyclohexenylacetonitrile *(1b)* is in equilibrium with *(1a)*[4]. Under the reaction conditions it reacts with *(1a)* to give 2-(1-cyclohexenyl)-3,3-pentamethyleneglutaronitrile *(2)* in 20% yield. The structure given for *(2)* is in good agreement with the C—H—N analysis and with the ^1H-NMR, IR, and MS data.



(1b) *(2)*

Procedure for the synthesis of (1a):

A mixture of acetonitrile (1.0 mol), cyclohexanone (0.5 mol), and sodium *n*-octyl oxide (10 mmol) in benzene (100 ml) is boiled in a round bottomed flask fitted with water separator. After about 20 h the separation of water is so slow that the reaction may be terminated, 80—85% of the theoretical amount of water of reaction having been removed. The reaction mixture is washed with dilute H_2SO_4 and finally with H_2O. Distillation of the washed mixture affords 42.2 g (70%) of compound *(1a)*, b.p. 90 °C/10 torr. Recrystallization of the residue from the distillation with methanol yields 12.1 g (20%) of *(2)*, m.p. 107 °C.

Received: May 10, 1972 [Z 664a IE]
German version: Angew. Chem. *84*, 767 (1972)

[*] Dr. H. J. Arpe and Dr. I. Leupold
Farbwerke Hoechst AG
623 Frankfurt/Main 80, Postfach 800320 (Germany)

[1] *C. Ivanov* and *Y. Anghelova*, Dokl. Bolg. Akad. Nauk *19*, 739 (1966).

[2] *A. Uchida*, *S. Saito*, and *S. Matsuda*, Bull. Chem. Soc. Japan *42*, 2989 (1969).

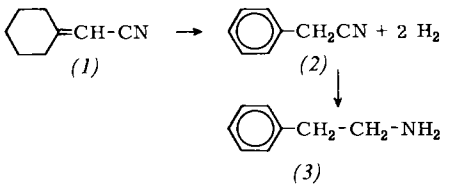
[3] *T. P. Vishnyakova* and *A. A. Koridze*, Zh. Obshch. Khim. *39*, 210 (1969).

[4] *G. Descotes* and *P. Laconche*, Bull. Soc. Chim. France *1968*, 2149.

Aromatization of Cyclohexylideneacetonitrile

By *H. J. Arpe* and *I. Leupold*[*]

Cyclohexylideneacetonitrile *(1)*, which is obtained in good yields from cyclohexanone and acetonitrile[1], can be catalytically converted into benzyl cyanide *(2)*, which, in turn, can be converted into β-phenylethylamine *(3)*.



Formation of benzyl cyanide is favored on ZnO catalysts, and that of β-phenylethylamine on Co catalysts.

Gaseous *(1)*, diluted with a threefold molar amount of nitrogen, is fed over a fixed bed catalyst, of which the first stage (450°C; residence time: 10 s) consists of SiO_2 with 1.3 wt-% ZnO and the second (150°C; residence time: 5 s) of SiO_2 with 39 wt-% of cobalt. If both stages are heated compound *(3)* is formed (50% yield), whereas *(2)* is formed in 80% yield if only the first stage is heated. The reaction products are condensed at −70°C and finally distilled. An hydrogenolytic cleavage of *(1)* to give toluene occurs as secondary reaction.

Received: May 10, 1972 [Z 664b IE]
German version: Angew. Chem. *84*, 767 (1972)

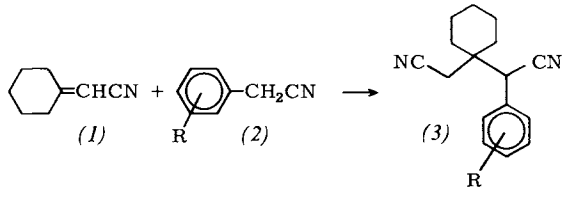
[*] Dr. H. J. Arpe and Dr. I. Leupold
Farbwerke Hoechst AG
623 Frankfurt/Main 80, Postfach 800320 (Germany)

[1] *H. J. Arpe* and *I. Leupold*, Angew. Chem. *84*, 722 (1972); Angew. Chem. internat. Edit. *11*, 767 (1972).

Simple Synthesis of Substituted Glutaronitriles

By *I. Leupold* and *H. J. Arp* [*]

The dimerization and formation of a substituted glutaronitrile containing a quaternary C-atom which we observed during the preparation of cyclohexylideneacetonitrile[1] induced us to investigate the reaction of cyclohexylideneacetonitrile *(1)* with nuclear-substituted benzyl cyanides *(2)*. It was found that the 2-aryl-3,3-pentamethyleneglutarodinitriles *(3)* are formed in high yields.



(3)	R	Yield (%)	M.p. (°C)
(a)	H	92	106
(b)	4-H_3	64	87
(c)	4-CH_3O	76	99
(d)	4-Cl	88	157
(e)	3-Br	82	88
(f)	4-Br	90	156

The IR, ^{1}H-NMR, and MS data are in complete agreement with the given structures.

General procedure:

A mixture of cyclohexylideneacetonitrile (0.1 mol), a nuclear substituted benzyl cyanide (0.1 mol), and potassium *tert*-butoxide (0.001 mol) is stored under an atmosphere of nitrogen at 50—80°C for 12 h. The solid melt is recrystallized from methanol, which can contain 10% acetonitrile; the product is dried under high vacuum.

Received: May 10, 1972 [Z 664c IE]
German version: Angew. Chem. *84*, 767 (1972)

[*] Dr. I. Leupold und Dr. H. J. Arpe
Farbwerke Hoechst AG
623 Frankfurt/Main 80, Postfach 800320

[1] *H. J. Arpe* and *I. Leupold*, Angew. Chem. *84*, 767 (1972); Angew. Chem. internat. Edit. *11*, 723 (1972).

Xenon Bis(pentafluoroorthoselenate) and Xenon Fluoride Pentafluoroorthoselenate

By *Konrad Seppelt*[*]

Disregarding the thermal stability of xenon difluoride, all the other xenon(II) compounds except the pentafluoroorthotellurate[1] are unstable. No explanation of this behavior has hitherto become available. Because of its high acid strength the recently discovered pentafluoroorthoselenic acid[2] should prove more suitable for preparation of stable compounds having high valences.

Reaction of xenon difluoride[3] with a small excess of $HOSeF_5$ in an all-Teflon distillation apparatus leads immediately to xenon bis(pentafluoroorthoselenate) *(1)*.

$$XeF_2 + 2HOSeF_5 \longrightarrow \underset{(1)}{Xe(OSeF_5)_2} + 2HF$$

(1) is a stable crystalline solid which can readily be purified by vacuum sublimation owing to its high melting point (m.p. 69°C) and vapor pressure (0°C, 0.05 torr; 25°C, 0.35 torr). The compound is thereby obtained as large yellow crystals. It was characterized by its mass spectrum [m/e = 316—329 ($XeOSeF_5$ 100%), 171—177 (SeF_5 8%), 168—174 ($OSeF_4$ 3%), 149—155 ($OSeF_3$ 17%), 141—148 (XeF 22%), 133—139 (SeF_3 37%), 130—136 ($OSeF_2$ 27%), 129—136 (Xe 59%), as well as SeF_2, OSeF, SeF, SeO, Se; 75 eV], its IR spectrum [mull in Kel-F oil (cm^{-1}): 787 m, 725 vs, 700 s, 612 s, 550 m, 430 s, 402 w, 307 m, 270 w, 249 m], its Raman spectrum [solution in $CFCl_3$ (cm^{-1}): 750 w dp, 725 m p, 692 m p, 639 s p, 613 w dp (νSeF and νSeO), 510 w p, 493 m dp (νSeO), 429 w p, 412 w p, 375 w dp, 299 s p (δSeF and δSeO), 197 w dp, 157 vs p, 130 s p, 77 m dp (δSeO and τ)], its ^{19}F-NMR spectrum [solution in $CFCl_3$, internal; 56.4 MHz: multiplet having AB_4 character, $\delta_A = -80.5$, $\delta_B = -69.4$ ppm; $J_{F_A-F_B} = 234$ Hz, $R = J/\Delta\delta = 0.346$, $J^{77}_{Se-F_A} = 1323$, $J^{77}_{Se-F_B} = 1318$ Hz], and its elemental analysis (F, Se, Xe).

[*] Dr. K. Seppelt [**]
Anorganisch-chemisches Institut der Universität
69 Heidelberg, Im Neuenheimer Feld 7 (Germany)

[**] I am grateful to Dr. *R. Geist* for recording the mass spectra.

(1) is sensitive to hydrolysis and reacts explosively with oxidizable substances. Solutions in freons are stable; CCl_4 and CH_3CN solutions are also temporarily stable. Its high solubility in nonpolar solvents indicates that *(1)* is largely covalent. Molten *(1)* is stable in a dry glass tube up to 100 °C; above 130 °C rapid decomposition occurs with evolution of xenon and vigorous attack of the glass surface. The striking yellow color of *(1)*, especially in concentrated solution, is shown by the UV spectrum to be attributable to an absorption at 3630 Å observed as the weakest member of a series of absorptions (2320, 2420, 2530, 2770, 3130, 3630 Å; solution in CH_3CN). The longer-wave absorptions must be due to bonded xenon since none of the compounds containing the F_5SeO investigated so far shows such absorptions.

An equimolar mixture of xenon difluoride and *(1)* liquifies completely within a few hours in a Teflon tube. The reaction course could be followed by means of the ^{19}F-NMR spectrum. Xenon fluoride pentafluoroorthoselenate *(2)* is formed in about 80% yield.

$$\underset{(1)}{XeF_2} + \underset{}{Xe(OSeF_5)_2} \rightleftharpoons \underset{(2)}{2\,FXeOSeF_5}$$

A purer product is obtained with an excess of XeF_2; *(1)* is almost completely consumed while XeF_2 crystallizes on cooling to 0 °C. Compound *(2)* prepared in this way is about 90% pure but undergoes dismutation corresponding to the equilibrium reaction.

(2) is a pale yellow liquid, m.p. ≈ -13 °C, that is very sensitive to hydrolysis. In spite of its low purity the following spectroscopic data could be recorded. Mass spectrum: *m/e* 335—348 ($FXeOSeF_5$ 5%), 316 to 329 ($XeOSeF_5$ 55%), 278—291 ($XeOSeF_3$ 2%), 171 to 177 (SeF_5 36%), 149—155 ($OSeF_3$ 40%), 141—148 (XeF 100%), and SeF_3, $OSeF_2$, Xe. IR spectrum (capillary film between CsI windows covered with FEP film; cm^{-1}): 772 s, 717 vs, 699 s, 610 m, 543 s, 422 s, 400 w, 250 w. Raman spectrum (cm^{-1}): 785 s dp, 764 w dp, 710 w p, 692 m p, 614 m p (νSeF and νSeO), 541 w dp, 501 vs p (νXeF and νXeO), 421 w dp, 416 mp, 399 w dp, 375 w dp, 416 m p, 399 w dp, 375 w dp (δSeF and δSeO), 173 s p (δOXeF) and 92 m dp (γOXeF).

The ^{19}F-NMR spectrum is particularly informative ($CFCl_3$, external): AB_4 multiplet, $\delta_A = -85.5$, $\delta_B = -68.5$ ppm; $J_{F_A-F_B} = 226$ Hz, $R = 0.246$, $J^{77}_{Se-F_A} = 1280$, $J^{77}_{Se-F_B} = 1300$ Hz; and a singlet, $\delta_{Xe-F} = +155.8$ ppm. The xenon isotope 129 (26% abundance, nuclear spin $\pm 1/2$) gives rise to a doublet that is symmetrically disposed about the main Xe—F peak: $J^{129}_{Xe-F} = 5790$ Hz. No coupling was observed between the fluorine atoms bound to xenon and to selenium.

The noble gas compounds discussed above appear to be of comparable stability to the analogous fluorotellurates; stability studies in inert vessels should provide even more information.

Received: May 25, 1972 [Z 665 IE]
German version: Angew. Chem. *84*, 715 (1972)

[1] *F. Sladky*, Monatsh. Chem. *101*, 1559 (1970).

[2] *K. Seppelt*, Angew. Chem. *84*, 212 (1972); Angew. Chem. internat. Edit. *11*, 630 (1972).

[3] Prepared according to: *W. E. Falconer* and *W. A. Sunder*, J. Inorg. Nucl. Chem. *29*, 1380 (1967).

Ring Opening of a Cyclopropyl Anion and Cycloaddition of the Allyl Anion[**]

By *Gernot Boche* and *Diether Martens*[*]

Since the advent of the rules for the conservation of orbital symmetry[1] particular interest has been shown towards the ring opening of the cyclopropyl anion, predicted to proceed in a conrotatory fashion[2]. Several examples are known of treatment of substituted cyclopropanes with bases leading directly to allyl anions[6, 7]. H/D exchange and isomerization experiments at the anionic center of the three-membered ring strongly suggest the intermediacy of cyclopropyl anions[6d, 6e, 7]. Nevertheless, many cyclopropyl anions are also known which do not exhibit ring opening to give allyl anion[8].

We have been able to prepare a cyclopropyl anion which undergoes electrocyclic isomerization to the allyl

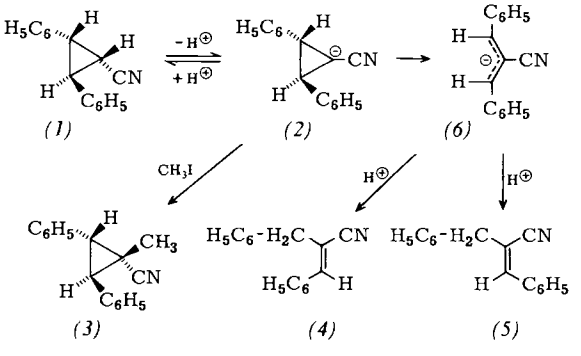


Table 1. Reaction of 1,3-diphenylallyl-2-carbonitrile anion *(6)* with alkenes [15].

Alkene	Reaction conditions	Product	M.p. (°C)	Yield (%)
Styrene	2 h, 25 °C	2,3,5-Triphenyl-cyclopentane-1-carbonitrile	134—135	65
trans-Stilbene	15 h, 25 °C	2,3,4,5-Tetraphenyl-cyclopentane-1-carbonitrile	120—120.5	59
1,1-Diphenylethylene	2 h, 25 °C	2,3,3,5-Tetraphenyl-cyclopentane-1-carbonitrile	186—186.5	69
Acenaphthylene	2 h, 25 °C	7,9-Diphenyl-6b,9a-dihydrocyclopent[*a*]-acenaphthylene-8-carbonitrile [a]	213—215 309—311	18 37

[a] Two cycloadducts are formed.

[*] Dr. G. Boche and Dipl.-Chem. D. Martens
Institut für Organische Chemie der Universität
8 München 2, Karlstrasse 23 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft. We are grateful to Frl. *G. Schneider* for preparative assistance.

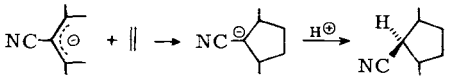
anion. The cyclopropyl anion *(2)* is formed instantaneously when *trans*-2,3-diphenylcyclopropane-1-carbonitrile *(1)* is united with two mol. equiv. of lithium diisopropylamide in tetrahydrofuran at $-30°C$.

Immediate reaction of *(2)* with methyl iodide at $-30°C$ gives *(3)* in 95% yield. Protonation of *(2)* with glacial acetic acid under the same conditions regenerates *(1)* in 93% yield.

However, if the reaction mixture is first allowed to warm to room temperature and then protonated a mixture (about 1:1) of the isomeric olefins *(4)* and *(5)*[9] is formed in 95% yield. Since *(1)* is no longer regenerated in this experiment[10], complete isomerization of cyclopropyl anion *(2)* to the red-violet allyl anion *(6)* must have occurred on warming.

Kinetic studies of the ring opening of the cyclopropyl anion *(2)* prepared with two and four mol. equiv. of lithium diisopropylamide indicated a valence isomerization *(2)* → *(6)* [half-life 27 min at 24.5 °C] which was independent of the base concentration; the activation parameters determined between -32.5 and -20.3 °C have the following values: $\Delta H^{\neq} = 19.0 \pm 1.5$ kcal/mol, $\Delta S^{\neq} = 2.5$ e.u.

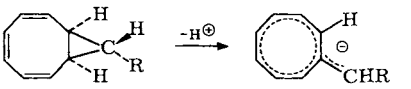
The reaction of an allyl anion with an olefin to give a cyclopentyl anion is the prototype of the symmetry-allowed 1,3-dipolar $[_{\pi}2_s + _{\pi}4_s]$ cy loaddition[11]. This reaction has not previously been described. The nearest approaches known hitherto are reactions of cyclic allyl anions with benzyne[12] and cycloadditions of 2-azaallyl anion to multiple bonds[13]. In addition, *Kauffmann*[14] has recently reported the formation of a five-membered ring adduct during the reaction of α-methylstyrene and lithium diisopropylamide with stilbene which was interpreted as involving an intermediate allyl anion.



(6) *(7)*

We found that the allyl anion reacts with the alkenes listed in Table 1 to give adducts isolable as cyclopentane derivatives *(7)* after protonation (or methylation).

Received: May 17, 1972 [Z 666 IE]
German version: Angew. Chem. *84*, 768 (1972)



(1a), R = CN *(2a)*, R = CN
(1b), R = $COOCH_3$ *(2b)*, R = $COOCH_3$

[1] *R. B. Woodward* and *R. Hoffmann*, J. Amer. Chem. Soc. *87*, 395 (1965).

[2] The conrotatory course was established on ring opening to give *trans,cis,cis,cis*-cyclononatetraenyl anion [3] and on ring opening of aziridines [4] and oxiranes [5] that are isoelectronic to cyclopropyl anion.

[3] *G. Boche, D. Martens*, and *W. Danzer*, Angew. Chem. *81*, 1003 (1969); Angew. Chem. internat. Edit. *8*, 984 (1969).

[4] a) *R. Huisgen, W. Scheer*, and *H. Huber*, J. Amer. Chem. Soc. *89*, 1753 (1967); b) *Th. Kauffmann, K. Habersaat*, and *E. Köppelmann*, Angew. Chem. *84*, 262 (1972); Angew. Chem. internat. Edit. *11*, 291 (1972).

[5] *A. Dahmen, H. Hamberger, R. Huisgen*, and *V. Markowski*, Chem. Commun. *1971*, 1192.

[6] a) *E. P. Kohler* and *J. B. Conant*, J. Amer. Chem. Soc. *39*, 1404 (1917); b) *E. P. Kohler* and *P. Allen jr.*, J. Amer. Chem. Soc. *50*, 884 (1928); c) *L. I. Smith* and *J. Showell*, J. Org. Chem. *17*, 827 (1951); d) *J. E. Mulvaney* and *D. Savage*, J. Org. Chem. *36*, 2592 (1971); e) *R. Huisgen* and *P. Eberhard*, J. Amer. Chem. Soc. *94*, 1346 (1972).

[7] Treatment of anti-*cis*-bicyclo[6.1.0]nona-2,4,6-triene-9-carbonitrile *(1a)* or -9-carboxylic methyl ester *(1b)* with lithium diisopropylamide leads to the anions *(2a)* and *(2b)* respectively: *D. Martens*, Diplomarbeit, Universität München 1971.

[8] For a review see [6d].

[9] The mixture of olefins *(4)* and *(5)* was synthesized independently.

[10] The NMR spectrum reveals the presence of 3% of *(1)* alongside 97% of *(4)* and *(5)*.

[11] *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. internat. Edit. *2*, 565 (1963); *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797, 833 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969); *A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey*, and *E. Spindler*, Chem. Ber. *100*, 2192, 2212 (1967).

[12] *G. Wittig* and *E. Knauss*, Chem. Ber. *91*, 895 (1958); *C. F. Huebner* and *E. M. Donoghue*, J. Org. Chem. *33*, 1678 (1968); *W. T. Ford, P. Radue*, and *J. A. Walker*, Chem. Commun. *1970*, 966.

[13] *Th. Kauffmann, K. Habersaat*, and *E. Köppelmann*, Angew. Chem. *84*, 261, 262 (1972) and literature cited there; Angew. Chem. internat. Edit. *11*, 290, 291 (1972).

[14] *R. Eidenschink* and *Th. Kauffmann*, Angew. Chem. *84*, 292 (1972); Angew. Chem. internat. Edit. *11*, 292 (1972).

[15] The structures of the adducts follow from elemental analyses, and NMR and mass spectra. The yields were not optimized.

The Mesityl Group as a Ring Current Probe in Transition Metal 1,2-Diimine Chelates

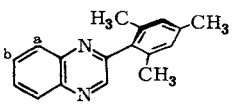
By *Günter Häfelinger, Rudolf G. Weissenhorn, Fritz Hack*, and *Gerlinde Westermayer*[*]

Overlapping of metal d_{t2g} orbitals with the π-electron system of the ligands to give a cyclically conjugated system, purportedly having aromatic[3] or quasiaromatic[4,5] properties, has been postulated in transition metal chelates of the type tris(*N,N'*-dimethylethanediimine)iron(II)[1,2]. Aromaticity or cyclic π-electron delocalization is detectable by the occurrence of a ring current effect[6]. Since the NMR chemical shifts of the ring protons[7] are too sensitive to the charge density distribution in the hetero π-electron system, chelates bearing mesityl substituents were synthesized in which deviations between the chemical shifts of the two equivalent *o*-methyl groups below and above the plane of the chelate ring and the *p*-methyl acting as an internal standard afford a means of detecting a ring current[8,9].

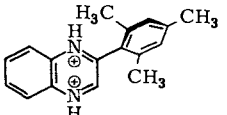
The 2-mesitylquinoxaline *(1)* serving as aromatic reference system exhibits a 0.25-ppm splitting of the methyl signals, a value that is comparable with 0.30 ppm in phenylmesitylene[8] and 0.45 ppm in bimesityl[8]. The splitting of 0.33 ppm in tetracarbonyl(mesityl-*N,N'*-dimethylethanediimine)molybdenum *(3a)* is also of the same order. Surprisingly, tris(mesityl-*N,N'*-dimethylethanediimine)iron(II) perchlorate *(3b)* gives a negative splitting of -0.15 ppm. Negative splitting was also observed in simple mesityl derivatives in which functional group and mesityl group are substantially coplanar (*e.g.* mesitaldehyde, -0.25 ppm; dimesitylacetylene[10], -0.20 ppm; bromomesitylene, -0.14 ppm; mesitylic acid, -0.05 ppm) while derivatives whose mesityl group is largely perpendicular to the functional

[*] Priv.-Doz. Dr. G. Häfelinger, Dipl.-Chem. R. G. Weissenhorn, Dipl.-Chem. F. Hack, and G. Westermayer
Lehrstuhl für Organische Chemie der Universität
74 Tübingen, Wilhelmstrasse 33 (Germany)

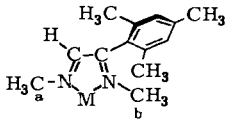
group as a result of steric constraints show small positive splittings (*e.g.* dimesityl ketone, 0.19 ppm; mesitylglyoxal, 0.15 ppm, dimesitylethanedione, 0.13 ppm).



(1)



(2)



(3a) M = $Mo^0(CO)_4$

(3b) M = $\frac{1}{3}Fe(ClO_4)_2$

the yellow oil solidifies to a mass of pale yellow crystals, m. p. 59 °C. Yield: 6.7 g (47.5%).

Tetracarbonyl(mesityl-N,N'-dimethylethanediimine)-molybdenum (3a):

A solution of mesitylglyoxal (3.52 g, 20 mmol) in methanol (30 ml) is united with 6 ml of a 7.3 M methanolic solution of methylamine (ice cooling) and the mixture then stirred for two hours at room temperature. After addition of a slurry of hexacarbonylmolybdenum (Schuchardt) (4.74 g, 18 mmol) in methanol (200 ml) stirring is continued for two days at room temperature and the mixture subsequently refluxed for 8 hours. Filtration of the boiling hot blackish violet solution is followed by removal of solvent. Crude yield: 6.5 g (88%) of black crystals that can be resolved into two components (red-violet, R_z 0.57; brown-yellow, R_z 0.8) by thin-layer chromatography (silica gel/methanol).

Cpd.	N=C<H	H_a	H_b	$\Delta(NCH_3)$	*m*-C—H	*p*-CH_3	*o*-CH_3	$\Delta(CH_3)$	Solvent
(1)	0.53	1.90 (m)	2.40 (m)	—	3.06	7.68	7.93	0.25	CCl_4
(2)	0.66	1.67	1.67	—	3.14	8.00	8.00	0.00	H_2SO_4
(3a)	2.05	5.85	6.26	0.41	3.08	7.67	8.00	0.33	CCl_4
(3b)	1.87 (t)	6.21	6.75 (t)	0.54	2.87	7.82	7.67	−0.15	$(CD_3)_2C{=}O$

The metal chelates of 1,3-diketones were found to give small splittings of around 0.15 ppm[8] that proved to be independent of the nature of the metal and of the same order of magnitude as in enolized ligands; no ring current was therefore detected in the metal chelates of 1,3-diketones. The Mo^0 and Fe^{2+} chelates under study on the other hand exhibit large splittings between the *o*- and *p*-methyl signals, albeit in differing directions. The value of 0.33 ppm for the Mo^0 chelate *(3a)* is larger than in phenylmesitylene and in 2-mesitylquinoxaline *(1)* and therefore evidences a ring current effect. However, the splitting could be influenced by the field effect of the two axial carbonyl groups. Consideration of models, however, indicates that the *o,o'*-methyl groups lie in the region of downfield shift due to the anisotropic cone of the carbonyl group.

The negative splitting of −0.15 ppm in the Fe^{2+} chelate could arise from the positive charge of the central ion reducing the overall electron density compared with that in the Mo^0 chelate. It therefore provides no indication of a diamagnetic ring current. The NMR spectrum of the reference compound *(1)* in concentrated sulfuric acid, in which the formation of the dication *(2)* can be assumed, shows coincidence of the *o*- and *p*-methyl signals, *i.e.* a negative shift of the splitting by 0.25 ppm as a result of protonation of the nitrogen atom.

It would therefore appear that the mesityl group represents a probe not only for ring current effects but also for varying electron densities in ring systems. Further studies designed to shed more light on this behavior are currently in progress.

2-Mesitylquinoxaline (1):

A solution of *o*-phenylenediamine (6.2 g, 57 mmol) in methanol (100 ml) is added dropwise under nitrogen to a solution of mesitylglyoxal[11] (10 g, 57 mmol) in methanol (100 ml) at room temperature. The red solution is refluxed for 5 hours, dried with sodium sulfate after cooling, and the solvent then stripped off. The residual reddish brown oil is distilled twice *in vacuo*, b. p. 162—164 °C/0.55 torr. After the second distillation Column chromatography (200 g silica gel 0.2—0.5 mm, column diameter 4.5 cm) of 800 mg of crude product in chloroform afforded 100 mg of *(3a)* as black crystals having a metallic luster.

Tris(mesityl-N,N'-dimethylethanediimine)iron(II) perchlorate (3b):

A solution of mesitylglyoxal (5.28 g, 30 mmol) in methanol (60 ml) is treated with 10 ml of a 7.3 M methanolic solution of methylamine as described for *(3a)*. After addition of solid iron(II) perchlorate hexahydrate (3.27 g, 9 mmol) stirring is continued for four hours and the solvent is then stripped off and the residue dried overnight over phosphorus pentoxide *in vacuo*. A portion (2 g) of the lustrous black crystals was dissolved in methanol (20 ml), filtered and, after dilution with more methanol (60 ml), reprecipitated by a 5:2 mixture of ether and light petroleum (400 ml). Yield: 1.25 g (62%) of brownish red crystals.

Received: June 11, 1972 [Z 667 IE]
German version: Angew. Chem. *84*, 769 (1972)

[1] *P. Krumholz*, J. Amer. Chem. Soc. *75*, 2163 (1953).

[2] *P. Krumholz*: Structure and Bonding. Springer, Berlin 1971, Vol. 9, p. 139.

[3] *P. E. Figgins* and *D. H. Busch*, J. Amer. Chem. Soc. *82*, 820 (1960).

[4] *E. Bayer*, Angew. Chem. *73*, 533 (1961).

[5] *E. Bayer, H. Fiedler, K.-L. Hock, D. Otterbach, G. Schenk*, and *W. Voelter*, Angew. Chem. *76*, 76 (1964); Angew. Chem. internat. Edit. *3*, 325 (1964).

[6] *J. A. Elvidge* and *L. H. Jackman*, J. Chem. Soc. *1961*, 859.

[7] *E. Bayer, E. Breitmaier*, and *V. Schurig*, Chem. Ber. *101*, 1594 (1968).

[8] *M. Kuhr* and *H. Musso*, Angew. Chem. *81*, 150 (1969); Angew. Chem. internat. Edit. *8*, 147 (1969).

[9] *B. Bock, K. Flatau, H. Junge, M. Kuhr*, and *H. Musso*, Angew. Chem. *83*, 239 (1971); Angew. Chem. internat. Edit. *10*, 239 (1971).

[10] *H. E. Zimmerman* and *J. R. Dodd*, J. Amer. Chem. Soc. *42*, 6507 (1970).

[11] *A. R. Gray* and *R. C. Furon*, J. Amer. Chem. Soc. *56*, 739 (1934).

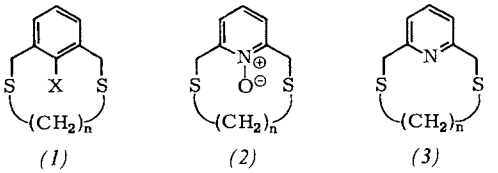
Spatial Requirements of Pyridine *N*-Oxide Oxygen[1][**]

By *Fritz Vögtle* and *Helga Risler*[*]

The spatial requirements of the oxygen in pyridine *N*-oxides have apparently not yet been studied. The polar O← N group, having *ca.* 40% double bond character according to recent calculations[2], is particularly interesting because it can exert polarizing effects in different directions[3].

The method we adopted in our approach to this problem was based on proton magnetic resonance studies on compounds of type *(1)*. For a series of substituents (X = H, F, Cl, Br, CH_3, C≡N, OCH_3) we first determined the smallest number of ring members for which the bridge could still pass by the intraannular group X despite incipient steric hindrance[1,4]. Substituents giving the same number of ring members were distinguished by the ring inversion barrier ($\Delta G_C^{\ddagger}$ values). The numbers of ring members and the $\Delta G_C^{\ddagger}$ values determined in this way give a kind of calibration curve for the determination of the spheres of influence of further internal substituents[5].

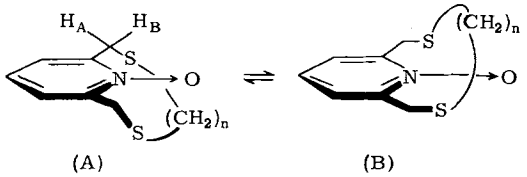
In the case of pyridine *N*-oxide oxygen, determination of the energy barriers to the intramolecular inversion process A⇌B in pyridinophane *N*-oxides *(2)* revealed detectable steric interactions between the oxygen atom of the *N*-oxide group and the hydrogen atoms of the bridge at $n = 6$, on going from large to small numbers of ring members. Those compounds having many ring members *(2f)* to *(2i)* exhibited no significant steric



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

(a), n = 2
(b), 3
(c), 4
(d), 5
(e), 6
(f), 7
(g), 8
(h), 9
(i), 10

interaction in the NMR; ring inversion A⇌B is therefore essentially unhindered here. In contrast, the cyclic compounds *(2a)* and *(2b)* containing fewer bridging members are conformationally rigid; the benzyl protons give an AB system in the accessible temperature range ($\Delta G_C^{\ddagger} > 23$ kcal/mol).



(A) (B)

The intermediate representatives *(2c)* to *(2e)* exhibit temperature-dependent ^{1}H-NMR spectra. The ring inversion barriers ($\Delta G_C^{\ddagger}$) decrease in the expected order: *(2c)* > 21.3 kcal/mol; *(2d)* = 15.8 kcal/mol; and *(2e)* = 12.7 kcal/mol.

The AB system of the benzyl protons of *(2d)*, which broadened at room temperature, is compared with the ^{1}H-NMR spectrum of *(1d)*, X = F, in Figure 1. The latter compound shows temperature-dependent benzyl signals in almost the same temperature range ($T_c = 37$ °C; $\Delta G_C^{\ddagger} = 15.2$ kcal/mol), which is attributed to steric hindrance of the "rocking process" analogous to A⇌B. The lower ring inversion barrier ($T_c = -55$ °C; $\Delta G_C^{\ddagger} = 10.5$ kcal/mol)[4] determined for the fluorine compound *(1e)*, $n = 6$, than for the pyridinophane *N*-oxide *(2e)* having the same number of ring members is also in agreement with this finding.

The inversion barrier of *(1c)* ($T_c = 185$ °C, $\Delta G_C^{\ddagger} = 22.6$ kcal/mol), in contrast to that of *(2c)*, could still just be determined by the coalescence point method.

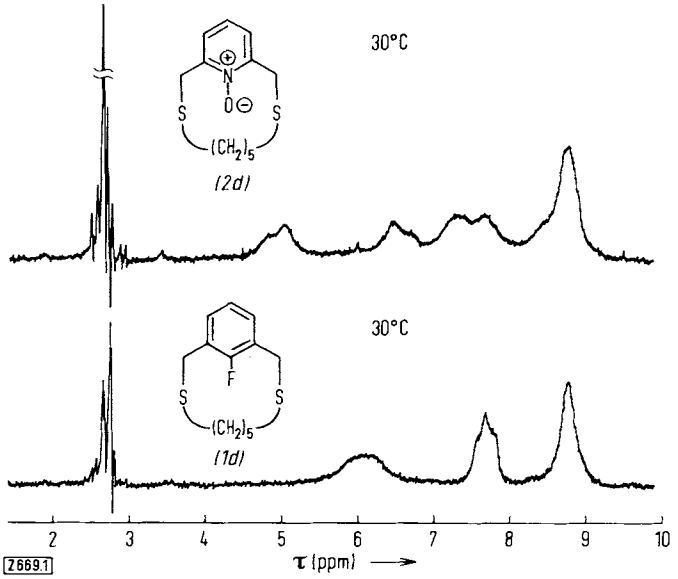


Fig. 1. ^{1}H-NMR signals of compounds *(1d)*, X = F, and *(2d)* [in $CDCl_3$; 60 MHz].

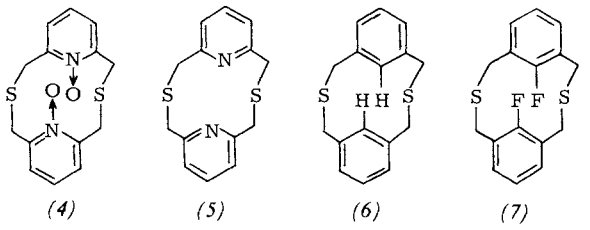
The considerable increase in spatial requirements on going from pyridine to pyridine *N*-oxide is clear from the fact that even in pyridinophane *(3)* having a shorter bridge ($n = 3$) no steric interaction can be observed[4].

Studies on the series *(4)* to *(7)* substantiate our finding that the spatial requirements of the aromatically bonded fluorine atom and the aromatic *N*-oxide oxygen are of the same order of magnitude. Whereas *(5)* and *(6)* are conformationally flexible[6], *(4)* and *(7)* exhibit temperature-dependent CH_2 resonances. The methylene absorption of *(4)* at room temperature consists solely of an extensively broadened AB system (Table 1). Although the coalescence temperature of *(7)* (157 °C) is higher than that of *(4)*, the $\Delta G_C^{\ddagger}$ values cannot be directly deduced from this system since the inversion processes are between non-isolable, energetically non-equivalent *syn* and *anti* conformers[5,6].

The results quoted induced us to construct a spatial model of the pyridine *N*-oxide group according to *Brieglieb*'s method[7] in a transformation ratio $1:(1.5 \times 10^8)$, which is compared in plan and side view with the F—$C_{arom.}$ "calotte"[8] in Figure 2. It can be seen that the "calotte" of the quaternary nitrogen atom in aromatic six-membered rings resembles very closely that of the $C_{arom.}$ atom[7,9]. If commercially available Stuart-Briegleb models are used in conjunction with the O← N "calotte" for constructing the described pyridinophane *N*-oxides then steric interactions are obtained which are compatible with the measurements laid down for such models.

[*] Prof. Dr. F. Vögtle and H. Risler
Institut für Organische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



(4) (5) (6) (7)

[3] *J. D. Roberts* and *M. C. Caserio*: Basic Principles of Organic Chemistry. Benjamin, New York–Amsterdam 1965, p. 1004.

[4] *F. Vögtle*, Tetrahedron *25*, 3231 (1969); Tetrahedron Lett. *1969*, 3193.

[5] *F. Vögtle* and *P. Neumann*, Tetrahedron *26*, 5299 (1970).

[6] *F. Vögtle* and *L. Schunder*, Chem. Ber. *102*, 2677 (1969); cf. also *B. R. Davis* and *I. Bernal*, J. Chem. Soc. B *1971*, 2307.

Table 1. Pyridinophane *N*-oxides synthesized.

	M.p. (°C)	Yield (%)	δ_{CH} (ppm) δ_A	δ_B($CDCl_3$)	Δν(Hz)	J_{AB} (Hz)	T_c (°C)	$\Delta G_c^{\ddagger}$ (kcal/mol)
(2a)	152—154	8	5.05	3.78	95	11.5	—	—
(2b)	107—109	7	5.29	3.09	122	13	—	—
(2c)	98— 99	30	5.22	2.86	141	13	> 180	> 21.3 ($C_6H_5)_2O$
(2d)	147—148	50	5.05	3.38	100	13	61	15.8 ($C_6H_5)_2O$
(2e)	138—140	32	4.90	3.50	84	14	−4	12.7 ($CDCl_3/C_5H_5N$)
(2f)	89	7	4.1	—	—	—	—	—
(2g)	73— 75	24	4.15		—	—	—	—
(2h)	117—120	18	4.03		—	—	—	—
(2i)	54— 55	31	4.05		—	—	—	—
(4)	211 (dec.)	13	5.57	3.40	130	16	54	—

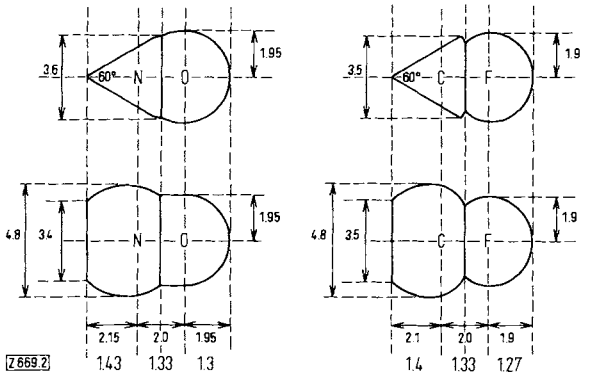


Fig. 2. Space-filling model of the aromatic *N*-oxide group and the aromatically bound fluorine atom (large numerals: Å; small numerals: cm).

Experimental:

2,(*n* + 3)-Dithia[*n* + 4](2,6)pyridinophane *N*-oxides *(2)*: A solution of 2,6-bis(bromomethyl)pyridine *N*-oxide[10] (2.81 g, 10 mmol) in benzene (250 ml) and a solution of 1,*n*-alkanedithiol (10 mmol) and NaOH (0.8 g, 20 mmol) in H_2O/ethanol (1:25) (250 ml) are simultaneously added dropwise over 5 to 7 h from two fine dropping funnels to stirred boiling ethanol (1 liter) by means of a "dilution principle apparatus"[11]. After 16 hours' boiling the reaction mixture is evaporated down and the residue extracted with hot chloroform. The chloroform solution is concentrated and chromatographed on neutral alumina (activity grade II to III) with benzene. The crude product obtained on concentration of the eluate is recrystallized from methylcyclohexane. Melting points, yields, and ^{1}H-NMR data are summarized in Table 1.

Received: June 20, 1972 [Z 669 IE]
German version: Angew. Chem. *84*, 770 (1972)

[1] Steric Interactions in the Interior of Cyclic Compounds, Part 21.—Part 20: *F. Vögtle, P. Neumann*, and *M. Zuber*, Chem. Ber. 1972, in press.

[2] For a review, see *P. Hamm* and *W. v. Philipsborn*, Helv. Chim. Acta *54*, 2363 (1971); cf. also *R. Gleiter, D. Schmidt*, and *J. Streith*, *ibid. 54*, 1645 (1971).

[7] *G. Briegleb*, Fortschr. Chem. Forsch. *1*, 642 (1950); in *E. Müller*: Methoden der organischen Chemie. 4th Edit., Thieme-Verlag, Stuttgart 1955, Vol. 3/1, pp. 545.

[8] See list No. PH 17 issued by Leybold, Köln-Bayental.

[9] X-ray structure analyses of pyridine *N*-oxides were consulted in determining the bond lengths and angles: *R. Desiderato* and *J. C. Terry*, Tetrahedron Lett. *1970*, 3203; *R. S. Sager* and *W. H. Watson*, Inorg. Chem. *7*, 1358 (1968); *8*, 308 (1969).

[10] *S. Kasuga* and *T. Taguchi*, Chem. Pharm. Bull. *13*, 233 (1965).

[11] *F. Vögtle*, Chem. and Ind. *1972*, 346; Chemiker-Ztg. *1972*, in press.

Photoisomerization of 2-[2-(*N*-Ethoxycarbonyl-*N*-allylamino)ethyl]benzaldehyde

By *Wolfgang Oppolzer* and *Kathrin Keller*[*]

In connection with our investigations of the synthetic application of intramolecular *o*-quinodimethane cycloadditions[1] we have found that irradiation (high-pressure mercury-vapor lamp) of a toluene solution of the aldehyde *(1)*[3], prepared from 2-(2-bromoethyl)-benzaldehyde[2], leads to formation of a 3:1 mixture of the stereoisomeric benz[*e*]indoles *(2)* and *(3)* in 69% yield. The major product *(2)* (m.p. 126—128 °C) crystallized out, and the oily secondary product *(3)* could be isolated by crystallization and subsequent alkaline hydrolysis of its dinitrobenzoate *(5)* (m.p. 105 to 110 °C). The constitutions and configurations given in the formulas *(2)* and *(3)* for the photoproducts are supported, *inter alia*, by the following arguments:

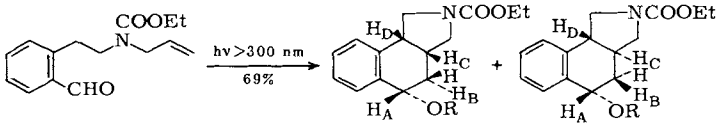
Firstly: NMR double resonance experiments show a diaxial coupling of the proton H_B of the dinitrobenzoate derivative *(4)* (m.p. 89—91 °C) of the major product *(2)*, thus revealing the *cis* relationship of the protons H_A and H_C. In the ester *(5)*, on the other hand, the axial proton H_B couples with an equatorial H_A and an axial H_C, thus indicating the *trans* relationship of H_A and H_C in this compound.

[*] Dr. W. Oppolzer and Dipl.-Chem. K. Keller
Pharmazeutisch-Chemische Forschungslaboratorien,
SANDOZ AG
CH-4002 Basel (Switzerland)

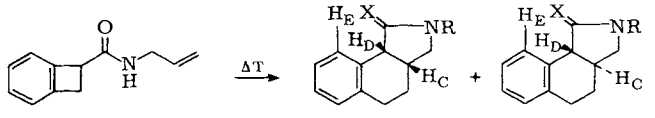
Table 1. Characteristic NMR data of benz[*e*]isoindoles ($CDCl_3$, coupling constants J in Hz, chemical shift δ in ppm).

Compound	$^3J_{AB}$	^3J_B	$^3J_{CD}$	δH_D	δH_E
(4)	12	12	?	?	—
(5)	4	12	?	?	—
(7)	—	—	7—8	3.55	7.55
(8)	—	—	10	3.18	8.22

Secondly: Thermal isomerization of the benzocyclobutene *(6)* at 155 °C leads to a mixture of the lactams *(7)* (m.p. 171—172 °C and *(8)* (m.p. 203—205 °C)[4], which can be separated by chromatography and whose



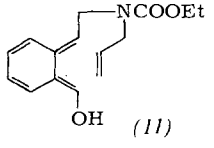
(1) *(2)*: R = H *(3)*: R = H
(4): R = 3,5-Dinitrobenzoyl *(5)*: R = 3,5-Dinitrobenzoyl



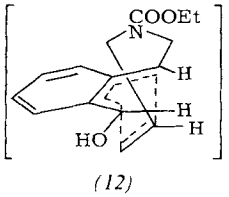
(6) *(7)*, X = O, R = H *(8)*, X = O, R = H
(9), X = H_2, R = COOEt *(10)*, X = H_2, R = COOEt

configurations are evident from the NMR data given in Table 1. Reaction of the *cis*-lactam *(7)* with aluminum hydride[5] and ethyl chloroformate yields the same urethane *(9)*[6] as is formed on hydrogenolysis (Pd—C/H_2) of the major photoproduct *(2)* whose H_C and H_D protons must therefore be *cis* to each other. Analogous correlation of the *trans*-lactam *(8)* with the secondary photoproduct *(3)* reveals the *trans* relationship of the protons H_C and H_D in the latter.

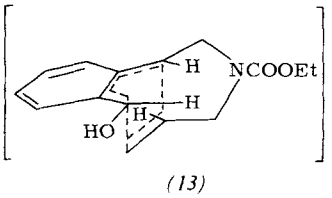
From the above it is evident that the benzylic hydrogens H_A and H_D are *cis* to each other in both photoproducts *(2)* and *(3)*. This observation provides supporting evidence for the mechanistic conclusions drawn from studies of the photochemistry of *o*-toluylcarbonyl compounds[7]. Hence the reaction *(1)* → *(2)* + *(3)* may be explained by a mechanism involving a 1,5 H shift of



(11)



(12)



(13)

the excited aldehyde *(1)* to give a triplet dienol, which is converted into the ground state of the *trans,trans*-quinodimethane *(11)*. The non-isolable intermediate *(11)*[8] is obviously capable of undergoing a rapid thermal [4s + 2s] cycloaddition[9] to the neighboring olefinic double bond leading to the major product *(2)* *via* the *endo* transition state *(12)* and to the secondary product *(3)* *via* the *exo* transition state *(13)*.

Experimental:

A solution of the aldehyde *(1)* (4.5 g) in toluene (200 ml) was irradiated under a slow stream of nitrogen with a high-pressure mercury-vapor lamp (Hanau TQ 81); the solution was water-cooled during the irradiation.

After four hours no starting material could be detected in the thin-layer chromatogram (SiO_2, benzene/ethyl acetate 3:1)—only one new spot was recognizable. After removal of the solvent the oily residue was chromatographed with benzene/ethyl acetate 1:1 on a 25-fold amount of silica gel. The eluate, after removal of solvent, was shown by NMR spectroscopy to consist solely of a 3:1 mixture of products *(2)* and *(3)* (3.1 g, 69%), from which 1.4 g of the major product *(2)* could be isolated by crystallization from ether/pentane. Reaction of the remaining mother liquor with 3,5-dinitrobenzoyl chloride/pyridine and sixfold recrystallization of the resulting ester mixture afforded 0.41 g of the dinitrobenzoate *(5)* (m.p. 105 to 110 C), which on hydrolysis with 2 N ethanolic KOH at 25 C for 20 min yielded 0.23 g of the oily photoproduct *(3)*.

Received: June 9, 1972 [Z 658 IE]
German version: Angew. Chem. *84*, 712 (1972)

[1] *W. Oppolzer*, J. Amer. Chem. Soc. *93*, 3833, 3834 (1971); *W. Oppolzer* and *K. Keller*, *ibid.* 3836.

[2] *A. Rieche* and E. Schmitz, Chem. Ber. *89*, 1254 (1956).

[3] Conversion of 2-(2-bromoethyl)benzaldehyde into the oily aldehyde *(1)* was achieved in 70% yield by the following series of operations: a) acetalization with triethyl orthoformate/ethanol/toluenesulfonic acid, 18 h, 25 °C; b) heating under reflux with 20 equivalents of allylamine, 7 h; c) acylation with 1.1 equivalents of ethyl chloroformate + 2 equivalents of pyridine in methylene chloride; and d) acetal cleavage with 2 N HCl in dioxane/water (1:1), 30 min, 25 °C.—We thank Dr. *G. Wersin* for preparation of the 2-(2-bromoethyl)benzaldehyde diethyl acetal.

[4] In boiling dichlorobenzene the *trans*-lactam *(8)* epimerizes into the thermodynamically more stable *cis*-lactam *(7)*. This process is catalyzed by traces of acid and is obviously responsible for the fact that only the *cis*-lactam *(7)* was isolated after thermolysis of the benzocyclobutene *(6)* in a steel autoclave at 190 C; cf. Ref. [1], p. 3833.

[5] *N. M. Yoon* and *H. C. Brown*, J. Amer. Chem. Soc. *90*, 2927 (1968).

[6] The identity of the oily urethane *(9)* prepared by the two independent routes was confirmed by NMR and IR spectroscopy.

[7] *N. C. Yang* and *C. Rivas*, J. Amer. Chem. Soc. *83*, 2213 (1961); *F. Nerdel* and *W. Brodowski*, Chem. Ber. *101*, 1398 (1968); *G. Porter* and *M. F. Tchir*, Chem. Commun. *1970*, 1372; *S. M. Mellows* and *P. G. Sammes*, *ibid. 1971*, 21; *B. J. Arnold* and *P. G. Sammes*, *ibid. 1972*, 30.

[8] A stereoisomeric *trans*-alkyl-*cis*-hydroxyquinodimethane can hardly be considered to compete with the *trans-trans*-quinodimethane *(11)* as a cycloaddition partner because of its short lifetime and for steric reasons; cf. Ref. [7].

[9] According to *F. Nerdel* and *W. Brodowski* [7] the photoaddition of *o*-methylbenzophenone to maleic and fumaric acids proceeds stereospecifically with preservation of the olefinic configuration.

CONFERENCE REPORTS

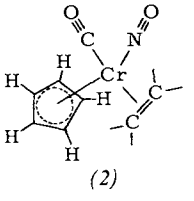
Transition-metal π-Complexes with Activated Olefins

By *Max Herberhold*[*]

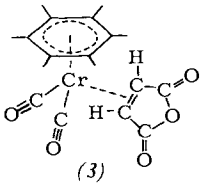
The great importance of monoolefin π-complexes formed as intermediates in homogeneous catalysis (*e. g.* during oxidation of ethylene to acetaldehyde, hydroformylation, dimerization of olefins, Ziegler-Natta polymerization, and hydrogenation of olefins) calls particularly for model study of stable olefin π-complexes. Both the factors that influence the formation of π-complexes by an olefin, and the extent of interaction between the olefin and its neighboring ligands have been investigated for the case of complex formation by olefins with photochemically produced carbonylmetal fragments ($[Cr(CO)_5]$, $[C\,H_5Mn(CO)_2]$,$[C_5H_5Cr(CO)(NO)]$ or $[C_6H_6Cr(CO)_2]$).

In addition to olefinic hydrocarbons, "electron-poor" olefins such as tetracyanoethylene (TCNE) and maleic anhydride (MA) can also be introduced as monodentate π-olefin ligands in carbonylmetal complexes; with cyanoolefins (acrylonitrile, fumarodinitrile) a competing complex formation by way of the lone pair of electrons on the nitrogen atom of the cyano group must be taken into account[1]. In all π-complexes the acceptor properties of the olefin play a decisive role; this is true also for the coordination compounds of the "electron-rich" olefin tetramethoxyethylene (TME)[2]. Different olefin ligands can be best compared in the system olefin-dicarbonylcyclopentadienylmanganese *(1)*, where not only the complex with ethylene[3] but also complexes of the persubstituted derivatives TCNE and TME[2] have been obtained.

There are considerable electronic interactions to be observed between the π-bonded olefin and its neighbor ligands, and these are transmitted through the central metal; clearly the donor-acceptor properties of the individual ligands compete with one another. In the system *(1)* there is an approximately linear relation between the Cotton-Kraihanzel valence force constants $k(C{\equiv}O)$[4] of the two CO ligands and the chemical shift $\tau(C_5H_5)$ in the ^{1}H-NMR spectrum (in D_6-acetone)[5]; an analogous relationship has been found to exist in the system *(2)* between the IR stretching frequencies $\nu(C{\equiv}O)$ and $\nu(N{\equiv}O)$, respectively, and the chemical shift $\tau(C_5H_5)$[6]. In complexes of type *(3)* both

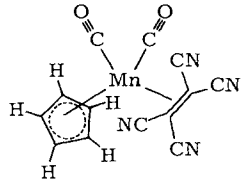


(2)

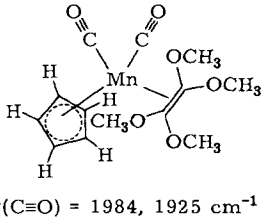


(3)

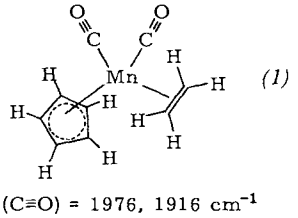
the C≡O stretching frequencies of the carbonyl ligands and the C=O stretching frequencies of the anhydride group of maleic anhydride (MA) are determined by the substituents on the π-bonded aromatic six-membered ring, whose influence can be characterized by the sum $\Sigma\sigma_p$ of the Hammett substituent parameters. Maleic anhydride is a stronger electron-withdrawing ligand than carbon monoxide[7].



$\nu(C{\equiv}O)$ = 1992, 1966 cm^{-1}



$\nu(C{\equiv}O)$ = 1984, 1925 cm^{-1} (in cyclohexane)



(1)

$\nu(C{\equiv}O)$ = 1976, 1916 cm^{-1}

Lecture at Regensburg, Germany, on February 7, 1972
[VB 340 IE]
German version: Angew. Chem. *84*, 773 (1972)

[*] Doz. Dr. M. Herberhold
Anorganisch-chemisches Laboratorium
der Technischen Universität
8 München, Arcisstrasse 21 (Germany)

[1] *M. Herberhold* and *H. Brabetz*, Angew. Chem. *81*, 921 (1969); Angew. Chem. internat. Edit. *8*, 902 (1969).

[2] *M. Herberhold* and *H. Brabetz*, Z. Naturforsch. *26b*, 656 (1971).

[3] *H. P. Kögler* and *E. O. Fischer*, Z. Naturforsch. *15b*, 676 (1960).

[4] *F. A. Cotton* and *C. S. Kraihanzel*, J. Amer. Chem. Soc. *84*, 4432 (1962).

[5] *M. Herberhold* and *C. R. Jablonski*, Chem. Ber. *102*, 767, 778 (1969).

[6] *M. Herberhold* and *H. Alt*, unpublished work.

[7] *M. Herberhold* and *C. Jablonski*, J. Organometal. Chem. *14*, 457 (1968).

Optical Properties of Cholesteric Liquid Crystals

By *Horst Stegemeyer*[*]

Nematic and cholesteric liquids have largely similar structures: they show the parallelism of the molecular axes that characterizes all liquid crystals; the molecular centers of gravity are distributed statistically. Cholesteric phases, which are formed only by optically active, formanisotropic molecules, have additionally a helical arrangement of the molecular axes in relation to the preferred axis, which causes striking optical properties: namely an optical rotatory dispersion (ORD) of extremely high amplitude, selective reflection of light within a narrow spectral region, and a circular dichroism (CD) of almost 100%.

Since chiral centers in the individual molecules are responsible for formation of the helical structure, it is to be expected that chiral molecules which do not themselves form liquid crystals will induce a helical structure in nematic phases. Such a phase transformation nematic → cholesteric has been demonstrated for various systems, where the chirality of the added non-mesomorphic molecules may be caused by asymmetric carbon atoms or by dissymmetry of the whole molecular skeleton[1]. The extent of the induced optical activity depends on the strength of the interactions between the dissolved molecules and the solvent molecules. The position of the induced CD bands is strongly temperature-dependent, as is the case in "normal" cholesteric phases. The concentration-dependence of the ORD amplitude reaches a maximum at *ca.* 2 mol-%. The decrease in this effect at increasing concentrations can be explained qualitatively as follows: Since the optically active molecules do not show strong anisotropy, they disturb the parallel arrangement of the rod-like solvent molecules, so that eventually the long axes are distributed statistically in space, whereby the fundamental cause of the appearance of helical structure is abolished.—The induced optical rotation is larger by a factor of 10^3 than the molecular rotation of the dissolved non-mesomorphic molecules in isotropic solution. Provided that the interaction between the dissolved molecules and the nematic solvent suffices, the effect can be used to detect small amounts of optically active substance.

If achiral molecules are dissolved in cholesteric liquid crystals, a Cotton effect is induced within their absorption bands, this overlying the anomalous rotatory dispersion of the cholesteric phase and having the same sign as the latter. The CD is smaller than that of the cholesteric phase ($< 10\%$). The effect disappears above the clearing point. Further, since the molar amplitude of the ORD curves is extremely high, a chiral distortion of the chromophores by solvation can be excluded. The helical structure of the solvent molecules is in fact transferred to the spatial distribution of the preferred axes of the dissolved molecules, so that the incident light "sees" a chiral system of coupled chromophores[2].

Lecture at Münster, Germany, on March 27, 1972 [VB 342 IE]
German version: Angew. Chem. *84*, 720 (1972)

[*] Prof. Dr. H. Stegemeyer
Stranski-Institut für Physikalische Chemie
der Technischen Universität
1 Berlin 12, Strasse des 17. Juni 135 (Germany)

[1] *H. Stegemeyer* and *K.-J. Mainusch*, Naturwissenschaften *58*, 599 (1971).

[2] *K.-J. Mainusch* and *H. Stegemeyer*, Z. Phys. Chem. N. F. *77*, 210 (1972).

Kinetics and Mechanism of the Formation of Transition-Metal Complexes

By *Hartmut Diebler*[*]

Complex formation with simple ligands in aqueous solution occurs in general by a dissociative (or S_N1) mechanism in which replacement of the first H_2O molecule in the innermost coordination sphere of the hydrated metal ion represents the rate-determining step. The rate constant k_i assigned to this reaction step is characteristic of a given metal ion and can be determined from the bimolecular rate constant k_f for complex formation if the formation of the outer-sphere complex (stability constant K_o) is taken into account[1]:

$$k_f = K_o \cdot k_i$$

For metal ions with closed outer electron shells the values of k_i depend mainly on the radius and charge of the metal ion as well as on the coordination number. With transition-metal ions, however, effects due to specific configurations of the only partly filled 3d electron shell are also observed. Thus a contribution of crystal field stabilization energy to the activation energy of the substitution process leads to a decrease in the reaction rate of ions with d^3 (V^{2+}, Cr^{3+}) and d^8 (Ni^{2+}) configurations, whereas the Jahn-Teller distortion occurring with d^4 and d^9 configurations gives rise to extremely high k_i values (*ca.* $10^9\ s^{-1}$ for Cr^{2+} and Cu^{2+}). The dissociative nature of the substitution mechanism apparently still holds for ions with a Jahn-Teller distortion[2].

However, numerous reactions are known which do not fit into this simple scheme. In the case of trivalent metal ions, hydrolysis often prevents an unambiguous interpretation of the kinetics of complex formation with basic ligands (indistinguishability of the reaction pathways $M^{3+} + L^{n-} \rightarrow ML^{(3-n)+}$ and $MOH^{2+} + HL^{(n-1)-} \rightarrow ML^{(3-n)+}$, where M = metal and L = ligand)[3]. Nevertheless, there is evidence that for some trivalent metal ions the substitution mechanism has associative (or S_N2) character. This is indicated, for instance, by some of the experimentally determined activation parameters for ligand exchange and by the ligand-dependence of the substitution rate observed with V^{3+} [4]. It might be that the availability of an empty t_{2g}-orbital in the case of V^{3+} (and also of Ti^{3+}) facilitates the formation of a transition state with an increased coordination number.

Reactions with more complicated ligands frequently lead to deviations from "normal" behavior. Complex formation of β-amino acids with metal ions is usually distinctly slower than that with the corresponding α-compounds. Obviously it is not the replacement of the first water molecule but rather the ring closure step that is rate-determining in the reactions with the β-amino acids[5]. Particularly drastic decreases in the reaction rate are found with some multidentate macrocyclic ligands, which owing to a lack of flexibility do not allow a rapid stepwise replacement of solvate groups from the metal atom. Very rigid ligands (porphyrins) probably require *simultaneous* removal of several solvate groups[6].—Monoprotonated bidentate ligands also often react slower by orders of magnitude than the corresponding unprotonated ligands; here the rate-

[*] Dr. H. Diebler
Max-Planck-Institut für Biophysikalische Chemie
34 Göttingen-Nikolausberg, Postfach 968 (Germany)

determining step is the dissociation of the proton from the monodentate-bound intermediate[7].

Surprisingly, some very strongly basic bidentate ligands react appreciably *faster* than predicted by the simple mechanism of complex formation. As an explanation a mechanism involving internal conjugate-base formation has been proposed[8].

Lecture at Konstanz on June 8, 1972 [VB 343 IE]
German version: Angew. Chem. *84*, 773 (1972)

[1] *M. Eigen*, Ber. Bunsenges. Phys. Chem. *67*, 753 (1963).

[2] *H. Diebler* and *P. Rosen*, Ber. Bunsenges. Phys. Chem., in press.

[3] *D. Seewald* and *N. Sutin*, Inorg. Chem. *2*, 643 (1963).

[4] *R. C. Patel* and *H. Diebler*, Ber. Bunsenges. Phys. Chem., in press.

[5] *K. Kustin et al.*, J. Amer. Chem. Soc. *88*, 4610 (1966); *89*, 3126 (1967).

[6] *D. K. Cabbiness* and *D. W. Margerum*, J. Amer. Chem. Soc. *92*, 2151 (1970).

[7] *H. Diebler*, Ber. Bunsenges. Phys. Chem. *74*, 268 (1970).

[8] *D. B. Rorabacher*, Inorg. Chem. *5*, 1891 (1966).

ABSTRACTS

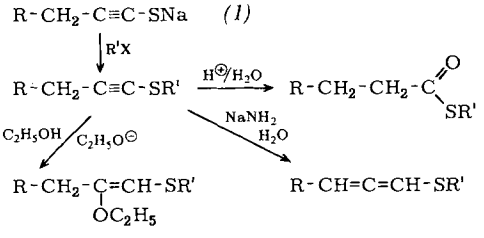
Reviews

Abstracts of selected progress reports and review articles

Recent developments in the synthetic organic chemistry of sulfur are considered by *L. Field* in an article dealing with more than 50 classes of sulfur compounds and including experimental procedures. Primary alkanethiols are accessible by the following reaction:

$$R{-}Cl + Na_2CS_3 \rightarrow R{-}S{-}CS_2Na \xrightarrow{H^{\oplus}} R{-}SH + CS_2$$

The unknown alkynethiols are available as thiolates *(1)* for reaction with electrophiles and nucleophiles:



Thiobenzoates and thiobenzamides can be prepared according to:

$$Ar{-}H + ClC(S){-}X \xrightarrow{AlCl_3} Ar{-}C(S){-}X$$

Syntheses of thiocarbonic acid derivatives, mercaptals and mercaptols, disulfides and polysulfides, sulfenic acid derivatives, sulfides, thials and thiols are accompanied by detailed discussions of dimethyl sulfoxide as solvent and oxidizing agent, and of the dimsyl anion *(2)*

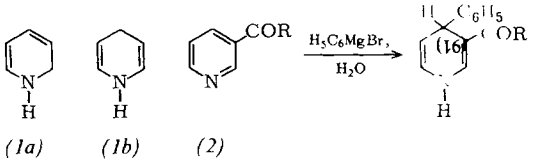
$$R{-}COOCH_3 + [H_3C{-}S(O){-}CH_2]^{\ominus} \xrightarrow{DMSO}$$

$$R{-}C(O){-}CH_2{-}S(O){-}CH_3 \xrightarrow{Al(Hg)} R{-}C(O){-}CH_3$$

Further sections are devoted to sulfonium compounds, sulfinic acids, sulfones, sulfenes, sulfonic acids, and derivatives of sulfurous and sulfuric acid. [Some Recent Developments in Synthetic Organic Sulfur Chemistry. Synthesis *1972*, 101—133; 213 references]

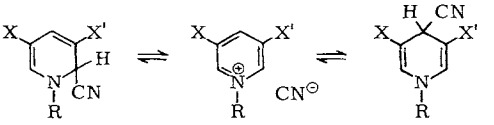
[Rd 509 IE–M]

The chemistry of dihydropyridines (excluding pyridinemethenes, ketodihydropyridines, pyridonimines, benzodihydropyridines, quinolizidines) *(1)*, which are important intermediates in syntheses and reactions of pyridine and of great biological import, are summarized in a detailed review by *U. Eisner* and *J. Kuthan*. By far the most representatives of *(1)* have the 1,2- *(1a)* or 1,4-dihydro structure *(1b)*. Possible syntheses from pyridines or pyridinium salts include reduction with $NaBH_4$, addition of organometallic compounds *e.g.* to *(2)*, dithionite reduction, or



(1a) *(1b)* *(2)*

addition of cyanide ion. Treatment of pyridines or pyridinium salts with metals effects transfer of an electron into the LUMO to give a radical that dimerizes or undergoes further reduction. Silylation of pyridines in the presence of Pd affords mixtures of type *(1a)* and *(1b)*. Hantsch synthesis and related condensations provide numerous representatives of *(1)*. Their most striking property is their oxidation to pyridines. Reduction leads to tetrahydro- and hexahydro derivatives. Whereas nucleophilic addition to *(1)* and protonated *(1)* and cycloadditions and ring

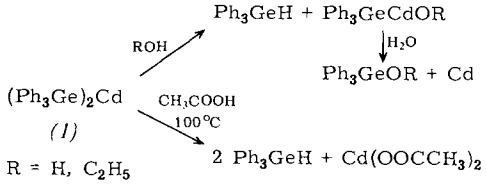


X = X' = CN, R = CH_3

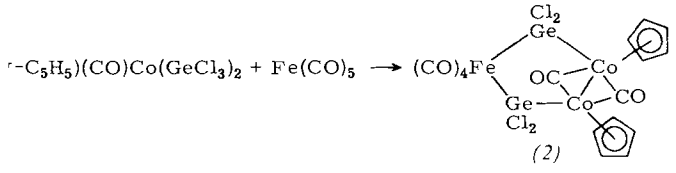
opening have been extensively studied, only few isomerizations are known. Our knowledge of the photochemistry of *(1)* is also fragmentary. [The Chemistry of Dihydropyridines. Chem. Rev. *72*, 1—42 (1972); 611 references]

[Rd 510 IE –M]

Publications on organogermanium compounds from 1970 have been reviewed by *B. C. Pant*. Compounds having Ge-metal bonds, *e.g. (1)*, appear to be valuable for further syntheses. The metal heterocycle *(2)* has been shown to



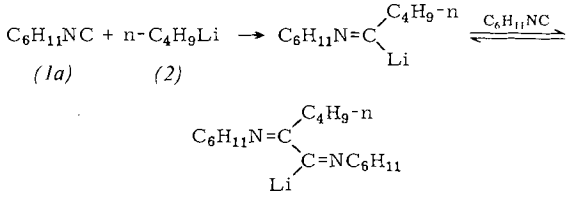
have a remarkable structure by X-ray methods. Heterocycles containing C, Si, N, and/or O in addition to Ge were also considered. 1,3-Digermacyclobutane derivatives polymerize readily.—Further sections deal with, *e.g.* organo-



germanium compounds with Ge—N, Ge—P, Ge—O, Ge—S, Ge—Se, and Ge—Te bonds as well as physicochemical studies. [Germanium. Organometal. Chem. Rev. B9, 205—247 (1972); 260 references]

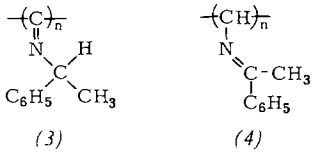
[Rd 512 IE –L]

The polymerization of isocyanides *(1)*, which has only been studied systematically during the past few years, is summarized by *F. Millic. (1)*, the only stable carbenes known apart from CO, have become readily accessible by a variety of recent methods. Self-condensation of *(1)* is of synthetic interest since not only high polymers but also heterocycles and oligomers can be obtained. Thus anionic initiators *(2)* produce dimers from *(1a)* in toluene at 0°C:

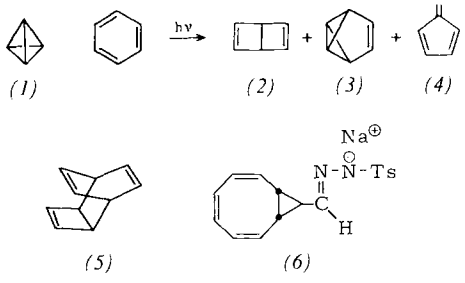


The synthesis of polyisocyanides can be divided into four types: Catalysis by protonic acids, with and without promotors (O_2, peroxides); catalysis by certain Lewis acids, especially BF_3; decomposition of metal-*(1)* complexes of suitable instability; spontaneous polymerizations and polymerization in the presence of powdered glass. Most polyisocyanides are insoluble. Optical data for poly-α-phenylethyl isocyanide suggest structure *(3)*, while *(4)* is less likely. [Polymerization of Isocyanides. Chem. Rev. *72*, 101—113 (1972); 138 references]

[Rd 515 IE –M]



Rearrangements of $(CH)_n$ compounds are the topic of a review by *L. T. Scott* and *M. Jones jr.* $(CH)_4$: Numerous studies have been undertaken with regard to the energetics of the highly strained molecules cyclobutadiene and tetrahedrane *(1)*. $(CH)_6$: Photolysis of benzene leads to Dewarbenzene *(2)*, benzvalene *(3)*, and fulvene *(4)*. Derivatives of further structural isomers are known. $(CH)_8$: Cyclooctatetraene has been most extensively investigated. Tricyclo-[3.3.0.$0^{2,6}$]octa-3,8-diene, barrelene, and tricyclo-



[4.2.0.$0^{2,5}$]octa-3,7-diene undergo interesting thermal or photochemical rearrangements. $(CH)_{10}$: The first representation of this series was *Nenitzescu*'s hydrocarbon *(5)*, which was followed by bullvalene. $(CH)_{10}$ compounds are obtained, *e.g.*, from cyclopropylcarbene presursors such as *(6)*. $(CH)_{12}$ isomers are also discussed. [Rearrangements and Interconversions of Compounds of the Formula $(CH)_n$. Chem. Rev. *72*, 181—202 (1972): 254 references]

[Rd 517 IE –M]

The chemistry of the higher oxidation states of manganese is reviewed by *W. Levason* and *C. A. McAuliffe*. Brief descriptions of the preparation and chemical properties are given along with redox potentials, crystal structures, magnetic moments, and vibrational frequencies. Special chapters are devoted to the electronic spectra of the tetraoxo anions of manganese(V)—(VII), the interpretation of which is not yet settled, and to the spectra of manganese(III) compounds which are interesting because of the strong Jahn-Teller distortion of their ground states. [Higher Oxidation State Chemistry of Manganese. Coord. Chem. Rev. *7*, 353—384 (1972); 294 references]

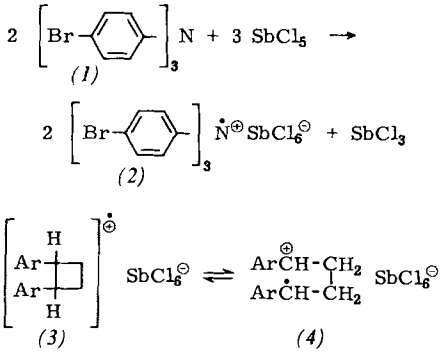
[Rd 518 IE –H]

The structure of metal complexes of some quadridentate Schiff bases is treated in a review by *M. Calligaris, G. Nardin*, and *L. Randaccio*. Atomic distances stemming from X-ray structural analyses are given, and the different possible conformations are discussed. This class of compounds is interesting a) because of their capability of reversibly binding molecular oxygen, and b) because they can be regarded as vitamin B_{12} models.

[Structural Aspects of Metal Complexes with Some Tetradentate Schiff Bases. Coord. Chem. Rev. 7, 385—403 (1972); 56 references]

[Rd 519 IE –H]

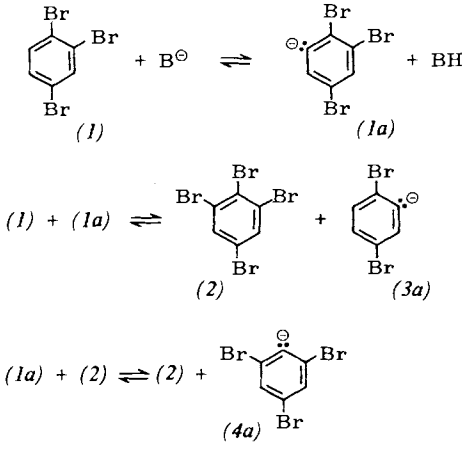
Cation radicals in electron transfer reactions are the subject of a report by *A. Ledwith*. The appearance of the species $M^{\cdot+}$ in mass spectrometry is well known; oxidation of the amine *(1)* to the cation radical *(2)* serves as example for the chemical synthesis. Compounds such as *(2)* can oxidize neutral molecules rapidly, *e.g.* cycloheptatriene derivatives to tropylium salts. Noteworthy is the quantitative oxidation of *N*-vinylcarbazole in CH_2Cl_2/CH_3OH to 1,4-dimethoxy-1,4-diphenylbutane. Interestingly, this methanolysis product is also formed from diphenylcyclobutane and



thus provides evidence for the formation of the intermediates *(3)* and *(4)*. Further examples of reactions which proceed *via* cation radicals are oxidations by bipyridylium salts and cyclodimerizations. [Cation Radicals in Electron Transfer Reactions. Accounts Chem. Res. 5, 133—139 (1972); 52 references]

[Rd 520 IE –L]

The base-catalyzed halogen dance and other reactions of aryl halides are described by *J. F. Bunnett*. In the halogen dance 1,2,4-tribromobenzene *(1)*, for example, is mainly converted into 1,3,5-tribromobenzene *(4)* on reaction with potassium amide/ammonia; also produced are 1,3- and 1,4-dibromobenzene *(3)*, 1,2,4,5- and 1,2,3,5-tetrabromobenzene and significant amounts of 3,4- and 3,5-dibromoaniline. This finding demonstrates that several reactions are involved, the most important of which are the following: From *(1)* arises



the anion *(1a)*, which reacts further with *(1)* to give *(2)* [and *(3a)*], which in turn acts as cocatalyst in the transfer of positive bromine ions to *(4a)*. The ions *(3a)* and *(4a)* are then protonated to *(3)* and *(4)*. [The Base-Catalyzed Halogen Dance, and Other Reactions of Aryl Halides. Accounts Chem. Res. 5, 139—147 (1972); 57 references]

[Rd 521 IE –L]

The exploration of biochemical mechanisms by tritium labeling is reviewed by *A. R. Battersby*. The substrate can be labeled in the following ways: (i) proton exchange at activated sites; (ii) tritiation of carbanions; (iii) reductions; (iv) syntheses from commercially available T-labeled intermediates. The possible applications of the methods are illustrated by examples such as the enzymatic deamination of phenylalanine, the biosynthesis of colchicine, haemanthamine, morphine, and terpenoids and indole alkaloids. [Some Applications of Tritium Labeling for the Exploration of Biochemical Mechanisms. Accounts Chem. Res. 5, 148—154 (1972); 40 references]

[Rd 522 IE –L]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

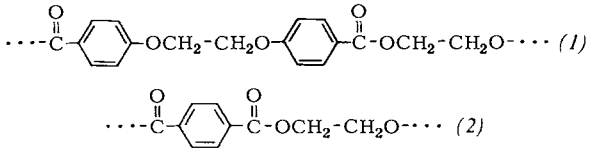
Polymer-based synthetic fibers with antibacterial properties contain 5-nitrofurfural, β-(5-nitro-2-furyl)acrolein, 1-[β-(5-nitro-2-furyl)acrylidenamino]hydantoin, 3-(5-nitro-2-furfurylidenamino)-2-oxazolidone, diphenylamine, 8-hydroxyquinoline, or combinations of these compounds as antibacterial agents. It is reported that synthetic fibers modified with the compounds mentioned, unlike previously known bacteriostatic synthetic fibers, do not lose their antibacterial properties during use, *e.g.* on wet treatment or sterilization or under mechanical stresses. [DOS 1769993; Leningradskij Institut Textilnoj i Legkoj Promyschlennosti, Leningrad]

[PR 1 –A IE]

Crystalline polycarbonate fibers having a reduced tendency to shrink are obtained by two-stage fixing of drawn polycarbonate fibers. The drawn polycarbonate fibers are further stretched above the glass transition point in the first fixing zone, and are then relaxed below the crystallite melting range in the second fixing zone. The temperature ranges and fixing conditions are given. As a result of this two-stage fixation, which has been tested for drawn crystalline polycarbonates, particularly for those based on bis(monohydroxyaryl)alkanones and bis(monohydroxyaryl) sulfones, sulfoxides, sulfides, or ethers, the tendency to shrink is reduced in the fixed product, and contrary to expectations, the initially good mechanical and textile properties of the fibers are retained or even improved. [DOS 1785137; Farbenfabriken Bayer AG, Leverkusen]

[PR 2 –A IE]

A new composite fiber contains a polymer A having at least 75 wt.% of repeating units with the formula *(1)* and a polymer B having at least 75% of repeating units with the formula *(2)*. The polymers mentioned may contain an admixture of up to 25% of glycols other than ethylene glycol and aromatic or aliphatic carboxylic acids or polymers such as polystyrene, polyethylene, nylon 6, or nylon 6,6. The polymer A must exhibit a shrinkage of less than



(1)

(2)

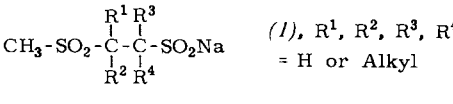
8% on boiling, and must exhibit stronger shrinkage than the polymer B under goffering conditions. The polymer B lies on the inside of the spiral in the goffered fiber. The new composite fibers are characterized *inter alia* by high elastic recovery and a high Young's modulus. [DOS 2009413; Asahi Kasei Kogyo K.K., Osaka]

[PR 4 –A IE]

Solid, non-tacky polyimide polymers based on linear, heat-curable polyimides of benzophenonetetracarboxylic dianhydride and a saturated C_{3-12} diamine containing not more than a 2% excess of the dianhydride or diamine can be used as the binding layer between a polyimide film and a copper foil as sheathing for insulated wires and as an adhesive. The polyimides, which can be stored in the form of solid, dry powders and exhibit good adhesion after heat-curing, have an intrinsic viscosity of about 0.1 to about 2.0, measured in a 0.5% solution in *m*-cresol. The softening point is around 150 to 300°C. 10 wt.% of polymer is almost completely soluble in 90 wt.% of solvent at 25°C. [DOS 2103500; Minnesota Mining, St. Paul]

[PR 5 –A IE]

Compositions containing block polymers of vinyl chloride can be prepared at −50 to 0°C if the block polymerization is carried out in the presence of systems that consist of a peroxy compound that yields active oxygen and a reducing compound having the general formula *(1)*. Small quantities of water lead to a uniform reaction, particularly at the



(1), R^1, R^2, R^3, R^4 = H or Alkyl

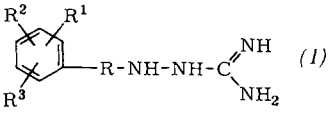
beginning of the polymerization. The polymers produced by this process are suitable for the production of textile fibers, pipes that can withstand high temperatures, and calendered sheets for vacuum forming. [DOS 1770971; Produits Chimiques, Pechiney-Saint-Gobain, Paris]

[PR 7 –E IE]

Aqueous graft and/or block copolymer emulsions having high solids contents and film-forming ability are obtained by polymerization of vinyl monomers in an aqueous reaction mixture in the presence of polyvinyl alcohol and at least one salt of cerium(IV) as the polymerization initiator. The mixture consists of 1) 82—65 parts by weight of vinyl monomer(s) and 2) 18—35 parts by weight of polyvinyl alcohol having an average degree of polymerization of 450 to 1200 and a degree of hydrolysis of 96 to 99%; the polymerization is carried out until the solids content of the final emulsion is 22—32 wt.%. The concentration of the cerium(IV) salt is not critical. Examples of suitable vinyl monomers are acrylates, methacrylates, styrene, α-methylstyrene, *p*-chlorostyrene, acrylonitrile, methacrylonitrile, vinyl chloride, vinylidene chloride, and vinyl esters of fatty acids. It is possible to copolymerize these monomers with small quantities of other monomers, such as acrylic, methacrylic, crotonic, maleic, fumaric, and itaconic acids or their esters, as well as acrylamide and methacrylamide. The reaction is preferably carried out at pH < 6.0, particularly < 3.0. The emulsions are suitable for the production of paints, adhesives, and coating and impregnating compositions, as well as for cellophane or plastic films. [DOS 2138202; Daicel Ltd., Osaka]

[PR 8 –E IE]

Alkylaminoguanidine derivatives *(1)* are suggested as antidiabetics and as drugs for the treatment of obesity. The compounds *(1)* are known, and can be prepared by methods described in the literature.

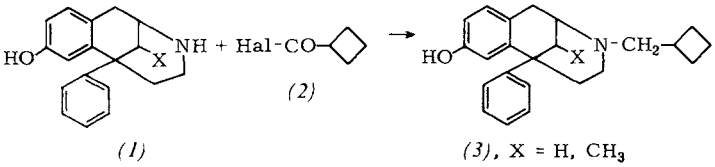


(1)

R^1, R^2, and R^3 are H, F, Cl, alkyl (C_{1-4}), or alkoxy (C_{1-4}), with the condition that two CF_3 groups may not be attached to neighboring carbon atoms; R = —$(CH_2)_n$— (n = 2,3,4,5) or —O—$(CH_2)_m$— (m = 2,3,4). [DOS 2139801; Sandoz AG, Basel]

[PR 21 –K IE]

New racemic and optically active 2-cyclobutylmethyl-5-phenyl-6,7-benzomorphans *(3)* are obtained by reaction of the benzomorphans *(1)* with the acyl halides *(2)*, followed by reduction. The benzomorphans *(3)* and their

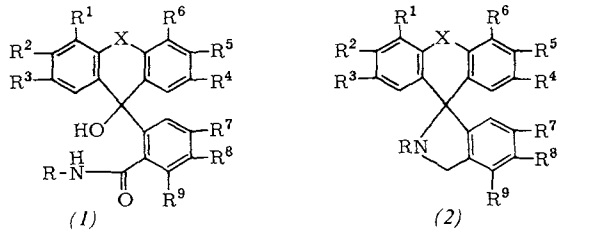


(1) *(2)* *(3)*, X = H, CH_3

salts are characterized by analgesic and antitussive effects. They are practically free from habit-forming characteristics, and act as morphine antagonists. [DOS 2041658; CIBA-Geigy AG, Basel]

[PR 22 –N IE]

Spiroisoindolines *(2)* are obtained as follows: ring closure of the benzamides *(1)* in the presence of acids or acid anhydrides leads to the spiroisoindolinones, which are reduced with hydrides to form the spiroisoindolines *(2)*. These compounds *(2)* with X = —O—, —S—, —CH_2—S— have



(1) (2)

X = direct linkage, —O—, —S—, —CH_2—S—, >N—R^{10}; R^{10} = CH_3, C_2H_5;

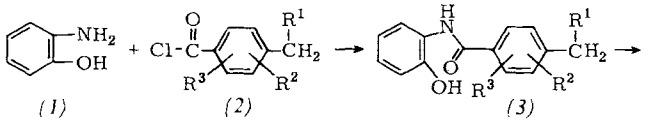
R = alkyl (C_1—C_3);

R^1—R^9 = H, Cl, *O*-alkyl (C_1—C_3) (not more than two substituents being different from H)

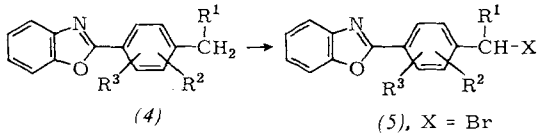
analgesic effects. If X is a direct linkage or >NR^{10}, they can be used as hypoglycemic agents. The same is true of adducts of *(2)* with acids. [DOS 2146340; Sandoz AG, Basel]

[PR 23 –N IE]

4-(2-Benzoxazolyl)phenylacetic acids, alcohols, esters, and amides and their pharmaceutically acceptable salts are



(1) (2) (3)



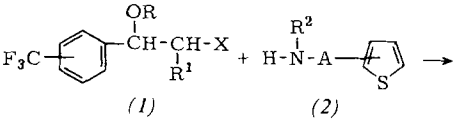
(4) (5), X = Br; (6), X = CN; (7), X = COOH

R^1 = H, CH_3; R^2, R^3 = H, halogen

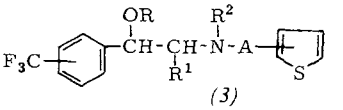
characterized by anti-inflammatory activity. They also exhibit analgesic and antipyretic activity. The preferred compounds are those having the formula *(7)*, which can be obtained by reaction of the aminophenol *(1)* with a benzoyl chloride *(2)* to form the amide *(3)*, ring closure to form the benzoxazole *(4)*, bromination to give *(5)*, conversion into the nitrile *(6)*, and acid hydrolysis. [DOS 2145203; Merck & Co. Inc., Rahway, N. Y.]

[PR 24 –N IE]

Anorectic *N*-thienylalkyl-β-phenylethylamines *(3)* are obtained by reaction of the phenylethyl halides *(1)* with thienylalkylamines *(2)*. The racemic or optically active



(1) (2)



(3)

R = alkyl (C_1—C_3); R^1 = H, CH_3; R^2 = H, alkyl (C_1—C_3)
A = alkylene (C_1—C_3); X = halogen

amines *(3)* and their acid adducts, apart from their anorectic action, exhibit only a slight sedative effect. [DOS 2145894; Smith, Kline & French Laboratories, Philadelphia, Pa.]

[PR 25 –N IE]

BOOK REVIEWS

Die Verarbeitung des Erdöls (The Processing of Petroleum). By *B. Riediger*. Springer-Verlag, Berlin–Heidelberg–New York 1971. 1st Edit., xvii, 1088 pp., 319 figures, 131 tables, bound DM 220.—.

This excellently produced work, provided with numerous tables and, in some cases, full-page figures, gives a critical account of the processing of petroleum. A description of the crude oils available for processing and the properties of the intermediates and finished products is followed by a consideration of the constructional units of petroleum processing plants. Distillation of crude oil and its primary products, thermal cracking on residual oil or coke, thermal reformation, and corresponding catalytic steps represent the main processes and consequently occupy about one half of the book.

There follows a description of the so-called auxiliary operations, which are actually highly interesting and important processes, and the plant involved, *e.g.* polymerization, alkylation, and isomerization. The author also goes into refinery processes for the removal of undesirable contaminants such as sulfur, nitrogen, and oxygen. Then come solvent methods for separation of asphalt and high-boiling oils, solvent-extraction and dewaxing of lubricants, and the production of bitumen.

High-pressure catalytic hydrogenation for maximum production of gasoline or middle distillates from heavy oil or residues and for refinement is devoted the space it deserves as a modern process. The latest processes for the production of town gas, synthetic gas, and hydrogen from petroleum products round off the descriptions of processes. The final chapter, which also covers 100 pages, is concerned with the planning of complete refineries. A comprehensive author, geographical, and subject index concludes the work.

The book provides both the constructer and designer as well as the operator of refineries with even more than the information collected on over 1000 pages since the detailed references to the original literature facilitate serious study of individual problems. The clear arrangement and the wealth of subject matter make the book a valuable supple-

ment to the available literature on petroleum technology and science because of the exemplary way in which it goes into the chemical structure and uses of the products and the chemistry of the individual processes. Particular mention should be made of the references to the historical development of important processes and equipment which make the book very interesting reading for the older expert too.

Theoretical fundamentals, chemistry, economic necessity, and statistics of the demand for petroleum products precede the descriptions of the processes, thereby contributing significantly to an understanding of the subject.

In the preface the author stresses that he has no intention to deal with the rapidly expanding field of petrochemistry in the present work. Perhaps he will change his mind for his experience in this field too would be sure to enrich the current literature.

Hans Weller [NB 51 IE]

The Chemistry of Synthetic Dyes. Vol. IV. Edited by *K. Venkataraman*. Academic Press, New York–London 1971. 1st Edit., xix, 548 pp., numerous figures, bound $ 28.50.

The present book in the second of four volumes[*] reporting on the progress made in the last twenty years in the field of dyestuff chemistry. They are intended as supplementary volumes to *Venkataraman*'s classis two-volume standard work covering this discipline up to about 1950.

An idea of the contents and the main emphasis of the book can best be gained from a glance at the titles and the sizes of the seven chapters by nine different authors, some of whom are well known experts: 1. Application of Dyes by Dyeing (*O. Glenz*, 74 pages); 2. Application of Dyes in Textile Printing (*K. Neufang*, 27 pages); 3. Basic Dyes (*N. R. Ayyangar* and *B. D. Tiak*, 58 pages); 4. Cationic Dyes for Synthetic Fibers (*D. R. Baer*, 50 pages); 5. Cyanine Dyes (*G. E. Ficken*, 130 pages); 6. The Photographic Color Development Process (*J. Bailey* and *L. A. Williams*, 46 pages); 7. Photochemistry of Dyes (*H. Meier*, 126 pages). These chapters are preceded by a preface by the editor, a list of contents of the already published volumes, and a provisional list of contents of those that have yet to appear. The book closes with a good author and subject index. The clear formulas, reaction equations, and tables deserve special praise, and a certain amount of nonuniformity in the charge symbols (+ or ⊕) in the formulas does little to mar the overall impression.

The editor has succeeded well in matching the undoubtedly very different manuscripts submitted by the various authors to one another to give a well balanced blend of theoretical and practical articles, as is reflected in some 2000 literature references including more than 600 patents. It can hardly be expected that multiple authorship on this scale will not produce some slight degree of inconsistency. Thus some repetition and overlapping occurs between chapters 3 and 4. As examples, it will suffice to mention the designations "basic" and "cationic" dyestuffs, mμ and nm, and the various symbols used for indicating concentrations such as [ ], *c*, or *C*. These and a number of printing errors, which are all trivial in nature, are by no means able to detract from the tremendous value of the book.

Like the preceding volumes, the present book depicts the field of dyestuff science within the context of the principles of modern inorganic, organic, and physical chemistry. It can therefore be recommended without reservation to every modern and receptive dyestuff chemist.

Paul Rys [NB 54 IE]

[*] Cf. Angew. Chem. internat. Edit. *11*, 547 (1972).

Chemie 1, Anorganisch (Chemistry 1, Inorganic). By *H.-H. Vogt*. Südwest Verlag, München 1972. 1st Edit., 167 pp., bound, DM 12.80.

"The present volume purposely refrains from any kind of specialization. It provides a foundation of chemical theory as a stepping stone to the specialist literature." Thus a part of the foreword—so far so good. However, what should one make of the statement on page 21 (after a conventional introduction to what chemistry is all about) that: "The smallest particles of an element still exhibiting the properties of the element in question are called atoms"?—That is the chemistry of a bygone age and was no more true then than now. With regard to uniformity of properties the author would probably be surprised if he could compare an atom of mercury with a drop of that element.—Atomic weight and molecular weight (instead of relative masses) are introduced, and concerning the molecule one is told: "Because the atoms in a molecule are held together by special binding forces the properties of the molecules differ from those of their constituent atoms". *Schrödinger*'s classical warning against believing what comes out must also be inside seems not to apply here.—And finally a sample of the "logical presentation" proclaimed in the foreword: on page 36 reduction is removal of oxygen (nothing else), on page 73 it becomes take-up of electrons. That is how chemistry was taught while the novelty of these discoveries still stood in the way of intellectual detachedness. We have advanced several decades since then and this kind of logic has begun to acquire rather a musty air.—The reviewer must admit that he did not enjoy reading the book.

H. Grünewald [NB 60 IE]

Errata

In the communication "Electron Lone Pairs" in Organic Sulfides and Disulfides' by *H. Bock* and *G. Wagner* [Angew. Chem. internat. Edit. *11*, 150 (1972)] the following correction should be made:

In Table 3, second from last row, the figure "8.75" should read "7.75".

ANGEWANDTE CHEMIE

Volume 11 · Number 9
September 1972
Pages 739–860

International Edition in English

Conformational Analysis in Heterocyclic Systems: Recent Results and Applications[1]

By Ernest L. Eliel[*]

This review deals with the following aspects of conformational analysis in saturated heterocyclic systems: 1. Conformational equilibria in 2-aryl and 2-ethynyl-1,3-dioxanes in various solvents. 2. The generalized anomeric effect in perhydro-1,3-diazines and its origin. 3. Unexpected conformational equilibria in 5-heterosubstituted 1,3-dioxanes. 4. Normal and anomalous solvent effects in conformational equilibria of 1,3-dioxanes with heteroatoms at C-5. Calculation of solvent effects. Correlation of ΔG^0 as a function of solvent with solvatochromic transition energy $E_T(30)$; a new scale of "solvent polarity". 5. Interplay of hydrogen bonding with dipolar, non-bonded and eclipsing interactions in 5-hydroxymethyl-1,3-dioxanes. 6. Highly stereoselective H-D exchanges in anancomeric 1,3-dithianes. 7. Potential distortion of a cyclohexane or 1,3-dioxane ring by a *tert*-butyl substituent. Evidence from ^{1}H-NMR and ^{13}C-NMR investigations and from X-ray structure analysis.

1. Introduction

The universal importance, in chemistry and molecular physics, of the subject of conformational analysis has been recognized by the award of the 1969 Nobel prize to two of the principal exponents of the field: *D. H. R. Barton* and *O. Hassel*[2,3]. Several comprehensive summaries of the field[4–6] as well as accounts of recent symposia[7–9] are available.

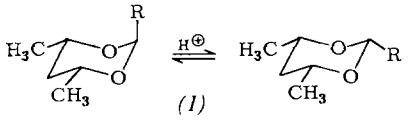
In recent years, interest in the conformational analysis of small molecules has shifted away from six-membered carbocyclic rings to rings of other sizes and to saturated heterocyclic rings; particular interest has been directed toward conformational interpretation of physical properties, notably NMR spectra (including ^{19}F and ^{13}C as magnetic nuclei), barrier measurements and *a priori* calculations of molecular conformation by either molecular mechanical or quantum mechanical methods. There has also been much activity in the application of conformational analysis to macromolecules, both natural and synthetic.

[*] Prof. Dr. E. L. Eliel
Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556
Present address: Department of Chemistry
University of North Carolina
Chapel Hill, North Carolina 27514 (USA)

The present review deals mainly with recent advances in the conformational analysis of saturated heterocycles[10] and with some more general applications of conformational methodology. Because of limitations of space, the topics to be discussed are confined to work presently in progress or recently completed in the author's own laboratory: conformational equilibria in 2-substituted 1,3-dioxanes, the generalized anomeric effect, equilibria in 1,3-dioxanes with heterosubstituents at C-5, the effect of solvent on conformation of dipolar molecules, hydrogen bonding and conformation, stereoselective H-D exchanges in sulfur-containing heterocycles, and ring distortion by substituents, especially as revealed by ^{13}C-NMR spectroscopy. Attention should, however, be drawn to some novel contributions to the field from other laboratories: conformational enthalpies by heats of combustion[11], by microcalorimetric determination of reaction heats[12] and by mass spectrometry[13], quantitative correlation of conformation with boiling point[14], correlation of NMR spectra with the shapes of six-membered rings[15] and molecular mechanical calculation of conformational energy in heterocycles[16].

2. Conformational Energies in 2-Substituted 1,3-Dioxanes

Previous study[17] of a number of 2-substituted 1,3-dioxanes of type *(1)* has shown that the preference of the substituent for the equatorial position is generally much greater than in cyclohexane, *i.e.* $-\Delta G^0(1) > -\Delta G^0$(cyclohexyl-X). An exception occurs for alkoxy substituents, which, because of the anomeric effect[18], prefer the axial position at C-2 in a 1,3-dioxane.



(1)

This finding is easily explained on the basis of the geometry of the 1,3-dioxane ring[19]: because of the shorter C—O (as compared to C—C) bond length, an axial substituent at C-2 in a 1,3-dioxane is closer to the *syn*-axial hydrogens than a similar substituent in cyclohexane, and this effect is enhanced by the puckering which has been observed in this region of the ring (torsional angle C O C O = 63°)[19].

In view of this finding, it seemed at first sight surprising that the $-\Delta G^0$-value for phenyl (Table 1, entries 1—3) is nearly the same as the corresponding value in cyclohexane (3.1 kcal/mol)[20]. This apparent mystery has been resolved as the result of a recent publication[21] in which it was pointed out that the preference for the equatorial conformation of phenyl in cyclohexane is only partly due to the repulsion of the ring and the *syn*-axial hydrogens in the axial conformation. A substantial part of the energy difference derives from the fact that equatorial phenyl prefers a conformation in which the phenyl ring bisects the cyclohexane chair ("parallel conformation") whereas in axial phenyl, the *syn*-axial hydrogens make this conformation prohibitive and force the ring into a flatside-on ("perpendicular") conformation. In this conformation the major source of the steric interaction is the compression of the *ortho*-hydrogens of the phenyl ring with the equatorial hydrogens at C-2 and C-6 in the cyclohexane chair. Clearly, this compression disappears in a 2-phenyl substituted 1,3-dioxane where the CH_2-groups of the cyclohexane chair are replaced by bare oxygen atoms. Under these circumstances, even equatorial phenyl prefers the perpendicular conformation, as shown by X-ray evidence[19], and the only significant difference between equatorial and axial phenyl is the interaction of the axial ring with the *syn*-axial hydrogens. Although this interaction is greater than in cyclohexane because of the shorter interatomic distances[10d] (cf. the case of the ethynyl group discussed below), the absence of the "*ortho*-interaction" (see above) fortuitously compensates almost exactly for the greater *syn*-axial compression, with the result that $-\Delta G^0$(phenyl) is the same in cyclohexane as at C-2 in 1,3-dioxane. It is also of interest that $-\Delta G^0$(phenyl) is solvent dependent (Table 1, entries 1—3) suggesting the contribution of a polar (anomeric) effect which favors axial phenyl; calculation actually confirms the contribution of this effect[16a]. It is not yet, however, clear why introduction of the strongly electron-withdrawing *p*-CF_3 group does not affect $-\Delta G^0$ and, if anything, diminishes the influence of solvent (Table 1, entries 4—6). Perhaps the fact that the phenyl ring is the positive end of the F_3C—C_6H_4 dipole introduces a reverse anomeric effect[22] into 4,6-dimethyl-2-*p*-trifluoromethylphenyl-1,3-dioxane which compensates for the overall effect of the enhanced dipole.

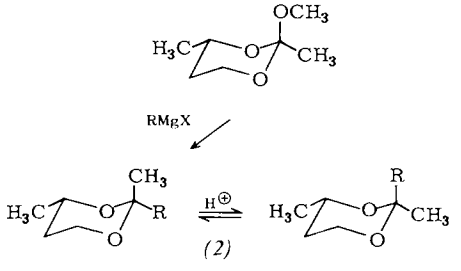
Table 1. Conformational energies $-\Delta G^0$ for 2-substituted 4,6-dimethyl-1,3-dioxanes of type *(1)* at 25 °C [17, 23].

No.	R	Solvent	$-\Delta G^0$ [kcal/mol]
1	C_6H_5	hexane	2.85 ± 0.02
2	C_6H_5	ether	3.12 ± 0.01
3	C_6H_5	CH_3CN	3.40 ± 0.03
4	*p*-F_3C—C_6H_4	hexane	3.08 ± 0.01
5	*p*-F_3C—C_6H_4	ether	3.16 ± 0.01
6	*p*-F_3C—C_6H_4	CH_3CN	3.30 ± 0.01
7	C_6H_5—C≡C	CCl_4	−0.32 ± 0.03
8	C_6H_5—C≡C	ether	0.00 ± 0.02
9	C_6H_5—C≡C	CH_3CN	0.59 ± 0.01
10	HC≡C	CCl_4	−0.21 ± 0.02
11	HC≡C	ether	−0.06 ± 0.02
12	HC≡C	CH_3CN	0.94 ± 0.01

Entries 7—9 (Table 1) show the operation of a substantial anomeric effect for the phenylethynyl group, and entries 10—12 imply the same for the ethynyl group itself; in a non-polar solvent (CCl_4) both groups prefer the axial conformation. In a polar solvent (acetonitrile) the equatorial preference of the phenylethynyl group is about 0.6 kcal/mol and that of ethynyl group 0.9 kcal/mol which, in view of the more crowded C-2 axial situation in the dioxane, would seem to be in agreement with the reported values of 0.2—0.41 kcal/mol[20,24] for axial ethynyl in cyclohexane. The concordance is satisfying, especially in view of the fact that the cyclohexyl value[24] was found indirectly assuming additivity of ΔG^0-values of geminal substituents—an assumption which has not always proved to be correct in 5,5-geminally di-

substituted 1,3-dioxanes[10f,25]. A preliminary determination[23] of the $-\Delta G^0$ value for the vinyl group has given a value of between 2 and 3 kcal/mol indicating that the group is somewhat "smaller" than methyl ($-\Delta G^0$ = 4 kcal/mol[17]) but substantially larger than ethynyl, as is to be anticipated from consideration of Dreiding models. Once again the value for the 2-substituted dioxane is substantially larger than that (1.35 kcal/mol) found for cyclohexane, again by an indirect method involving geminal disubstitution[26].

Table 2 shows $-\Delta G^0$-values for the 2,2-geminally disubstituted 1,3-dioxanes of type *(2)*[23,27]. Values calculated assuming additivity are indicated also. The agreement for methyl-ethyl and methyl-isopropyl is reasonable, especially if one considers that the ethyl and isopropyl groups engender additional methyl/methyl,



(2)

Table 2. Conformational energies $-\Delta G^0$ for 2,2-geminally disubstituted 2,4-dimethyl-1,3-dioxanes of type *(2)* at 25 C.

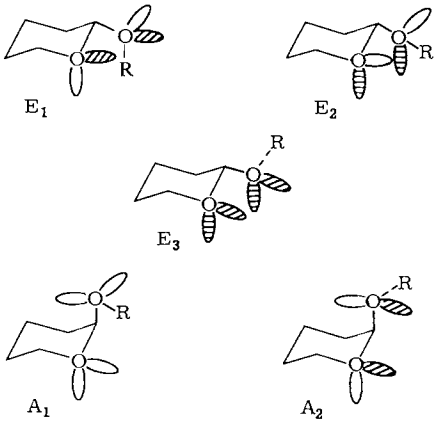
R	$-\Delta G^0$ [kcal/mol] found	calculated
C_2H_5	0.32 [27a], 0.28 [27b]	0.41 [27b]
$(CH_3)_2CH$	0.63 [27a], 0.54 [27b]	0.96 [27b]
C_6H_5	−2.42	−0.86 [a]

[a] Assuming additivity of ΔG^0 of CH_3 and R.

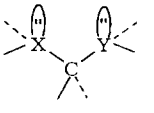
gauche interactions with the geminal methyl group when they are axially place. The vastly greater-than-calculated preference of phenyl for the axial position, in competition with methyl, has its parallel in 1-phenyl-1-methylcyclohexane[21]. In that compound it is due to the fact that the geminal methyl group forces the normally parallel equatorial phenyl group to be perpendicular, with resulting increased steric compression. In 1,3-dioxane this cannot, *per se*, be the reason for the non-additivity, since equatorial phenyl is already perpendicular (see above). However, it turns out[16a] that in cyclohexane, axial perpendicular phenyl causes a much more serious bending of the 2- and 6-equatorial hydrogens of the cyclohexane ring toward their axial partners (which is energetically quite unfavorable) than does equatorial perpendicular phenyl; it is the absence of this effect that makes the axial phenyl so highly favored in 2,4-dimethyl-2-phenyl-1,3-dioxane. The calculated value is 2.7 kcal/mol[16a]. The configurations of the compounds shown in Table 2 follow not only from the chemical shifts of the 2-alkyl substituents but also from the method of synthesis[28].

3. The Generalized Anomeric Effect

The preference of axial over equatorial C-1 alkoxy groups (aglycones) in pyranose sugars has been known for some years and has been called the "anomeric effect"[18,22,29,30]. A related effect has been seen in acyclic molecules such as dimethoxymethane, which has *gauche* conformations around the O—CH_2 bonds[31,32]. The solvent dependence of the effect has been studied in simple 2-alkoxytetrahydropyrans[33]; the axial preference of the alkoxy group is diminished in highly polar solvents, such as acetonitrile. It was concluded that dipole-dipole repulsion played a substantial part in the effect, and since component dipoles of C—N and C—O bonds are directed along the axis of the unshared electron pairs, the effect was rationalized[33] in terms of such "pair-pair repulsions". It was subsequently shown[34] that, of the five sterically reasonable conformations of a 2-alkoxytetrahydropyran, only one axial one (A_1) and one or two equatorial ones (E_1 and/or E_2) are appreciably populated, with A_1 (zero pair-pair repulsion) having preference over E_1 and E_2 (one pair-pair repulsion).



The idea was generalized to propose that the arrangement *(3)* was an unfavorable one, and, for obvious reasons, the effect was called[10c,35] the "rabbit ear effect".

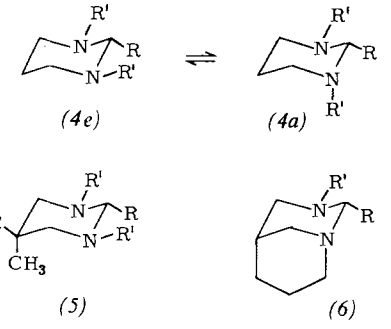


(3)

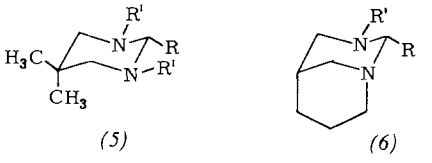
Since, however, this phenomenon is merely a more general manifestation of what has long been known as the "anomeric effect" (see above), *R. U. Lemieux*[22,36] and the author[10d] have agreed to call it "generalized anomeric effect".

A controversy has developed over the source of the effect. We had originally thought that it was responsible for the axial preference of one of the *N*-methyl groups in *N,N'*,2-trimethylperhydro-1,3-diazine[35] *[(4a)* ($R = R' = CH_3$); see also Ref.[36]]. More recent studies[37], using model compounds *(5)* and *(6)* ($R = R' = CH_3$) have indicated the magnitude of this axial preference to amount to about 0.55 kcal/mol (Table 3, entry 1).

On this basis, the generalized anomeric effect in *(4)* ($R = R' = CH_3$) would amount to about 1.2 kcal/mol, taking into account that 0.42 kcal/mol of the preference for *(4a)* is due to its entropy-of-mixing advantage



(4e) *(4a)*



(5) *(6)*

(DL-pair, RT ln 2) and that in the absence of the generalized anomeric effect, *(4e)* should be preferred by about 1 kcal/mol. However, dipole moment measurements of *(4)* ($R = H$)[38] did not confirm the preference for the *N*-axial conformation (Table 3, entries 2—5).

Table 3. Nitrogen inversion equilibria in 2-substituted *N,N*-dialkylperhydro-1,3-diazines of type *(4)*. The conformation energies ΔG^0 quoted are corrected by RT ln 2.

No.	R′	R	ΔG^0 [kcal/mol]	T[°K]
1	CH_3	CH_3	−0.13 [35, 37]	303
2	CH_3	H	0.54 [38]	
			0.65 [37]	196 ± 5
			0.4 [39]	
3	C_2H_5	H	0.62 [38]	
			0.63 [37]	192 ± 4
4	$(CH_3)_2CH$	H	> 1.8 [38]	
			0.83 [37]	200
5	$(CH_3)_3C$	H	large [38]	
6	$C_2H_5(CH_3)_2C$	H	1.03 [37]	200

NMR measurements[37,39] of *(4a)* ($R = H$; Table 3, entries 2—4, 6) at low temperatures (to stop ring inversion) support the dipole moment results at least for $R' =$ methyl or ethyl. (For secondary and tertiary R′ the agreement between dipole and NMR measurements is not good; but since both methods may be subject to systematic errors, it is not clear which one gives more accurate results.) Thus for *(4)* ($R = H$, $R' = CH_3$; Table 3, entry 2) the diequatorial conformer *(4e)* is preferred by 0.4—0.65 kcal/mol, which allows only about 0.5 kcal/mol for the generalized anomeric effect. Moreover, contrary to expectation, the equilibria *(4e)* ⇌ *(4a)* for $R = H$ and varying R′ seem to be independent of the polarity of the solvent[40]. The conclusion seems inescapable that the preference for *(4a)* ($R = R' = CH_3$) is caused in the main by something other than the generalized anomeric effect. Our best hypothesis, at present, is that perhydro-1,3-diazine, like 1,3-dioxane[19] is a "hyperchair", *i.e.* puckered up in the N-1/C-2/N-3 region (torsional angle 1-2-3-4 or 3-2-1-6 > 60°). The effect of this puckering is to make interaction of an equatorial group at C-2 with an equatorial substituent on nitrogen larger than the corresponding interaction with the group on nitrogen axial.

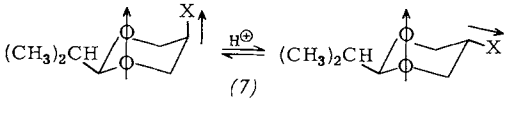
Wolfe et al.[41] have recently performed an *ab initio* calculation on the hypothetical fluoromethanol molecule, F—CH_2—O—H, and find the *gauche* conformation preferred over the *anti*. While this result might have been formally predicted on the basis of repulsion of unshared pairs, the calculation indicates no such repulsion but suggests that the preference for the *gauche* conformation rests on a dominant nuclear-electron attraction involving the C—F and C—O *bond* electrons which is greater when these electrons are *gauche* than when they are *anti*. *Wolfe et al.* have therefore rejected the "rabbit-ear" picture of the generalized anomeric effect as being misleading; specifically they say that their calculation indicates that the "effect cannot be ascribed in any straightforward way to coulombic interaction." Nevertheless, it seems to be an experimental fact—based on the observed solvent effects mentioned earlier—that a classical dipole-dipole repulsion must, in many instances, form part of the anomeric and generalized anomeric effect.

Our present hypothesis is that the nuclear-electron attraction postulated by *Wolfe et al.*[41] as well as "classical" electrostatic repulsion both contribute to the generalized anomeric effect to a greater or lesser extent. There may be cases, such as the *N,N*′-dialkylperhydro-1,3-diazines, where, as judged from the absence of solvent effects, classical dipole-dipole repulsion contributes little to the total effect; whereas in other cases, for example in 2-alkoxytetrahydropyrans, dipole-dipole repulsions must be substantial, as evidenced by a strong solvent response. It should be mentioned here that yet another interpretation of the anomeric effect in terms of double bond—no bond resonance (or its molecular orbital equivalent) has been given in the literature[42].

4. 1,3-Dioxanes with Hetero-substituents at C-5

4.1. Solvent Effects

Equilibria in 5-alkyl substituted 1,3-dioxanes of type *(7)* had been studied previously[43]; because of the absence



(7)

of the *syn*-axial hydrogens at O-1 and O-3, the $-\Delta G^0$ values for 5-substituents are substantially less than corresponding values in cyclohexane. For example, $-\Delta G^0$ for *(7)* (X = *tert*-butyl) is only 1.4 kcal/mol as compared to over 5 kcal/mol in cyclohexane, indicating that there is no appreciable compression of the alkyl group by the unshared electrons of the ring oxygens. These studies have been extended to hetero-substituted dioxanes[44]. Because of the existence of a ring dipole [in *(7)*] one might have expected that an electron-withdrawing substituent X in the axial position at C-5 would suffer destabilization by dipole-dipole repulsion, unless there is a compensating attraction, *e.g.* by intramolecular hydrogen bonding. The summary of findings in Table 4 indicates that this prediction is not uniformly borne out.

Table 4. Conformation energies $-\Delta G^0$ of 5-substituted 2-isopropyl-1,3-dioxanes of type *(7)* and cyclohexane derivatives RX [20] in ether at 25 °C; R = cyclohexyl.

X	CH_3	OH	OCH_3	$OCOCH_3$	F	Cl	Br	NO_2
	$-\Delta G^0$ [kcal/mol]							
(7)	0.80	0.41	0.83	0.0	−0.62	1.26	1.44	−0.38 [b]
RX	1.70	0.74 [a]	0.55	0.71	0.28	0.53	0.48	1.10

	CN	$COOCH_3$	CH_2OH	CH_2OCH_3	SCH_3	$SOCH_3$	SO_2CH_3	$COCH_3$
(7)	0.21	0.82	−0.27	0.05	1.7	−0.60 [b]	−1.16 [c]	0.53
RX	0.24	1.27	1.65 [44a]	1.40 [44b]	1.07	*ca.* 1.5	*ca.* 2.5	1.5 [44c]

[a] In 1,2-dimethoxyethane.
[b] In carbon tetrachloride.
[c] In cyclohexane.

The $-\Delta G^0$ values for hydroxyl are summarized in Table 5[25,44]; it is clear from infrared spectral studies[45] that axial hydroxyl in solvent cyclohexane is intramolecularly hydrogen bonded, which accounts for its stabilization. Association in more concentrated solution favors the equatorial isomer somewhat and displaces the equilibrium toward it. In strong hydrogen-donating or hydrogen-accepting solvents the intramolecular hydrogen bond of axial hydroxyl is destroyed or at least its advantage offset; ΔG^0-values for such solvents are similar to those for cyclohexanol, perhaps by an accidental compensation of various factors.

Table 5. ΔG^0 values for 5-hydroxy-2-isopropyl-1,3-dioxane *(7)* (X = OH) in various solvents at 25 °C; for comparison: values for 4-*tert*-butylcyclohexanol [45a].

Solvent	Conc. [mol/l]	ΔG^0 [kcal/mol] *(7)* (X = OH)	4-*t*Bu—$C_6H_{10}OH$
C_6H_{12}	0.05	+0.89 [a]	−0.60
	0.10	+0.86 [a]	−0.61
	0.20	+0.81 [a]	−0.61
$CHCl_3$		+0.91	
CH_3CN		+0.04	
$CH_3—O—CH_2—CH_2—O—CH_3$		−0.51	−0.74
$C_2H_5—O—C_2H_5$		−0.41	
$(CH_3)_2CHOH$		−0.71	−0.95

[a] At 80 °C.

A more unexpected situation is encountered for the halogen, methoxy and ethoxy substituents as summarized, for various solvents, in Table 6[46].

Table 6. ΔG^0 values for 5-halo-, 5-methoxy-, and 5-ethoxy-substituted 2-isopropyl-1,3-dioxanes of type *(7)* in various solvents at 25 °C.

Solvent (ε)	ΔG^0 [kcal/mol] F	Cl	Br	OCH_3	OC_2H_5
CCl_4 (2.2)	0.36	−1.40	−1.71	−0.90	−1.09
$(C_2H_5)_2O$ (4.2)	0.62	−1.26	−1.45	−0.83	−1.05
C_6H_6 (2.3)	0.83	−0.89	−1.17	−0.58	−0.82
$CHCl_3$ (4.7)	0.87	−0.94	−1.35	−0.16	−0.51
CH_3CN (37.5)	1.22	−0.25	−0.68	0.01	−0.19

Considering only the data in CCl_4, where dipole repulsion should be at a maximum, it is striking that axial fluorine is preferred over equatorial fluorine. The situation has some parallel in 1,2-difluoroethane, FCH_2CH_2F, in which the *gauche* isomers in the vapor have the same enthalpy as the *anti* conformation[47]. The reason for this apparent attractive interaction between fluorine atoms, or a fluorine and an oxygen atom, located *gauche* with respect to each other, is not known at this time; it may lie in a dominant nuclear-electron attraction similar to that in fluoromethanol[41].

It is of interest that whereas the oxygen-fluorine interaction is attractive, the oxygen-chlorine interaction is repulsive. A qualitatively similar situation is seen in the comparison of oxygen-oxygen (CH_3O group) with oxygen-sulfur (CH_3S group[48]. The data in Table 4 show that the ΔG^0 difference between CH_3S and CH_3O is greater at C-5 in dioxane (0.9 kcal/mol) than is is in cyclohexane (0.5 kcal/mol); the discrepancy is somewhat greater in solvent acetonitrile where, for the 5-substituted dioxane, $\Delta G^0_{OMe} = 0.0$ kcal/mol (Table 7) whereas $\Delta G^0_{SMe} = 1.1$ kcal/mol[48]. The enhanced repulsion of the second-row (and higher-row) atoms by the ring oxygens has also been reported by *Zefirov*[49] and is reasonably ascribed by him to an electron-electron repulsion involving the unshared electrons of the outer shell of the larger elements.

Comparing data in solvents carbon tetrachloride, ether, acetonitrile (Table 6) one sees the expected increase in proportion of the more polar equatorial isomers as the dielectric constant of the solvent increases. In the highest-dielectric solvent, acetonitrile, fluorine prefers the axial position by a factor of about 9; the ΔG^0-value for methoxy is nearly zero (suggesting absence of pair-pair repulsion between the ring oxygens and the methoxy oxygen) and the $-\Delta G^0$-value for chlorine (but not for bromine) is less than the value in the corresponding cyclohexyl halide (Table 4).

The effect of solvent on the equilibrium of the 5-halo- and 5-methoxy-1,3-dioxanes can be fairly well predicted

by a calculation employing classical electrostatic theory[46,50] taking into account the dipole and quadrupole moments of the substrates. Table 7 gives a comparison of the calculated and experimental ΔG^0-values; it should be stressed that the calculation only provides the differenece in ΔG^0 between solvents, and the way in which the calculated and experimental scales are made to coincide (the location of the origin of the scale, so to speak) is somewhat arbitrary. It is of interest that good agreement between calculated and experimental values is obtained at least in the case of the halogens (the

Table 7. Calculated and experimental $-\Delta G^0$-values [kcal/mol] for 5-halo- and 5-methoxy-2-isopropyl-1,3-dioxanes of type *(7)* in various solvents at 25 °C.

	X	F		Cl		Br		OCH_3	
Solvent	calc.	obs.		calc.	obs.	calc.	obs.	calc.	obs.
Vapor	0.6	—		2.2	—	.5	—	1.25	—
CCl_4	−0.37	−0.36		1.41	1.40	1.75	1.71	0.80	0.90
Et_2O	−0.78	−0.62		0.90	1.26	1.26	1.45	0.47	0.83
$CHCl_3$	−0.84	−0.87		0.85	0.94	1.21	1.35	0.43	0.16
CH_3CN	−1.43	−1.22		0.29	0.25	0.68	0.68	0.08	−0.01

case of methoxy is complicated by its potential conformational inhomogeneity) and that it is predicted that in the vapor phase, 5-fluoro-2-isopropyl-1,3-dioxane will be more stable when the fluorine is equatorial—a prediction which we hope to test.

It is clear from Table 6 that benzene does not fit into the treatment: although its dielectric constant is i ilar to that of carbon tetrachloride, the ΔG^0-values in the two solvents are quite different, benzene behaving as a more polar solvent than it actually is, as has been found elsewhere[51]. Chloroform also behaves anomalously toward solute 5-methoxy-2-isopropyl-1,3-dioxane, whose axial configuration is preferred in that solvent more than one would expect on consideration of dielectric constant (compare solvents ether and chloroform in Table 6); however, chloroform does not seem to show anomaly toward the halodioxanes (Tables 6 and 7). Solvent anomalies will form the topic of the next section.

4.2. Abnormal Solvent Effects

A more extensive study of solvent effects in the equilibria of the 5-methoxy- and 5-ethoxy-2-isopropyl-1,3-dioxanes *(7)* ($X = OCH_3$ or OC_2H_5) is shown in Table 8[52]. Since correlation of the data in terms of the dielectric constant ε or the usual function $(\varepsilon - 1)/(2\varepsilon + 1)$ proved unsuccessful, we decided to plot the ΔG^0-values against the solvatochromic energies E_T (30) of *Dimroth* and *Reichardt*[53,54]. The plot for the methoxy derivative is shown in Fig. 1 (a very similar plot was obtained for the ethoxy derivative) and corresponding plots for the halogen compounds are shown in Fig. 2.

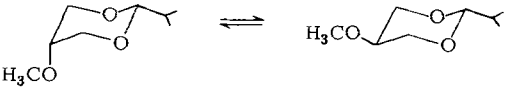
There is a good linear correlation if one excepts the data for methanol (not actually shown on the plots because they would have required reducing the scale) and with some provisos involving benzene, toluene, chloroform, deuteriochloroform and methylene chloride. The lack of correlation for methanol is not surprising considering

Table 8. Conformation energies $-\Delta G^0$ in 5-methoxy- and 5-ethoxy-2-isopropyl-1,3-dioxanes of type *(7)* in various solvents at 25 °C; correlation with the solvatochromic energies E_T (30).

No.	Solvent	ε	$-\Delta G^0$ [kcal/mol] CH_3O	C_2H_5O	E_T(30) [kcal/mol]
1	*n*-hexane	1.9	1.06	1.24	30.9
2	cyclohexane	2.0	1.03	1.23	31.2
3	CCl_4	2.2	0.90	1.09	32.5
4	C_6H_6	2.3	0.58	0.82	34.5
5	$C_6H_5CH_3$	2.3	0.71	0.94	33.9
6	$C_6H_5C(CH_3)_3$	2.3	0.83	1.01	33.7 [a]
7	$C_6H_3(CH_3)_3$	2.2	0.87	1.12	33.1 [a]
8	$(C_2H_5)_2O$	4.2	0.83	1.05	34.6
9	$CHCl_3$	4.7	0.16	0.51	39.1 [a]
10	$CDCl_3$	4.7	0.19	0.51	39.0 [a]
11	CH_3CCl_3	7.0	0.58	0.82	36.2
12	THF	8.2	0.65	0.86	37.4
13	CH_3COCH_3	21.4	0.34	0.56	42.2
14	$C_6H_5NO_2$	34.5	0.20	0.38	42.0
15	CH_3CN	37.5	0.01	0.19	46.0
16	CH_3OH	33.7	0.03	—	55.5

[a] *C. Reichardt*, Liebigs Ann. Chem. *752*, 64 (1971). The difference between $CHCl_3$ and $CDCl_3$ is real.

the strong specific hydrogen bonding interactions with this solvent which do not necessarily parallel E_T (which is a measure of solvent "polarity"). Chloroform deviates seriously only for the alkoxydioxanes, not for the halogen derivatives.



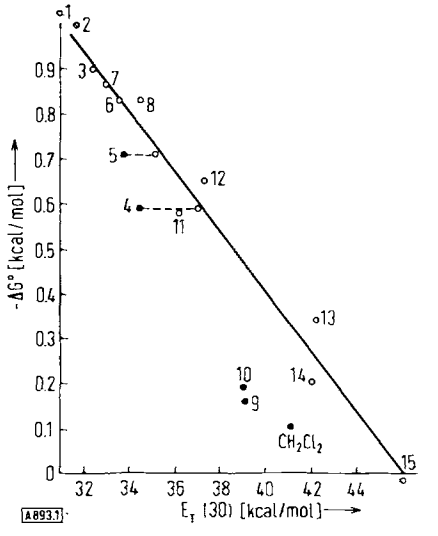


Fig. 1. Correlation between $-\Delta G^0$-values and solvatochromic energies E_T (30) for 2-isopropyl-5-methoxy-1,3-dioxanes *(7)* ($X = CH_3O$) in various solvents. The numbers refer to those in Table 8. Correlation coefficient $r = 0.988$.

It is usually believed that deviations from expected solvent behavior in the case of chloroform are due to hydrogen bonding, but we reject this hypothesis for several reasons: 1. Deuteriochloroform, though forming a less strong hydrogen bond than chloroform, deviates to about the same extent (Fig. 1). 2. Methylene chloride, which is a much less powerful hydrogen bonding solvent than chloroform is also anomalous (Fig. 1). 3. If hydrogen bonding were a major cause of the chloroform anomaly, one would expect the equatorial (less polar but more easily hydrogen bonded) alkoxy group

to be preferred, *i.e.* the chloroform point should lie above the correlation line in Fig. 1 (the methanol point does, indeed, lie above it). In fact, it lies below. We rather think that the anomaly has to do with the detailed (and as yet unknown) solvent structure of chloroform

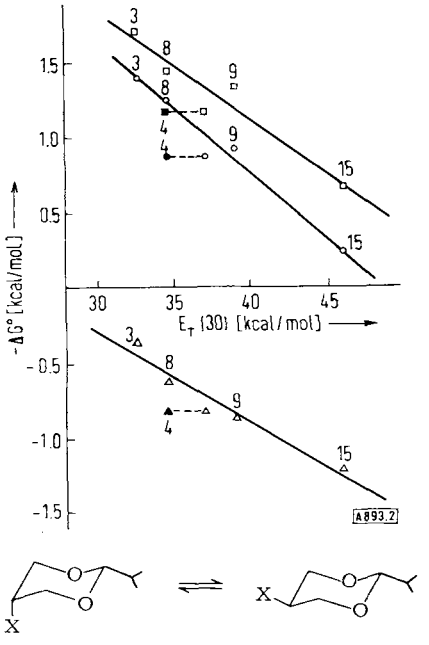


Fig. 2. Correlation between $-\Delta G^0$-values and solvatochromic energies E_T (30) for 2-isopropyl-5-halo-1,3-dioxanes of type *(7)* in various solvents. The numbers refer to those given in Table 8. (—△—△—) X=F, $r=0.972$ (—○—○—) X=Cl, $r=0.984$; (—□—□—) X=Br, $r=0.950$.

which may also account for its relatively high E_T value and the well-known fact that it is such a good solvent for polar solutes.

As far as aromatic solvents go, it is interesting (Fig. 1) that benzene, and, to a lesser extent, toluene, behave anomalously whereas mesitylene and *tert*-butylbenzene display near-normal behavior. In fact, the line fit for benzene and toluene can be much improved by changing their true E_T values of 34.5 and 33.9 to "adjusted" values of 37.1 and 35.3 respectively. It should be stated at this point that the correlation lines of Fig. 1 and Fig. 2 were drawn with these "adjusted" E_T values; both the "true" E_T points (black circles) and the adjusted points (open circles) are shown on the diagram. In Fig. 1, $CHCl_3$, $CDCl_3$ and CH_2Cl_2 have also been omitted from the correlation. It is clear that the correlation would be less good if the black points had been included; for example, for methoxy the correlation coefficient including *all* points is 0.917, and that including the "true" values for benzene and toluene, but not the halocarbons, is 0.963, as compared to a value of 0.988 when the adjusted values are used.

The $-\Delta G^0$ (OCH_3) values may provide a solvent scale which is more appropriate than existing scales.

Fig. 3 shows a plot of log k *vs.* E_T (30) for the rate of reaction

$$(n\text{-}C_3H_7)_3N + CH_3I \xrightarrow{k} (n\text{-}C_3H_7)_3\overset{\oplus}{N}CH_3 + I^{\ominus}$$

in eleven different solvents[55]. (Only those solvents for which $-\Delta G^0$ (OCH_3) values were also available have been included for reasons indicated below.) The correlation coefficient of 0.924 is quite good; if a wider array of solvents is included[56], the correlation coefficient drops somewhat, to 0.879. It had previously been noted[57] that the rates of Menshutkin reactions do not always parallel the dielectric constant of the solvent although, *grosso modo*, the reaction, involving a highly polar transition state, is faster in more polar solvents. In particular, benzene and chloroform had previously been seen to be "faster" solvents than their dielectric constants warrant. Fig. 9 suggests that correlation with E_T (30), in contrast, is quite reasonable. Again it may be

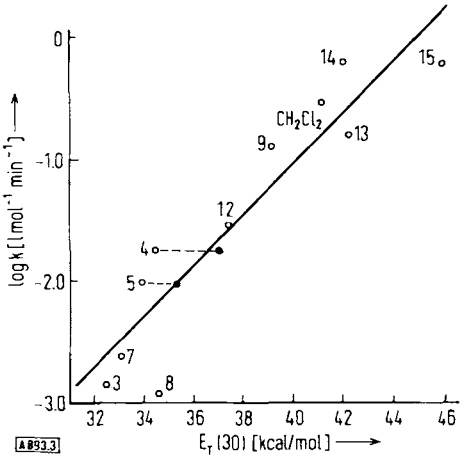


Fig. 3. Correlation between log k (Menshutkin reaction) and solvatochromic energies E_T (30) [55]. The numbers refer to those in Table 8. $r=0.924$.

noted that using "adjusted" (see above) values for benzene and toluene (solid circles) gives better correlations than "true" values (open circles; the open circle values were used in the construction of the correlation line). That the "adjusted" values give better correlations in both Fig. 3 and Fig. 1 suggests that a direct plot of log k (Menshutkin) *vs.* $-\Delta G^0$ (OCH_3) might give a better correlation than log k *vs.* E_T *without* the artifical device of adjusting the scale parameters for the aromatics. Fig. 4 bears out this contention and suggests that $-\Delta G^0$ (OCH_3) may indeed provide a good solvent scale for rates, in different solvents, of a reaction which involves a very polar transition state, such as the Menshutkin reaction.

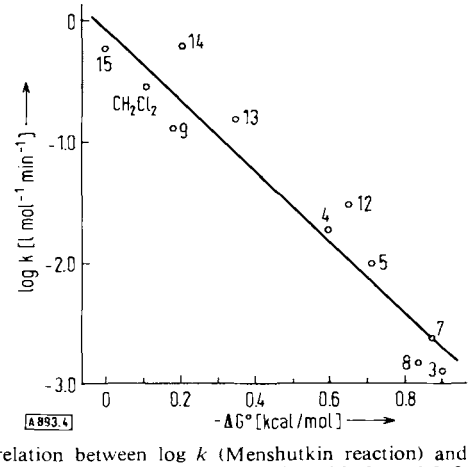


Fig. 4. Correlation between log k (Menshutkin reaction) and $-\Delta G^0$ (OCH_3). The numbers refer to those in Table 8. $r=0.958$.

One can only speculate as to the cause of the solvent anomaly for benzene and toluene which is not paralleled by *tert*-butylbenzene and mesitylene. We believe that the phenomenon is related to the extent of penetration of the aromatic molecule into the cavity formed by the solute. With a planar dye molecule (basis of E_T scale) or a sterically hindered solvent (*tert*-butylbenzene, mesitylene), this penetration may be low. For a sickle-shaped molecule, such as a 5-alkoxy- or 5-halo-1,3-dioxane and a solvent with flat molecules, such as benzene, a few solvent molecules may penetrate the solute cavity and may orient themselves in such a fashion as to assume dielectric properties different from those of the bulk solvent with its randomly oriented molecules. (For example, benzene may have a high microscopic dielectric constant along the direction of its π-electrons, *i.e.* at right angles to the plane of the ring.) These speculations remain to be supported by independent corroboration; the high polarizability of the aromatic solvents in their respective molecular planes may also be of significance.

4.3. 1,3-Dioxanes Containing 5-Nitro, 5-Acetyl, 5-Methylsulfinyl, and 5-Methylsulfonyl Groups

The ΔG^0-values for compounds of type *(7)* containing nitro, cyano and carbomethoxy groups in solvent acetonitrile are 1.0, 0.55 and −0.22 kcal/mol, respectively, compared to 0.38, −0.21 and −0.82 kcal/mol in less polar solvents (Table 4). The solvent effect is typical and the value for carbomethoxy seems unexceptional when compared to that of methyl (Table 4). The axial preference for CN in solvent acetonitrile suggests a net attraction between the cyano group and the ring oxygens. In this context it might be recalled that succinonitrile prefers the *gauche* conformation in the liquid phase[58].

In the case of the 5-nitro-2-isopropyl-1,3-dioxanes, a study[59] of the ultraviolet absorption of the two isomers disclosed a small but reproducible difference in λ_{max}, the equatorial isomer absorbing at 282 nm, the axial at 278 nm. A similar difference was found with the 5-methyl-5-nitro-2-isopropyl-1,3-dioxane isomers. The shift is reminiscent of that observed with simple nitro compounds when the solvent is changed from a non-polar one, such as hexane, to a polar one, such as ether[60]. The 282-nm absorption is due to an $n\rightarrow\pi^*$ transition and its shift to lower wavelengths is explained by a stabilization of the ground state by solvation of the (unshared) n-electrons. The transition state is not stabilized by this solvation (though, by the operation of the Franck-Condon principle, it must still have solvent associated with it). As a result, the energy gap for the $n\rightarrow\pi^*$ transition widens in polar solvents.

Applying these ideas to the present case, we may hypothesize that, in the case of the axial nitro compound, the polar O—C—O region of the dioxane ring provides "internal solvation" for the n-electrons of the oxygens of the NO_2-group; no corresponding solvation can occur with the equatorial isomer for steric reasons.

The energetic situation is depicted in Fig. 5; the difference between 278 and 282 nm translates itself into 1.5 kcal/mol of ground-state stabilization. It is assumed (Fig. 5) that the excited state is of the same energy for the two isomers; indeed, the absorption due to the $\pi\rightarrow\pi^*$ transition at 213.5 nm is exactly the same for the two. Since ΔG^0 for nitrocyclohexane is −1.11 kcal/mol[20] (cf. Table 4) the change in passing from the

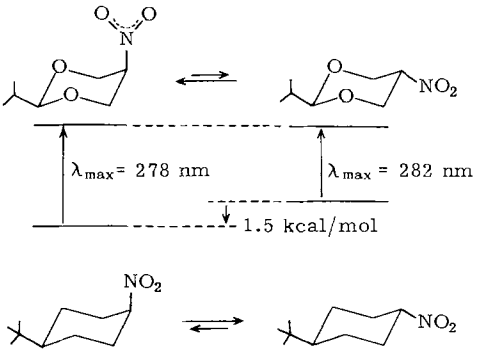


Fig. 5. Energetic situation in 5-nitro-2-isopropyl-1,3-dioxane (in acetonitrile) and 1-*tert*-butyl-4-nitrocyclohexane.

cyclohexane to the 1,3-dioxane system is 2.1 kcal/mol favoring the axial isomer. If 1.5 kcal/mol of this difference is due to "internal solvation" of the axial nitro group as indicated in Fig. 5, only 0.6 kcal/mol remain to be explained, and this can be easily accounted for by absence of the *syn*-axial hydrogen interactions which occur in axial nitrocyclohexane.

A similar, though perhaps somewhat less clear-cut situation is found in the 5-acetyl compound. Its ΔG^0-value, 0.53 kcal/mol in ether, 0.28 kcal/mol in acetonitrile is substantially smaller than the cyclohexane value of 1.5 kcal/mol and there is a shift in the absorption maximum from 281 nm in the equatorial isomer (solvent: cyclohexane) to 273 nm in the axial[61].

However, the most dramatic change is found in the methylsulfinyl and methylsulfonyl groups which show an equatorial preference of about 1.5 kcal/mol (RSO) and 2.5 kcal/mol (RSO_2) in cyclohexane, which is changed to an axial preference of 0.6 kcal/mol (CH_3SO) and 1.1 kcal/mol (CH_3SO_2), respectively, at C-5 in the dioxane[48]. Here, also, the large stabilization of the axial isomer reflects itself in the ultraviolet spectrum of the sulfoxide, which shows a change from the normal maximum (probably due to an $n\rightarrow d$ transition) at 208 nm, $\varepsilon = 3390$, to 202.5 nm, $\varepsilon = 1490$. (No corresponding change is seen in the *cis*- and *trans*-4-*tert*-butyl-1-methylsulfinylcyclohexanes, both of which absorb at 208 nm with the same intensity.) In the axial methyl sulfone, the long-range [H—CH_2SO_2C—H] coupling constant suggests that the methyl group is turned toward the *inside* of the ring. These findings suggest a strong electrostatic interaction (C—$O^-\cdots S$—O^-) between the axial sulfoxide and sulfone functions and the ring oxygens.

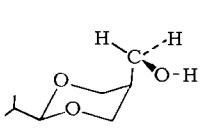
5. Hydrogen Bonding and Energy Minimization

Returning to Table 4 we have not yet discussed the axial preference of the hydroxymethyl group. It was at

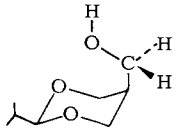
first believed[62] that this, like the corresponding preference of the OH-group, was due to intramolecular hydrogen bonding. The similarity of the ΔG^0 values for hydroxymethyl and methoxymethyl makes such an explanation unlikely; in any case, infrared studies disclosed the complete absence of any intramolecular hydrogen bond in *cis*-2-isopropyl-5-hydroxymethyl-1,3-dioxane *(8)*[63-65].

This finding is surprising, since the acyclic model, 3-methoxy-1-propanol, shows strong intramolecular hydrogen bonding[66]. Three hypotheses suggested themselves to explain the absence of bonding in *(8)*: 1) The CH_2OH group is turned outward (A_1) because the oxygen atom is too crowded inside the ring. 2) The OH is either turned upward (A_2) or outward (A_1) because of overriding dipole-dipole repulsion involving the unbonded ring oxygen dipole and the C—O—H dipole in the (disfavored) hydrogen bonded form A_3. 3) Eclipsing of the H—O—CH_2—C-5 and O—CH_2—C-5—C-4 segments in A_3 is too severe in the bonded form to allow bonding.

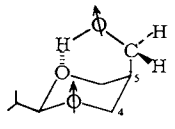
To test these hypotheses in turn, we synthesized the tertiary alcohol *(9)* in which now the oxygen should be



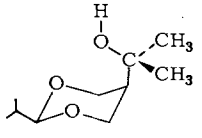
(8) A_1



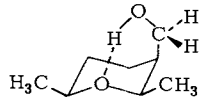
(8) A_2



(8) A_3



(9)



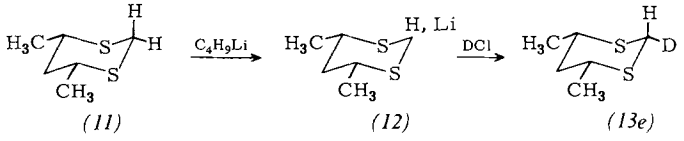
(10)

favored inside the ring, since the alternative conformations with methyl inside the ring are known not to be favorable[43]. *(9)* did show intramolecular hydrogen bonding, but the bonded conformation was of very low population, as indicated by the low intensity of the IR-band due to the "hydrogen bonded" hydroxy group. We conclude that crowding of the oxygen over the ring is not the major factor preventing hydrogen bonding in *(8)*.

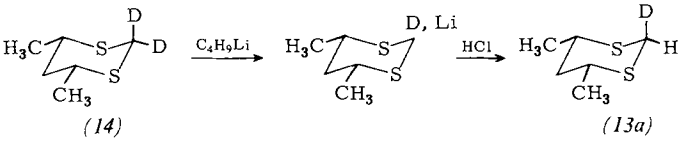
We next synthesized[67] the tetrahydropyran derivative *(10)*. This compound did show a strong intramolecularly bonded hydroxyl in the OH-stretching region of the infrared. The main difference between *(10)* and *(8)* is the absence of the second oxygen in the ring. It would therefore appear that dipole-dipole repulsion in the hydrogen bonded conformation of *(8)* is mainly responsible for the absence of an intramolecular hydrogen bond, with non-bonded repulsion in the "O-inside" conformation and bond eclipsing perhaps contributing in a minor way to the depopulation of that conformation.

6. Highly Stereoselective H-D Exchanges

We will now turn to a rather different topic. In the course of our work on alkyl-substituted[68] and hetero-substituted[69] 1,3-dithianes, we had occasion to apply the Corey-Seebach reaction[70] to an anancomeric[71] dithiane, namely the *cis*-4,6-dimethyl derivative *(11)*. Upon treatment of the resulting lithium derivative with



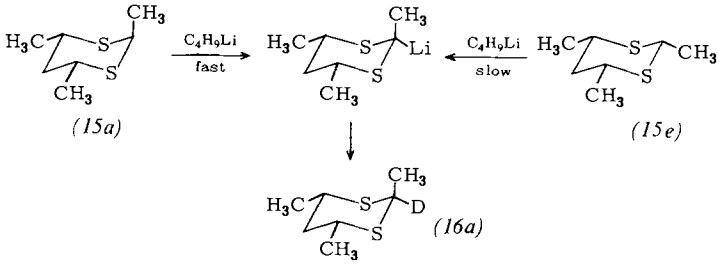
(11) *(12)* *(13e)*



(14) *(13a)*

DCl, we were surprised to find formation of the equatorial deuterium compound *(13e)* *to the exclusion* of the axial isomer *(13a)*. The latter was the exclusive product of lithiation of the 2,2-dideuterio compound *(14)* followed by treatment with HCl; comparison of the NMR spectra of *(13e)* and *(13a)* with those of synthetic mixtures of the two isomers indicated cross-contamination of less than 1%, probably less than 0.5%[72].

Lithiation of the isomeric trimethyl-1,3-dithianes *(15a)* and *(15e)* followed by treatment with DCl yielded exclusively the deuterated *trans,trans* isomers *(16a)*[72]. Since the result is the same in ether and in 1,2-dimethoxyethane[73] it would appear that we are dealing with a carbanion pair which prefers the equatorial conformation to the near exclusion of the axial and whose subsequent protonation occurs with retention of conformation[74]. Alkylation of the lithium derivative *(12)* with methyl iodide also proceeds exclusively from the equatorial side and yields *(15e)* free of *(15a)*[72].



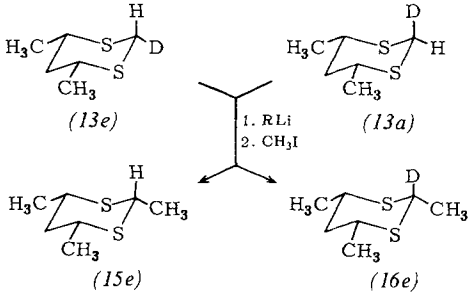
(15a) *(15e)* *(16a)*

Even qualitative observations show clearly that the lithium derivative of *(15a)* (involving removal of equatorial H-2) is formed much more rapidly than that from *(15e)* (removal of axial H-2). This observation suggests that not only is the equatorial lithium derivative preferred thermodynamically (see above)[*]—

[*] We assume that axial and equatorial RLi are readily interconverted by anion inversion.

more so than in 4-*tert*-butylcyclohexyllithium[75] but also that abstraction of equatorial hydrogen is more facile kinetically. In the case of 2-*tert*-butyl-*cis*-4,6-dimethyl-1,3-dithiane, in fact, only the stereoisomer with axial *tert*-butyl would form the lithium derivative readily, but the latter, on treatment with HCl, would return exclusively the axial *tert*-butyl isomer, despite the considerable tendency for the 2-*tert*-butyl group to be equatorial ($-\Delta G^0 = 2.7$ kcal/mol[68]).

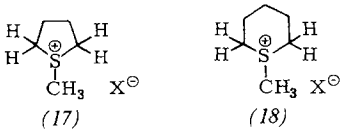
The thermodynamic tendency for the metal to be equatorial is obviously quite large, perhaps as high as 4—5 kcal/mol. Possibly of greater interest, however, is the kinetic tendency for a highly stereoselective hydrogen abstraction, since such highly stereoselective abstractions are common in enzyme chemistry[76]. To gauge the extent of the kinetic preference, we performed[77] the following experiment: The lithium derivatives obtained from *(13e)* and *(13a)* were methylated, so that there could be no confusion with starting material which had accidentally escaped lithiation. The methylated product *(15e, 16e)* was analyzed for deuterium mass spectrometrically. It should be noted that whereas there should be a kinetic preference for abstraction of



(13e) *(13a)* *(15e)* *(16e)*

equatorial H or D in both *(13a)* and *(13e)*, the isotope effect should counteract this preference in the case of *(13e)* but reinforce it in the case of *(13a)*. In fact, the product from *(13e)* retained 21 ± 5% deuterium (axial attack, 79 ± 5% equatorial attack) whereas that from *(13a)* contained 95 ± 2% deuterium (equatorial attack). From these figures one may calculate[77] a selectivity factor of *ca.* 9 favoring equatorial hydrogen abstraction and an isotope effect of *ca.* 2.5 (which appears reasonable).

For a "simulation" of enzyme systems, it would be desirable to have a reaction of higher stereoselectivity in the abstraction step. A highly stereoselective exchange reaction has recently been reported by *Fava et al.*[78]: The five-membered sulfonium salt *(17)* was reported to exchange only *two* of its four α-hydrogens (along with the three methyl hydrogens) with D_2O and base at 80°C. In an attempt to investigate this reaction in more detail, we studied the sulfonium salt *(18)* hoping to locate the hydrogens exchanged by proton NMR.



(17) *(18)*

This hope was not fulfilled, but we did succeed[79] in analyzing the exchange mass spectrometrically as a very clean succession of four pseudo-first-order reactions of relative rate constants 4.40:3.00:1.83:0.84. Interpretation of these constants requires assumptions as to the secondary isotope effect, if any, and as to the stereochemistry of the exchange itself. Assuming an isotope effect of unity and exchange with retention of configuration leads to the conclusion that the two rate constants for exchange of the α-hydrogens stand in a ratio of 3:1. This ratio may be as low as 1:1 or as high as 5:1 if one allows for a possible secondary isotope effect of ±30%.

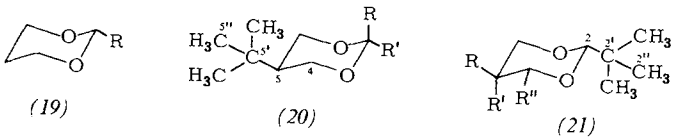
Since the exchange in the six-membered ring *(18)* was not very selective, we reinvestigated[79] the five-membered ring *(17)* also and found $k_1:k_2:k_3:k_4 = 5.66:3.00:0.48:0.22$. With the same assumption as above this yields relative rate constants of 30:1 for exchange of the α-hydrogens by D_2O in NaOH at 40°C, a ratio which is substantial if not quite as large as reported[78] by the previous investigators.

The reason why the exchange is more selective in the five-membered ring *(17)* than in the six-membered ring *(18)* is not obvious at the present time; it must be stressed that the assumption of exchange with retention may be wrong and that any exchange with inversion will serve to lower the observed ratios since it puts the second hydrogen in the place of the first where it will then exchange rapidly. Thus our rate ratios represent lower limits and it is possible that the lesser selectivity in the six-membered ring is only apparent and reflects a higher degree of exchange with inversion rather than retention in that ring compared to the five-membered one.

7. The Effect of a *tert*-Butyl Substituent on Ring Conformation

In 1955, *Winstein*[80] imparted considerable impetus to the study of conformational analysis in mobile systems when he proposed the use of a 4-*tert*-butyl substituent as a "holding group" in cyclohexane systems[80]. This trick has been used extensively since (for a review, see Ref.[81]), but recently the use of the *tert*-butyl group has been criticized (see Ref.[82] for references), since the *tert*-butyl group may (and, in some cases does) affect properties by distortional as well as through-space and through-bond effects.

This point has now been explored in several ways. In one investigation[82], 220-MHz NMR spectra of several 2-substituted 1,3-dioxanes of type *(19)* were analyzed; it was found that for substituents methyl, isopropyl, *tert*-butyl, and phenyl the vicinal coupling constants



(19) *(20)* *(21)*

were invariant at 12.4—12.5 Hz (4a/5a), 1.3 Hz (4e/5e), 5.0 Hz (4e/5a) and 2.6 Hz (4a/5e). The ^{1}H-NMR spectrum of the unsubstituted 1,3-dioxane at −135°C, *i.e.* well below its coalescence temperature, can be simulated very closely using the same coupling constants[83]. Thus, within the limits of error of this experi-

ment, the 2-alkyl groups have no palpable distortional effect; whatever effect might have gone undetected by the limits of accuracy of the simulation of the low-temperature spectrum must at least be the same for all alkyl groups.

Further evidence for the substantial absence of distortion comes from a study of ^{13}C-NMR spectra of a variety of 2-substituted 5-*tert*-butyl-1,3-dioxanes *(20)*[84]. The chemical shifts of C-4, C-5, C-5′ and C-5″ are tabulated in Table 9. Again there is no clear evidence for distortion, although the shift at C-5 for the 2-*tert*-butyl compound is somewhat different from that of the others, perhaps significantly so.

Table 9. Chemical shifts in the ^{13}C-NMR spectrum of various 2-substituted 5-*tert*-butyl-1,3-dioxanes *(20)*.

R	R′	−δ(TMS) [ppm] C-5	C-5′	C-5″	C-4
H	H	44.4 (44.5)	30.7 (31.3)	27.6 (27.0) [a]	68.5
CH_3	H	44.6	30.5	27.7	68.6
$(CH_3)_3C$	H	43.7	30.0	27.5	68.6
C_6H_5	H	44.0	30.6	27.9	69.3
CH_3	CH_3	44.2 (44.3)	31.0 (31.7)	27.5 (26.9) [a]	[60.1] [b]

[a] Values in parentheses are corrected for conformational inhomogeneity of the compounds in question.
[b] Not comparable.

In Table 10 are summarized effects of various 4- and 5-substituents on chemical shifts of a 2-*tert*-butyl group and its adjacent ring carbon in compounds of type *(21)*. Since the equatorial substituents at C-5 are in somewhat more crowded environment than those at C-2, one might have expected more palpable effects in this series which is more representative of substituted cyclohexanes. However, the data in Table 10 evidence no significant distortions at C-2 except in those cases where there is an axial substituent at C-5.

Table 10. Chemical shifts in the ^{13}C-NMR spectrum of 4- or 5-substituted 2-*tert*-butyl-1,3-dioxanes *(21)*.

R	R′	R″	−δ(TMS) [ppm] C-2	C-2′	C-2″
H	H	H	107.8	35.3	25.0
CH_3	H	H	107.7	35.3	24.9
$(CH_3)_3C$	H	H	107.2	35.0	25.0
H	H	CH_3	107.3	35.1	25.0
H	CH_3	H	108.1	35.3	24.7
CH_3	CH_3	H	108.4	35.0	25.2
H	$(CH_3)_3C$	H	108.6	35.2	25.1

Most recently, the structures of *trans*-4-*tert*-butylcyclohexyl *p*-bromobenzoate[85], the *cis*- and *trans*-4-*tert*-butylcyclohexyl *p*-toluenesulfonates[86] and *cis*-1-*p*-bromophenyl-4-*tert*-butylcyclohexane[87] have been studied by X-ray diffraction and, in some instances, compared with the structure of cyclohexane derivatives without *tert*-butyl substituents. While the *tert*-butyl group does undergo some bending and exerts slight compression on the ring hydrogens at C-3 and C-5, the studies suggest but very small deformations (not clearly outside experimental error limits) at C-1. It thus appears unlikely that the 4-*tert*-butyl group exercises a palpable distortional effect except in situations which are extremely sensitive to small geometric changes, *e.g.* in ^{19}F-NMR studies[88] and in chemical reactions involving highly compressed transition states or transition states with major changes, from the corresponding ground states, at C-1.

8. Conclusion

While conformational analysis in model systems for its own sake offers less of a challenge now than it did, say, twelve years ago, it continues to be an extremely useful tool in the investigation of more general chemical phenomena, such as non-bonded interactions between atoms, physical and chemical effects of unshared electron pairs, solvent effects and hydrogen bonding effects. Some hetero systems, notably those containing sulfur, provide a framework for potentially highly stereoselective reactions of possible biochemical import. Finally, the increasing importance of ^{13}C-NMR spectroscopy makes desirable a detailed investigation of all pertinent conformational factors affecting ^{13}C chemical shifts. We are continuing research in these various areas.

Collaboration with Professor David M. Grant, University of Utah, Professor Alan J. Jones, University of Alberta, and Professor Raymond J. Abraham, University of Liverpool is gratefully acknowledged. The work here described was carried out by a number of able coworkers: Mr. William F. Bailey, Dr. Harold Banks, Mrs. Janet E. Dennis, Dr. Nicholas Dennis, Dr. Slayton A. Evans, Dr. Armando A. Hartmann, Dr. Otmar Hofer, Dr. Moses Kaloustian, Mr. Laurence D. Kopp, Dr. Sorin Mager, and Dr. Jean M. McKenna. Financial support was provided by the National Science Foundation, the Petroleum Research Fund of the American Chemical Society, the Air Force Office of Scientific Research, the U.S. Army Research Office and the Warner-Lambert Pharmaceutical Corporation.

Received: January 24, 1972 [A 893 IE]
German version: Angew. Chem. *84*, 779 (1972)

[1] This article is based in large part on a lecture presented by the author at the 23rd IUPAC Congress, Boston, Mass. in July 1971. Original publication: XXIII International Congress of Pure and Applied Chemistry. Butterworths, London 1971, Vol. 7. p. 219ff. The article (with minor updating) is reproduced here with the permission of the International Union of Pure and Applied Chemistry.

[2] For a brief summary of *Barton's* and *Hassel's* contributions, see *E. L. Eliel*, Science, *166*, 718 (1969).

[3] For a translation of *Hassel's* pioneering paper in the field and a reprinting of *Barton's* corresponding publication; see *N. L. Allinger* and *E. L. Eliel:* Topics in Stereochemistry Interscience, New York 1971, Vol. 6.

[4] *E. L. Eliel, N. L. Allinger, S. J. Angyal,* and *G. A. Morrison:* Conformational Analysis, Interscience, New York 1965.

[5] *M. Hanack:* Conformation Theory, Academic Press, New York 1965.

[6] *J. McKenna:* Conformational Analysis of Organic Compounds, The Royal Institute of Chemistry Lecture Series, London 1966, No. 1.

[7] Plenary Lectures delivered at Symposium on Conformational Analysis, Brussels 1969: Pure Appl. Chem. *25*, 465 (1971).

[8] *G. Chiurdoglu:* Conformational Analysis, Academic Press, New York 1971.

[9] Lectures delivered at Symposium on Conformational Analysis, XXIIIrd International Congress, IUPAC, Boston 1971; Pure Appl. Chem. Suppl. Vol. 7 (1971).

[10] For previous reviews, see a) *F. G. Riddell*, Quart. Rev. Chem. Soc. *21*, 362 (1967); b) *C. Romers, C. Altona, H. R.*

Buys, and *E. Havinga*, Top. Stereochem. *4*, 39 (1969); c) *E. L. Eliel*, Kemisk Tidskr. *81*, No. 6/7, p. 22 (1969); d) *E. L. Eliel*, Accounts Chem. Res. *3*, 1 (1970); e) *E. L. Eliel*, Pure Appl. Chem. *25*, 509 (1971).

[11] *K. Pihlaja* and *S. Luoma*, Acta Chem. Scand. *22*, 2401 (1968).

[12] *R. M. Clay*, *G. M. Kellie*, and *F. G. Riddell*, personal communication.

[13] *K. Pihlaja* and *J. Jalonen*, Org. Mass Spectrom. *5*, 1363 (1971).

[14] *G. M. Kellie* and *F. G. Riddell*, Chem. Commun. *1972*, 42.

[15] a) *J. B. Lambert*, J. Amer. Chem. Soc. *89*, 1836 (1967); b) *H. R. Buys*, Rec. Trav. Chim. Pays-Bas *88*, 1003 (1969).

[16] a) *N. L. Allinger*, personal communication; cf. *N. L. Allinger*, *J. A. Hirsch*, *M. A. Miller*, and *I. J. Tyminski*, J. Amer. Chem. Soc. *91*, 337 (1969); b) *R. J. Ouellette*, personal communication.

[17] *F. W. Nader* and *E. L. Eliel*, J. Amer. Chem. Soc. *92*, 3050 (1970).

[18] *R. U. Lemieux* and *P. Chu*, Abstr. Pap. Amer. Chem. Soc. 133 Meeting, p. 31N (1958); *R. U. Lemieux* in *P. de Mayo:* Molecular Rearrangements. Interscience, New York 1964, p. 723ff.

[19] *A. J. de Kok* and *C. Romers*, Rec. Trav. Chim. Pays-Bas *89*, 313 (1970).

[20] *J. A. Hirsch*, Top. Stereochem. *1*, 199 (1967). For some more recent $-\Delta G^0$ values, see also *F. R. Jensen*, *C. H. Bushweller*, and *B. H. Beck*, J. Amer. Chem. Soc. *91*, 344 (1969).

[21] *N. L. Allinger* and *M. T. Tribble*, Tetrahedron Lett. *1971* 3259.

[22] Cf. *R. U. Lemieux*, Pure Appl. Chem. *25*, 527 (1971).

[23] *E. L. Eliel* and *W. F. Bailey*, unpublished observations.

[24] *R. J. Ouellette*, J. Amer. Chem. Soc. *86*, 3089 (1964).

[25] *R. M. Enanoza*, Ph. D. Dissertation, University of Notre Dame, Notre Dame, Ind. 1971; *E. L. Eliel* and *R. Enanoza*, J. Amer. Chem. Soc., in press.

[26] *R. J. Ouellette*, *K. Liptak*, and *G. E. Booth*, J. Org. Chem. *31*, 546 (1966).

[27] a) *E. L. Eliel* and *J. M. McKenna*, unpublished observations; b) *K. Pihlaja et al.*, Suom. Kemistilehti, *B43*, 171, 175 (1970).

[28] Cf. *E. L. Eliel* and *F. W. Nader*, J. Amer. Chem. Soc. *92*, 584 (1970).

[29] *J. T. Edward*, Chem. Ind. (London) *1955*, 1102.

[30] *S. J. Angyal*, Angew. Chem. *81*, 172 (1969); Angew. Chem. internat. Edit. *8*, 157 (1969); *J.-C. Martin*, Ann. Chim. [14] *6*, 205 (1971); *N. S. Zefirov* and *N. M. Shechtman*, Usp. Khim. *40*, 593 (1971).

[31] *V. M. Kubo*, Sci. Pap. Inst. Phys. Chem. Res. Tokyo *29*, 179 (1936).

[32] *K. Aoki*, J. Chem. Soc. Jap. *74*, 110 (1953).

[33] *E. L. Eliel* and *C. A. Giza*, J. Org. Chem. *33*, 3754 (1968); see also *C. B. Anderson* and *D. T. Sepp*, Tetrahedron *24*, 1707 (1968); *G. O. Pierson* and *O. A. Runquist*, J. Org. Chem. *33*, 2572 (1968).

[34] *A. J. de Hoog*, *H. R. Buys*, *C. Altona*, and *E. Havinga*, Tetrahedron *25*, 3365 (1969); *A. J. de Hoog* and *H. R. Buys*, Tetrahedron Lett. *1969*, 4175.

[35] *R. O. Hutchins*, *L. D. Kopp*, and *E. L. Eliel*, J. Amer. Chem. Soc. *90*, 7174 (1968).

[36] *H. Booth* and *R. U. Lemieux*, Can. J. Chem. *49*, 777 (1971).

[37] *E. L. Eliel*, *L. D. Kopp*, *J. E. Dennis*, and *S. A. Evans*, Tetrahedron Lett. *1971*, 3409.

[38] *R. A. Y. Jones*, *A. R. Katritzky*, and *M. Snarey*, J. Chem. Soc. *B 1970*, 131.

[39] *F. G. Riddell* and *D. A. R. Williams*, Tetrahedron Lett. *1971*, 2073.

[40] *J. E. Dennis* and *E. L. Eliel*, unpublished observation.

[41] *S. Wolfe*, *A. Rauk*, *L. M. Tel*, and *I. G. Csizmadia*, J. Chem. Soc. *B 1971*, 136.

[42] *C. Altona*, Ph. D. Thesis, University of Leiden 1964; cf. Ref. [10b] therein pp. 73—77.

[43] *E. L. Eliel* and *M. C. Knoeber*, J. Amer. Chem. Soc. *90*, 3444 (1968).

[44] *E. L. Eliel* and *M. K. Kaloustian*, Chem. Commun. *1970*, 290.

[44a] *E. L. Eliel*, *D. G. Neilson*, and *E. C. Gilbert*, Chem. Commun. *1968*, 360.

[44b] *G. W. Buchanan* and *J. B. Stothers*, Chem. Commun. *1967*, 1250.

[44c] *E. L. Eliel* and *M. C. Reese*, J. Amer. Chem. Soc. *90*, 1560 (1968).

[45] *N. Baggett*, *M. A. Bukhari*, *A. B. Foster*, *J. Lehmann*, and *J. M. Webber*, J. Chem. Soc. *1963*, 4157; *S. A. Barker*, *A. B. Foster*, *A. H. Haines*, *J. Lehmann*, *J. M. Webber*, and *G. Zweifel*, *ibid. 1963*, 4161.

[45a] *E. L. Eliel* and *E. C. Gilbert*, J. Amer. Chem. Soc. *91*, 5487 (1969).

[46] *R. J. Abraham*, *H. D. Banks*, *E. L. Eliel*, *O. Hofer*, and *M. K. Kaloustian*, J. Amer. Chem. Soc. *94*, 1913 (1972).

[47] *P. Klaboe* and *J. R. Nielsen*, J. Chem. Phys. *33*, 1764 (1960).

[48] *E. L. Eliel* and *S. A. Evans*, unpublished observations.

[49] *N. S. Zefirov*, *V. S. Blagoveshchensky*, *I. V. Kazimirchik*, and *N. S. Surova*, Tetrahedron *27*, 3111 (1971).

[50] *R. J. Abraham* and *G. Gatti*, J. Chem. Soc. *B 1969*, 961.

[51] *D. J. Sikkema*, Ph. D. Dissertation, University of Leiden 1969.

[52] *E. L. Eliel* and *O. Hofer*, unpublished observations.

[53] *K. Dimroth*, *C. Reichardt*, *T. Siepmann*, and *F. Bohlmann*, Liebigs Ann. Chem. *661*, 1 (1963).

[54] Reviews: *C. Reichardt*, Angew. Chem. *77*, 30 (1965); Angew. Chem. internat. Edit. *4*, 29 (1965); Lösungsmittel-Effekte in der Organischen Chemie. Verlag Chemie, Weinheim 1969.

[55] *C. Lassau* and *J.-C. Jungers*, Bull. Soc. Chim. Fr. *1968*, 2678.

[56] We thank Professor *C. Reichardt*, Marburg, Germany for making available to us a plot of these data.

[57] *E. L. Eliel* and *M. S. Newman* in: Steric Effects in Organic Chemistry. Wiley, New York 1956, p. 70.

[58] *W. E. Fitzgerald* and *G. J. Janz*, J. Mol. Spectrosc. *1*, 49 (1957).

[59] *E. L. Eliel*, *N. Dennis*, and *M. S. Kaloustian*, unpublished observations; see also *B. Kedzierski*, *H. Piotrowska*, and *T. Urbanski*, Chem. Ind. (London), *1971*, 1302.

[60] *N. S. Bayliss* and *E. G. McRae*, J. Phys. Chem. *58*, 1006 (1954).

[61] *E. L. Eliel* and *S. Mager*, unpublished observations.

[62] *J. Delmau*, *J.-C. Duplan*, and *M. Davidson*, Tetrahedron *23*, 4371 (1967).

[63] *R. Dratler* and *P. Laszlo*, Tetrahedron Lett. *1970*, 2607.

[64] *E. L. Eliel* and *H. D. Banks*, J. Amer. Chem. Soc. *92*, 4730 (1970).

[65] *J. Delmau*, personal communication, Nov. 5, 1969.

[66] *A. B. Foster*, *A. H. Haines*, and *M. Stacey*, Tetrahedron *16*, 177 (1961).

[67] *E. L. Eliel* and *H. D. Banks*, J. Amer. Chem. Soc. *94*, 171 (1972).

[68] *E. L. Eliel* and *R. O. Hutchins*, J. Amer. Chem. Soc. *91*, 2703 (1969).

[69] *A. A. Hartmann*, Ph. D. Dissertation, University of Notre Dame, Notre Dame, Ind. 1971.

[70] Cf. *D. Seebach*, Synthesis *1*, 17 (1969).

[71] *M. Anteunis*, *D. Tavernier*, and *F. Borremans*, Bull. Soc. Chim. Belg. *75*, 396 (1966).

[72] *A. A. Hartmann* and *E. L. Eliel*, J. Amer. Chem. Soc. *93*, 2572 (1971).

[73] *E. L. Eliel* and *A. Abatjoglou*, unpublished observations.

[74] Similar observations have been made by *T. Durst* and by *M. Nishio* (personal communications).

[75] *W. H. Glaze*, *D. M. Selman*, *A. L. Ball*, and *L. E. Bray*, J. Org. Chem. *34*, 641 (1969).

[76] *D. Arigoni* and *E. L. Eliel*, Top. Stereochem. *4*, 127 (1969).

[77] *E. L. Eliel*, *A. Abatjoglou*, and *A. A. Hartmann*, J. Amer. Chem. Soc. *94*, 4786 (1972).

[78] *G. Barbarella*, *A. Garbesi*, and *A. Fava*, Helv. Chim. Acta *54*, 341 (1971).

[79] *E. L. Eliel* and *O. Hofer*, unpublished observations.

[80] *S. Winstein* and *N. J. Holness*, J. Amer. Chem. Soc. *77*, 5562 (1955).

[81] *E. L. Eliel*, *N. L. Allinger*, *S. J. Angyal*, and *G. A. Morrison:* Conformational Analysis. Interscience, New York 1965, p. 48ff.

[82] *H. R. Buys* and *E. L. Eliel*, Tetrahedron Lett. *1970*, 2779.

[83] *E. L. Eliel* and *W. F. Bailey*, unpublished observation.

[84] *A. J. Jones*, *E. L. Eliel*, *D. M. Grant*, *M. C. Knoeber*, and *W. F. Bailey*, J. Amer. Chem. Soc. *93*, 4772 (1971). Regarding ^{13}C-NMR spectra of 1,3-dioxanes, see also *G. M. Kellie* and *F. G. Riddell*, J. Chem. Soc. *B 1971*, 1030.

[85] *R. Parthasarathy*, *J. Ohrt*, *H. B. Kagan*, and *J. C. Fiaud*, Tetrahedron *28*, 1529 (1972).

[86] *V. James* and *J. McConnell*, Tetrahedron *27*, 5475 (1971); *P. L. Johnson*, *J. P. Schaefer*, *V. J. James*, and *J. F. McConnell*, *ibid.*, in press; *P. L. Johnson*, *C. J. Cheer*, *J. P. Schaefer*, *V. J. James*, and *F. H. Moore*, *ibid.*, in press.

[87] *G. Berti*, *B. Macchia*, and *F. Macchia*, Tetrahedron Lett. *1971* 3205.

[88] *E. L. Eliel* and *R. J. L. Martin*, J. Amer. Chem. Soc. *90*, 682 (1968).

Polycrystalline Inorganic Fibers — Production, Properties, Applications[**]

By Gerhard Winter[*]

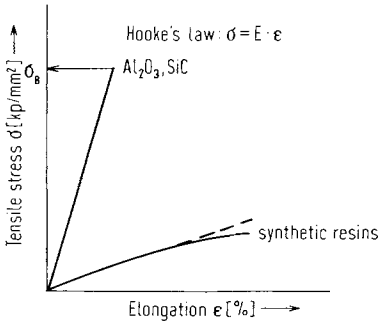
This progress report ends with the sentence: In the opinion of many experts, we are entering an "age of inorganic fibers". An attempt is made in the article to outline the present stage of development and the outlook for one of the most interesting fields of modern materials science.

1. Introduction

The technology of fiber-reinforced materials is one of the fastest-expanding fields of modern materials science. From the number of publications and patents, it can be seen that interest in these materials has avalanched during recent years. This development is based on a wide range of inorganic fibrous materials with extraordinary properties, a large part of this range being constituted by polycrystalline inorganic fibers.

2. Definitions

Certain mechanical properties will often arise in the following discussion. It is therefore convenient to recall the meanings of the various physical properties (Fig. 1).



Tensile strength: σ_B [kp/mm²]
Specific strength: $\frac{\sigma_B}{\varrho}$ [km], ϱ = density
Specific modulus: $\frac{E}{\varrho}$ [km], $E = \frac{\sigma}{\varepsilon}$ = modulus of elasticity
Bending moment of a round rod: $M \sim \frac{E \pi d^3}{32}$; d = diameter
A900.1

Fig. 1. Stress-strain diagram of solids. Hooke's law, definitions.

If a body is stressed by application of a tensile stress σ, an elongation ε occurs. σ and ε are proportional to each other in the range of validity of Hooke's law, and the slope of the linear plot is the proportionality factor, the elastic modulus E. E is a material constant. Materials having low elastic moduli, such as synthetic resins, are less able to withstand elongation than materials having high elastic moduli, such as Al_2O_3, SiC, or steel. The maximum tensile stress that can be withstood by a brittle body is its tensile strength σ_B. σ_B, unlike E, is not a material constant, but may have lower or higher values according to the quality of the structure of the material. The rigidity of a body depends not only on its geometric shape but also on its elastic modulus, and can be described by the bending moment M required to produce a certain bending: $M \sim \pi E d^3/32$, *i. e.* of two bodies with identical cross sectional areas and the same shape of cross section, the one with the higher elastic modulus is the more rigid. As the diameter *e. g.* of a round rod is reduced, its rigidity decreases and its flexibility increases. Inorganic fibers consisting of materials with high elasticity moduli, *e. g.* SiC fibers, can therefore have the same flexibility as *e. g.* man-made organic fibers if their diameter is made correspondingly smaller. Since many polycrystalline inorganic fibers are intended for use as light structural materials, it is not only the absolute values of σ_B and E that are of interest, but also the specific values σ_B/ϱ, the specific tensile strength, and E/ϱ, the specific modulus (cf. Fig. 1).

The mechanical properties of some materials are given for comparison in Table 1[1-3].

Table 1. Mechanical properties of materials.

	Material	σ_B [kp/mm²]	E [kp/mm²]	ϱ [g/cm³]
I	Pine wood	7.8	1000	0.6
	Synthetic resins	4–10	300–500	0.9–1.5
II	Al_2O_3	26	36000	3.99
	SiC	11	49000	3.2
III	Titanium	50–90	11200	4.5
	Steel	40–90	21000	7.8

3. Classification of Inorganic Fibers

To obtain a general picture of the many inorganic fiber materials and to be able to arrange the polycrystalline fibers in a logical manner, it is convenient to divide these materials into three groups according to their internal structure, *i. e.* amorphous, monocrystalline, and polycrystalline fibers (Fig. 2)[4].

The amorphous fibers include glass, quartz, and alumina silica fibers, rock wool and slag wool, and carbon fibers that have not been subjected to graphitization or that can be crystallized only with difficulty if at all (vitreous carbon).

[*] Dr. G. Winter, Bayer AG
415 Krefeld-Uerdingen, Rheinuferstrasse (Germany)

[**] Based on a lecture to the "Solid State Chemistry" group of the GDCh on September 14, 1971, in Karlsruhe.

The monocrystalline fibers are represented by "whiskers", many of which exhibit outstanding mechanical properties because of their monocrystalline, defect-free structure.

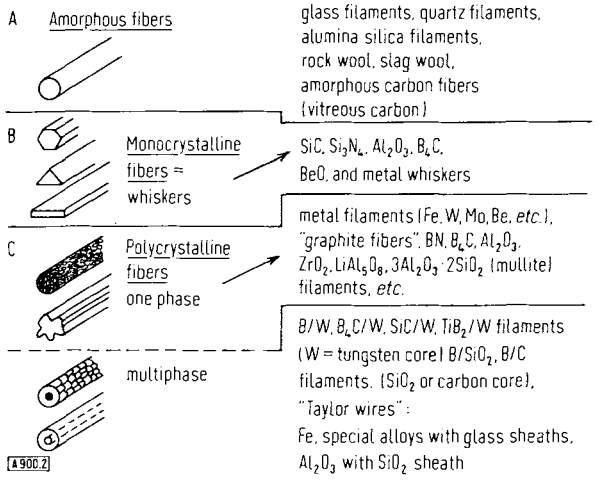


Fig. 2. Classification of inorganic fibers [4].

The third group comprises all other inorganic fibrous materials, which consist either entirely or mainly of countless small, firmly intergrown crystallites. Polycrystalline inorganic fibers consisting of only one phase include the metal fibers (Fe, W, Mo, Be, *etc.*), the "graphite fibers", BN and B_4C fibers, and the group of polycrystalline oxide fibers consisting of Al_2O_3, ZrO_2, Li-Al spinel, mullite, *etc.* The multiphase fibers contain either a core or a sheath of another material. The former include B, B_4C, SiC, or TiB_2 filaments deposited on a tungsten filament and boron filaments with carbon or SiO_2 filaments as cores, while the second group includes "Taylor wires" produced in a glass or quartz sheath, the crystalline inner part consisting of iron, special metal alloys, or oxides such as Al_2O_3.

4. Production

Many different methods are used for the production of inorganic fibers (Table 2).

1. The melt-spinning method, which is extensively used for the production of glass fibers, has so far been applied with only slight success to polycrystalline inorganic fibers. The main difficulties are the sharp viscosity changes that occur on solidification of molten oxides, the high melting points, and the problem of finding suitable containers and spinning nozzles. The production of boron and oxide fibers by this method is therefore still in the experimental stage.

ZrO_2 and Al_2O_3 fibers have been obtained in experimental quantities from rods rotating at a high speed in solar or arc furnaces[5]. On the other hand, a technical solution appears recently to have been found for the spinning of liquid steel to obtain filaments having a diameter of about 75 μm[6].

2. In the extrusion process (Fig. 3), gel or oxide particles, possibly with the aid of a plasticizer, are extruded in the form of filaments and then consolidated by sintering. The products obtained in this way have so far had only low tensile strengths, are relatively thick, and will probably be difficult to process because of the resulting low flexibility[7].

Table 2. Processes for the production of polycrystalline inorganic fibers.

1. Melt-spinning process:
   amorphous glass, quartz, and alumina silica filaments, rock and slag wool, polycrystalline boron, Al_2O_3, and ZrO_2 filaments, steel filaments.
2. Extrusion process:
   BeO and Al_2O_3 filaments.
3. Spinning process with organic supports:
   TiO_2, SiO_2, SiO_2/C, and SiC filaments.
4. Spinning of sols:
   Al_2O_3, ZrO_2, $LiAl_5O_8$, and $3Al_2O_3 \cdot 2SiO_2$ filaments.
5. Impregnation process ("relic fibers"):
   ZrO_2, Ta_2O_5, Al_2O_3, TiO_2, and BN filaments and webs.
6. Precursor conversion:
   cellulose, PAN filaments $\xrightarrow{\text{pyrolysis}}$ C filaments,
   B_2O_3 filaments $\xrightarrow{NH_3}$ BN filaments,
   C filaments $\xrightarrow{BCl_3/H_2}$ B_4C filaments.
7. Chemical vapor deposition on an existing filament:
   B/W, SiC/W, B_4C/W, TiB_2/W, B/SiO_2, and B/C filaments.
8. Wire bundle drawing process:
   Superalloys.
9. Taylor process:
   Fe, special alloy, and Al_2O_3 filaments.
10. Deposition from the gas phase:
    Fe and Fe-containing short fibers with a shell structure.

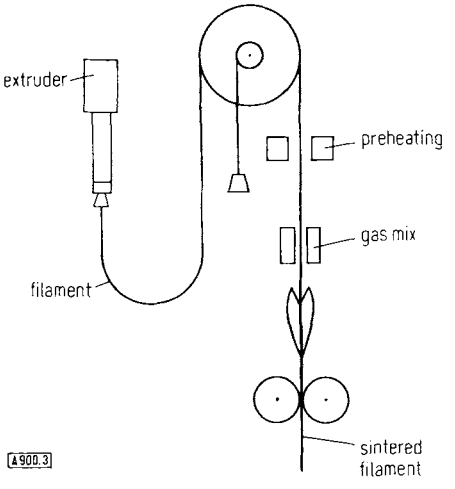


Fig. 3. Scheme of the extrusion process [7].

3. Spinning process with organic supports: Many inorganic substances, which exhibit no spinnability, cannot themselves be spun into fibers and require a spinnable organic support. For example, viscose rayon dope can be used for the production of fibers containing SiO_2; the viscose rayon dope is mixed with water glass, spun, and after coagulation of the rayon fibers in the acid precipitant bath, the products are heated in air to obtain SiO_2 fibers or in an inert atmosphere to obtain SiO_2 fibers containing carbon (Fig. 5). Under certain conditions, it has been found possible to convert the latter into β-SiC filaments without loss of flexibility by an *in-situ* reaction (Fig. 6)[8].



Fig. 4. Fracture surface of a flame-sintered Al_2O_3 filament produced by the extrusion process [7].

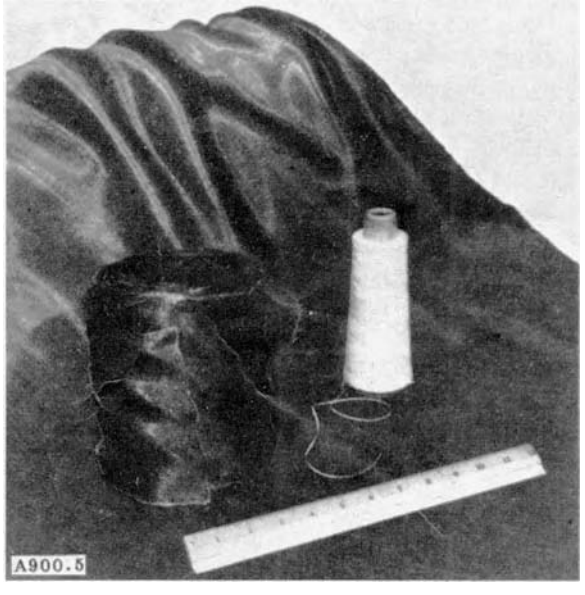


Fig. 5. SiO_2 and SiO_2/C filaments [8].

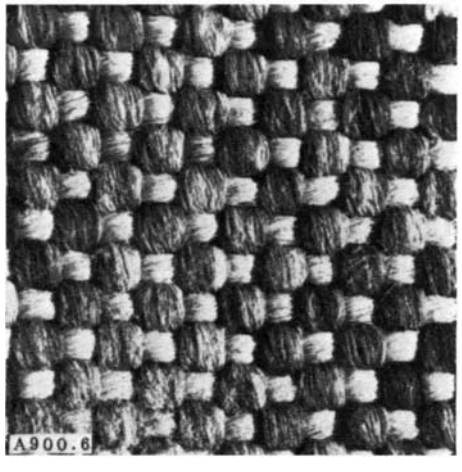


Fig. 6. SiC fiber web [8].

4. Some inorganic sols can be brought into a spinnable state by certain procedures. These sols are then suitable for the production of inorganic fibers by conventional spinning methods. The spun sol fibers are converted into gel fibers by drying in a spinning shaft, the volatile components are eliminated by heating, and the oxide skeleton is sintered. In this way, filaments with good mechanical properties in some cases have been obtained, examples being Al_2O_3, $LiAl_5O_8$, $MgAl_2O_4$, ThO_2, TiO_2, ZrO_2, and $3Al_2O_3 \cdot 2SiO_2$ (mullite) filaments[9].

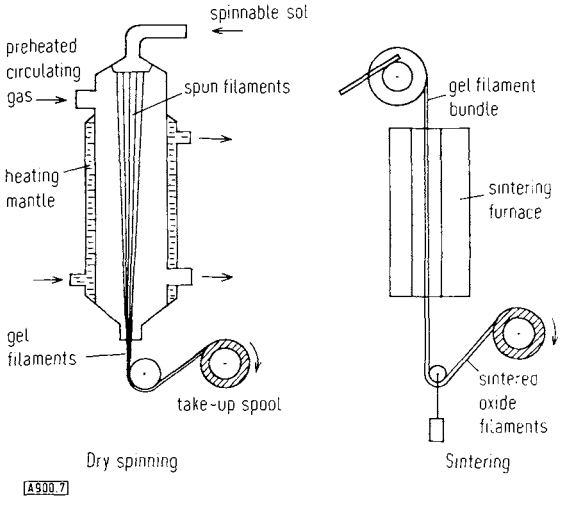


Fig. 7. Spinning of sols (schematic).

5. Relic fibers can be produced by a process developed by Union Carbide, in which single rayon filaments or entire webs are impregnated for a long time with inorganic salt solutions and then subjected to controlled pyrolysis and sintering, in the course of which the organic components are burnt off. Unlike in the similar process for the production of Welsbach gas mantles, where relatively brittle webs are produced, it was possible by this method to obtain

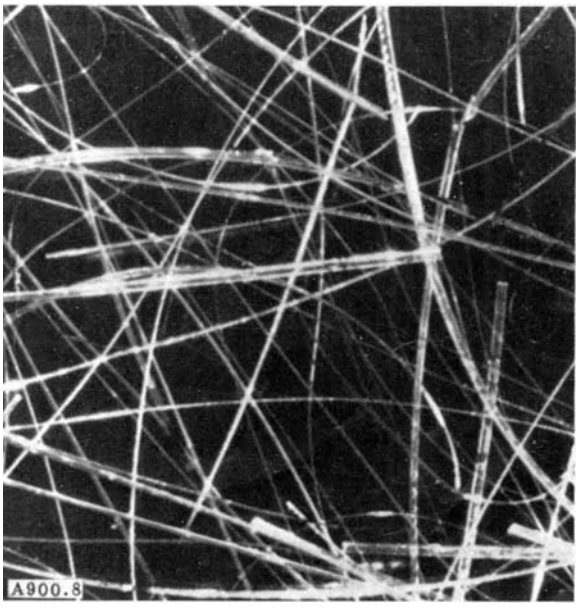


Fig. 8. ZrO_2 filaments, produced by the sol spinning process [5].

fibers and entire webs having useful tensile strengths. Single fibers of ZrO_2 also have useful properties for reinforcing purposes. BN fabrics are also reported to be obtainable in this way[10].

6. By precursor conversion, existing non-fusible organic filaments, which are usually obtained by conventional methods of the fiber-spinning industry, are transformed into carbon or graphite fibers, which are particularly interesting for reinforcing purposes. The source of carbon in this method is cellulose or polyacrylonitrile (PAN) fibers. The American process starts with cellulose fibers, which must be carbonized and stretched by up to 50% of their length at temperatures above 2400 °C in order to orient the graphite crystallites in the fiber direction, to give the fibers the high elastic modulus required for reinforcement. The British process (Fig. 9), which is superior, avoids this difficult step and begins with PAN fibers, which are first subjected to an oxidizing pretreatment below 300 °C, the shrinkage of the fibers (and this is the decisive step) being prevented by firm clamping so that preorientation in the direction of the fiber axis is provided for the graphite crystallites to be formed later. This is followed by a carbonization step at 1000 °C. For the production of graphite fibers with particularly high tensile strengths (type HT = high tensile) the fibers are then heated at 1600—2000 °C, while for the production of fibers with high moduli (type HM = high modulus) they are heated at 2600—2800 °C[11].

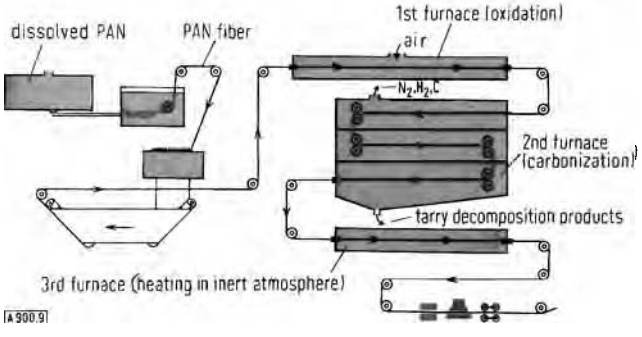


Fig. 9. Process for the production of carbon fibers (schematic) [11].

Numerous efforts have been made to replace the relatively expensive starting fibers rayon and PAN by cheaper materials. However, attempts to spin tar, pitch, lignin, *etc.* into fibers and to carbonize the fibers gave amorphous carbon fibers with low elastic moduli. Crystalline fibers with high elastic moduli were obtained only by the difficult and once again expensive step of graphitization under stress at 2600—2850 °C just below the breaking strength of the fibers[12].

BN filaments (Fig. 10) are produced by reaction of B_2O_3 filaments spun from the melt with NH_3. On reaction of B_2O_3 fibers having a diameter of about 10 μm at temperatures below the melting point of B_2O_3, complete conversion into BN can be achieved in this way. The fibers are stabilized by high-temperature treatment[13]. Carbon filaments can be converted into B_4C in a similar manner by reaction with a BCl_3/H_2 mixture.

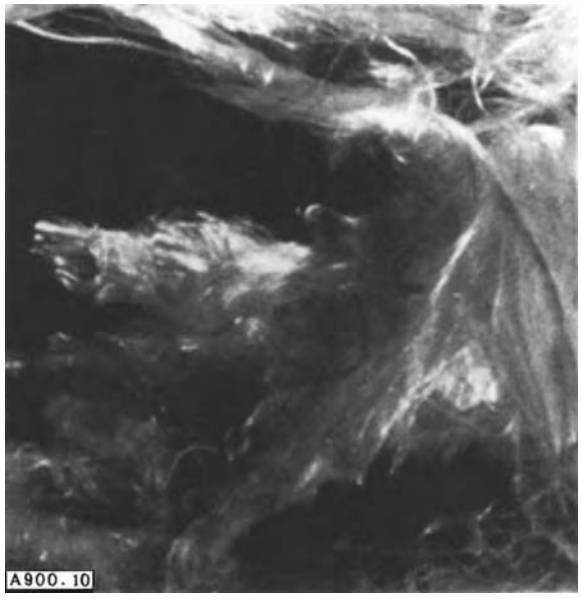


Fig. 10. BN fibers [5].

7. A number of filaments can be produced by chemical vapor deposition on heated tungsten wires approximately 15 μm in diameter at temperatures around 1200 °C. For the deposition of boron or of SiC, mixtures of BCl_3/H_2 or CH_3SiCl_3 are passed over the hot wire. Because of the high specific gravity of the tungsten core, the filament thickness must be built up to about 100 μm to obtain a filament having a low density. At this diameter, however, the filaments are very rigid and difficult to process. Similarly, this method (Fig. 11) can also be used for the production of B_4C and TiB_2 filaments, starting with $BCl_3/H_2/CH_4$ or $BCl_3/H_2/TiCl_4$ mixtures respectively. Attempts are also being made to replace the heavy tungsten core by a cheaper and lighter filamentary substrate. One step in this direction is the deposition of boron from B_2H_6 on carbon-coated, heated SiO_2 filaments or the deposition of boron on carbon filaments[14].

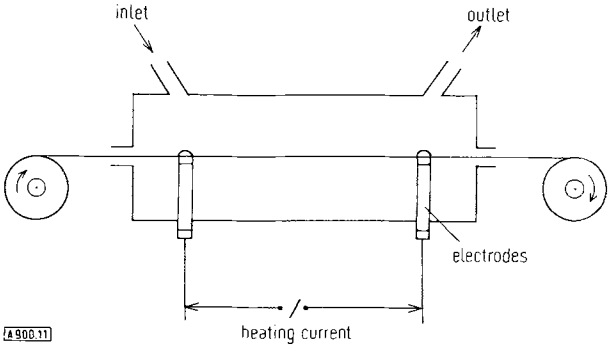


Fig. 11. Scheme of the chemical vapor deposition method [8].

8. For the production of metal filaments, methods have been developed that enable complete bundles of metal wires, which are either coated or embedded in a soft matrix, to be drawn through series of dies with decreasing diameters. A bundle of up to 100 wires made of superalloys, such as Chromel R or René 41, can be drawn in this way to a diameter of 12.7 μm[8].

9. Another process for the production of metallic microwires is the Taylor process, which was developed further *inter alia* by *Nixdorf* at the Battelle Institute. In this process, metals or alloys are melted in glass or quartz tubes and drawn out to extremely fine capillaries. The glass

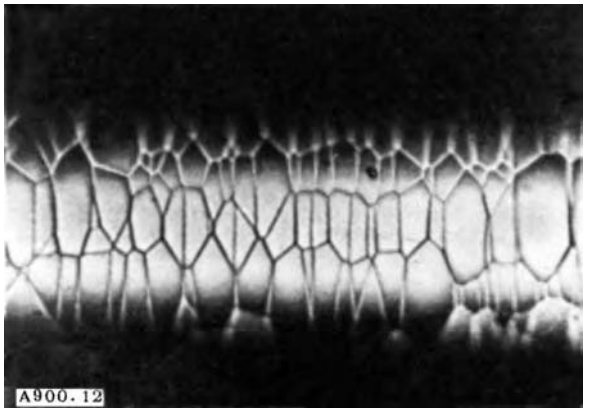


Fig. 12. Surface of a boron filament.

sheath can be removed by ultrasonic radiation, chemical etching, or mechanical crushing, and very fine metal filaments with high tensile strengths are obtained. Under certain conditions, filamentary single crystals can also be produced in this way. It is even possible to melt Al_2O_3 in a quartz tube, which is then drawn out to form a filament with an SiO_2 skin.

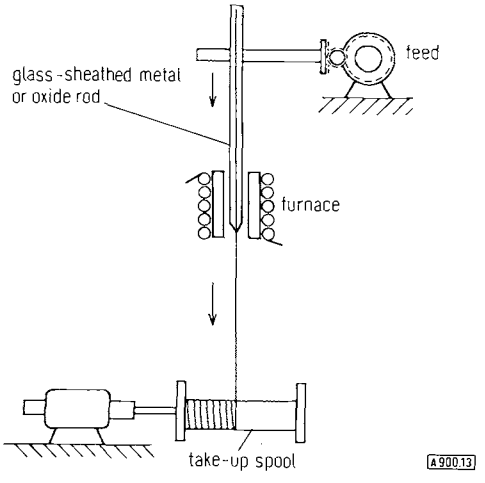


Fig. 13. Scheme of the Taylor process [15].

10. According to *Schladitz*, polycrystalline iron fibers having surprisingly high tensile strengths can be produced in the form of a felt by decomposition of pentacarbonyliron in a magnetic field. These short, polycrystalline metal fibers can be produced in many modifications, *e. g.* with a shell structure of various metals and non-metals. The process is reminiscent of the production of whiskers from the gas phase, but has the advantage of a much higher yields per unit time and volume[16].

The majority of the processes described can be carried out continuously and proceed with relatively high yields per unit time and volume, so that reasonable prices may be expected with mass production. Moreover, most of the filaments can be obtained in any desired lengths, so that the production of wound components or the parallel alignment of the fibers for components with anisotropic properties becomes much simpler than when whiskers are used. These advantages have gained a lead in development for polycrystalline inorganic fibers over whiskers, with which they cannot compete in many of their properties.

5. Properties

The properties of particular interest in polycrystalline inorganic fibers are their tensile strength, their elastic modulus, and the dependence of these properties on temperature, as well as their density and their thermal and chemical stability.

If one considers the tensile strength of compact ceramic bodies and compares this with the values calculated from the bond strengths, one finds that the strengths attained in practice are often two to three orders of magnitude lower than the theoretical values. To this fact, which has been known for a long time as the "crystal paradox", is added another remarkable observation, *i. e.* that macro single crystals of many substances have a lower mechanical strength than polycrystalline bodies of the same material. In the course of time, the search for an explanation of these phenomena produced many findings that have been of the utmost importance to the production of high-tensile polycrystalline inorganic fibers with high elastic moduli, and that have contributed in general to our understanding of the mechanical properties of solids.

One of the first attempts to calculate the theoretical strength of ionic crystals was made by *Polanyi* in 1921[17]. His formula for the calculation of the maximum tensile strength σ_{max}:

$$\sigma_{max} = \sqrt{\frac{4E\gamma}{L_0}} \qquad (1)$$

γ = surface energy,
E = elastic modulus,
L_0 = elongation necessary to cause fracture

was later modified by various workers, and can be expressed in its simplest form by eq. (2).

$$\sigma_{max} \approx \frac{E}{10} \qquad (2)$$

The strengths found from this formula (*e.g.* a value of approximately 4000 kp/mm^2 as the tensile strength of α-Al_2O_3) are not even approached in practice (cf. Table 1). An explanation for this is provided by *Griffith*'s fracture theory[18]. When a tensile stress is applied to a body, the externally acting force is not uniformly distributed in the interior, but gives stress concentrations at flaws in the

crystal structure, *e.g.* at a notch. At the tip of a notch, a stress σ_k of

$$\sigma_k = 2\sigma\sqrt{\frac{C}{r}} \tag{3}$$

σ = overall applied stress,
σ_k = stress at the notch tip,
C = half the length of an internal crack or depth of a surface crack,
r = radius of curvature at the notch tip

is reached. The greater C and the smaller r, the more easily will the tensile stress σ_k reach or exceed the theoretical strength value, whereupon breakage will occur in the case of a single crystal. For a polycrystalline body, however, the fracture of one crystallite does not necessarily lead to breakage of the entire body. The break will certainly extend over the entire crystallite, but it is fairly difficult for a growing crack to pass over into the differently oriented neighboring crystallites, and the fracture process consequently stops here. It is thus clear that the strength of polycrystalline bodies is partly dependent on the crystallite size; this is expressed in eq. (4).

$$\sigma = k \times K^{-a} \tag{4}$$

K = crystallite size,
k, a = empirical constants

High tensile strengths are therefore obtainable in polycrystalline bodies only if the crystallites are very small and if the surface is practically perfect and free from notches. The crystallite sizes of polycrystalline inorganic fibers are mostly less than 300 Å, and often even less that 100 Å.

The pores in the structure of a polycrystalline body have an effect similar to that of notches and cracks. They considerably reduce the tensile strength; this is expressed quantitatively by

$$\sigma = \sigma_0 \, x e^{-bP} \tag{5}$$

σ_0 = tensile strength at $P = 0$,
P = porosity,
b = empirical constant.

Whereas no clear dependence exists between the crystallite size and the elastic modulus, pores also considerably decrease the elastic modulus.

$$\sigma = k \times K^{-a} \times e^{-bP} \tag{6}$$

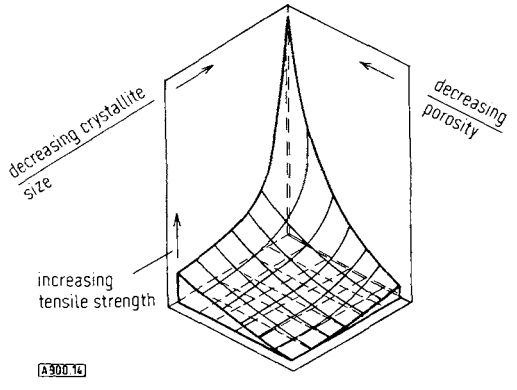


Fig. 14. Tensile strength as a function of crystallite size and porosity [19].

The combined influence of crystallite size and porosity on the strength of a polycrystalline inorganic body can be expressed, according to *Knudsen*, by eq. (6)[19], and is represented graphically in Figure 14.

However, this by no means completes the description of the factors affecting the strength of polycrystalline inorganic fibers. In the discussion of the *Griffith*'s fracture theory, mention was made of flaws in the crystal structure. According to *Seeger*, these defects can be divided into three groups:

1. Zero-dimensional defects *e. g.* lattice vacancies, interstitial atoms, atoms in incorrect lattice sites, foreign atoms.

2. One-dimensional defects (flaws that extend along open or closed lines in the crystal), *e. g.* dislocations (Figure 15) or acicular precipitations.

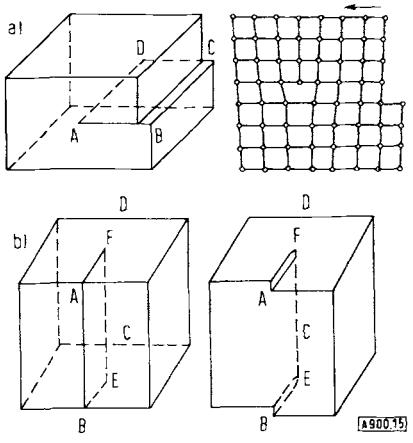


Fig. 15. Scheme of a) edge and b) screw dislocations [20].

3. Two-dimensional defects, *e.g.* grain boundaries or twin boundaries.

The structure of a real crystal, with its vacancies, foreign atoms, dislocations, *etc.*, is reproduced very vividly by a two-dimensional soap bubble model (Fig. 16)[20].

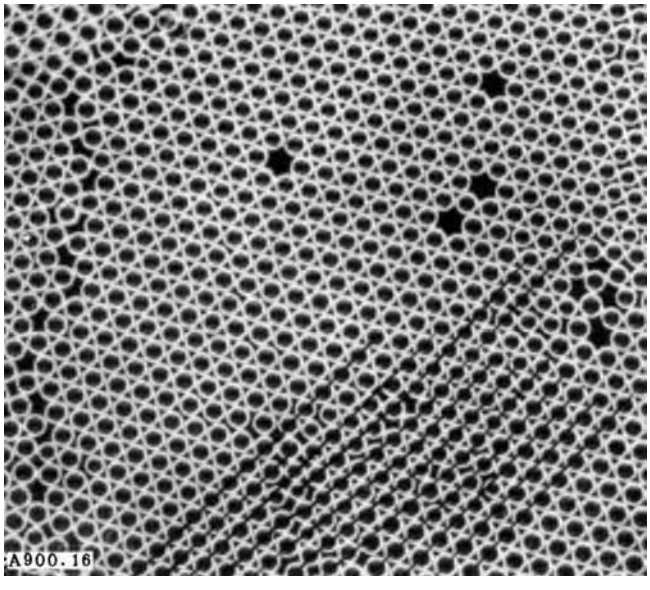


Fig. 16. Soap-bubble model of the defects in a crystal [20].

The dislocations are defects in the crystal lattice that begin to migrate under a tensile stress, and that can thus lead to slip processes and hence also to fracture. There are two fundamental ways of preventing this. Either one tries to produce bodies that are totally free from dislocations, or one tries to inhibit the movement of the dislocations.

The first method is used in the production of whiskers, where an effort is made to produce practically dislocation-free single crystals. The second method is the only one that can be used in the case of polycrystalline inorganic fibers. Several alternatives are available. Dislocations may be anchored by strong lattice distortions such as those resulting from vacancies or foreign atoms in lattice or interstitial sites. The number of dislocations also influences their mobility. Thus the dislocation density can be increased to such a degree by quenching heated bodies (freezing the flaws) or by cold deformation of metals that the dislocations anchor one another and their mobility is thus reduced.

It has already been mentioned that crystallite boundaries present obstacles to the propagation of cracks and to the migration of dislocations. The smaller the crystallite, the smaller is the length of the dislocation source to be activated, and the greater is the work required to set the dislocation in motion. Finely dispersed precipitates of a foreign substance, which can prevent the passage of a dislocation line when separated by certain distances, also present obstacles to dislocations[21].

Attempts are being made, with greater or lesser success, to bring these mechanisms into play in polycrystalline inorganic fibers. As can be seen in Table 3, the transition from the compact material to the fiber with high surface and internal perfection, taking into account the relationships discussed above, is accompanied by a considerable increase in strength. An impressive practical example for which many of these theoretical considerations have been confirmed is provided by the polycrystalline Fe fibers produced by *Schladitz* by decomposition of pentacarbonyliron in a magnetic field. These fibers contain crystallites having a size of 80 Å, and have a dislocation density of 1.5×10^{12} dislocation per cm^2, compared with about 10^6—10^8 in pure iron. The formation of the ideal lattice is suppressed by precipitation of Fe_3C crystallites at short distances from one another, and the dislocations are anchored by precipitation of 1.2% of carbon in interstitial sites. The fibers have tensile strengths of up to 700 to 800 kp/mm^2, *i.e.* approximately 60% of the tensile strength of good iron whiskers ($\approx$ 1300 kp/mm^2)[16].

Table 3. Comparison of mechanical properties of compact and fibrous materials [2,3].

	Compact material		Fiber	
	σ [kp/mm^2]	E [kp/mm^2]	σ [kp/mm^2]	E [kp/mm^2]
Steel	40–90	21000	420	20600
Al_2O_3	26	36000	210	(17500)
ZrO_2	14	18900	210	17500
SiC	11	48000	320	45000
Glass	3–9	7400	$\approx$200	7400

Table 4. Mechanical properties of various fibrous materials [4].

Fiber	M.p. [°C]	ρ [g/cm^3]	σ_B [kp/mm^2]	E [kp/mm^2]	σ_B/ρ [km]	E/ρ [km]
Amorphous						
E glass	700	2,55	200	7300	80	2850
SiO_2	1660	2,19	150	7300	70	3350
Polycrystalline single phase						
C—HT	3650	1.76	280	26500	160	15000
C—HM	3650	1.95	200	38000	105	19500
Al_2O_3	2040	3.15	200	17500	65	5550
ZrO_2	2715	4.84	200	35000	40	7200
BN	2980	1.90	140	9000	75	4750
$3Al_2O_3 \cdot 2SiO_2$	1920	2.9	245	17500	85	6050
W	3400	19.4	400	41000	20	2100
steel	1400	7.74	400	20500	50	2650
Be	1280	1.83	130	24500	70	13400
multiphase						
B/W	2300	2.7	350	40000	130	14800
B/SiO_2	2300	2.36	230	37000	95	15700
SiC/W	2690	3.5	320	45000	90	12850
Monocrystalline (whiskers)						
Al_2O_3	2040	3.96	2000	42000	500	10600
SiC	2690	3.21	2000	50000	620	15600
Fe	1540	7.83	1300	20500	165	2650
For comparison organic synthetic fibers		1.1—1.5	10—125	200—1500		

Table 4 shows a survey of the tensile strengths and elastic moduli obtained with polycrystalline inorganic fibers in comparison with those of other fibers. It can be seen that polycrystalline inorganic fibers have extraordinarily high tensile strengths, which are superior even to those of organic fibers and glass fibers, and are exceeded only by those of whiskers. They normally also exhibit the high elastic moduli found for the corresponding compact ceramic materials. In this respect, they are only slightly inferior to

whiskers. Fine metal filaments also stand comparison in this respect; however, with the exception of Be, when one considers the specific tensile strengths and specific moduli, they immediately lose ground because of their high specific gravity. These specific values, however, are decisive for use in light structural components, *e. g.* for aircraft and space applications.

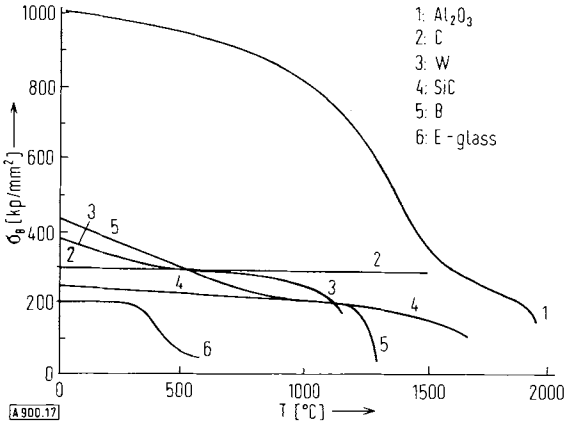


Fig. 17. Temperature dependence of the tensile strength of inorganic fibers [4]. Al_2O_3 as whiskers, all others as endless fibers.

Polycrystalline inorganic fibers naturally have extremely high melting points. However, this does not mean that they can be used up to these temperatures. Recrystallization at temperatures far below the melting point may lead to structural changes that drastically impair the mechanical properties. Moreover, the strength values decrease at higher temperatures because of the greater ease with which creep and slip processes occur.

Nevertheless, polycrystalline inorganic fibers are the strongest materials known at these temperatures, apart from whiskers. As can be seen from Figure 17, for example, graphite fibers still have a greater strength at 1500 °C than steel at room temperature.

6. Applications

The materials in common use can be roughly divided into three groups according to their properties (cf. Table 1). Materials of group I, which include, *e.g.* synthetic resins, are thermally unstable, easy to process, light, tough, impact-resistant materials having low strengths. Because of their low elastic modulus, they have little rigidity, and consequently cannot be used for the production of large load-bearing structural components. The ceramic materials of group II, *e.g.* Al_2O_3 or SiC, are relatively light and thermally stable, have very high elastic moduli and are therefore very rigid, but they are also very brittle and sensitive to impact, and have low strengths. They are also unsuitable for use alone as construction materials. The third group of materials, which within certain limits combines in itself the desirable properties of the other two groups (rigidity, strength, toughness, thermal stability), are the solid metals; however, these have the important disadvantage that, with few exceptions, they are too heavy.

The ideal situation would be achieved if the positive properties of groups I and II could be combined. This can be achieved in a composite material, in which fibers of a material from group II are embedded in a matrix of a material from group I; it is necessary to ensure good adhesion between the fiber and the matrix and good transfer of force. As will be shown later, however, other combinations are also possible.

The strengthening and stiffening mechanism that can act in such fiber-reinforced materials can be seen from the stress-strain diagram (Fig. 18). If a fiber-reinforced material with good adhesion between the fiber and the matrix is subjected to an elongation *a* by application of a tensile stress, the fiber with the high elastic modulus will bear most of the load (σ_f), while the matrix, because of its low elastic modulus, will bear the smaller share (σ_m); the function of the latter is to hold the fibers together and to transfer the tensile stress to the fibers. This combination principle has been followed in nature since the earliest times, examples being the strength and rigidity of bone material or of bamboo cane.

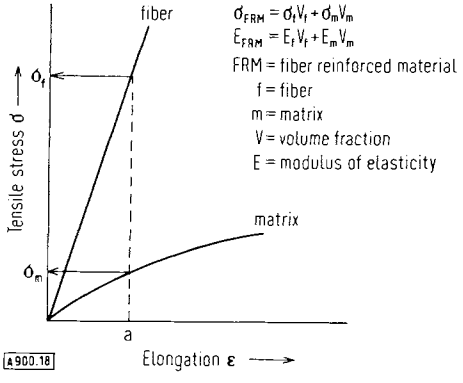


Fig. 18. Stress distribution in a fiber-reinforced material.

In the ideal case, the tensile strength of a fiber-reinforced material (FRM) σ_{FRM} is made up additively from the products of the tensile strength of the fiber σ_f and its volume fraction V_f on the one hand and the tensile strength of the matrix σ_m and its volume fraction V_m on the other. The same is true of the elastic modulus, and hence of the rigidity of the reinforced material.

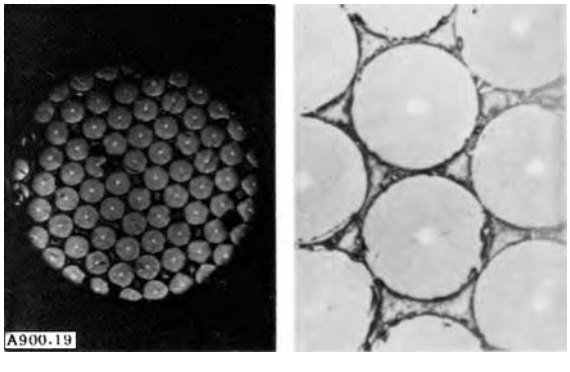


Fig. 19. Cross section through a boron-fiber reinforced material.

The most common case is the reinforcement and stiffening of synthetic resins. As can be seen from Table 5, it is possible in this way to obtain materials whose strength and rigidity is similar to that of steel, but which are lighter by a factor of four to five.

Despite the steady improvement of the heat resistance of synthetic resins, full use cannot be made of the outstanding high-temperature properties of polycrystalline inorganic fibers with synthetic resins as the matrix materials. As is shown by the example B/polyimide, the medium-temperature range is attainable, but metallic matrices will play a part in future for the high-temperature range. The metals offer higher heat resistance, higher elastic moduli, and in some cases toughness and hardness, as valuable properties in fiber-reinforced materials.

Table 5. Mechanical properties of fiber-reinforced materials [4].

Composite	Fiber content [vol.-%]	Density [g/cm³]	σ_B [kp/mm²]	E [kp/mm²]	Remarks
C/epoxy	59	1.5	140	14000	
B/epoxy	55	2.1	145	21000	
B/polyimide	69	2.1	200	24000	— tensile strength at 315 °C 130 kp/mm²
B/Al	50	2.7	125	24000	— tensile strength at 500 °C 70 kp/mm²
For comparison:					
Epoxy resin	0	1.2	10	300	
Aluminum	0	2.7	10	7000	
Building steel	0	7.8	50	21000	

Polycrystalline inorganic fibers above all improve the tensile strength at higher temperatures and reduce the density of the metals, with the result that the specific properties are improved. It is clear that such materials will find use wherever great strength is required at high temperatures, as in pressure vessels, in reactor engineering, and above all where weight saving is important, *i.e.* in aerospace technology where resistance to high temperatures is necessary. As can be seen from Figure 20, *e.g.* aluminum reinforced with boron fibers has a strength at 500 °C similar to that of steel at room temperature.

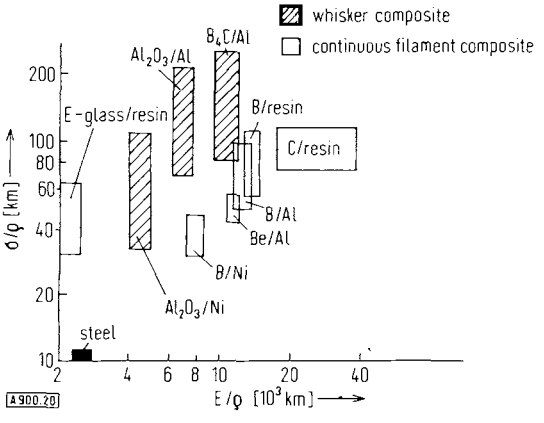


Fig. 20. Specific properties of various composite materials [4].

It is mentioned only to complete the picture that fiber reinforcement of ceramic materials is also possible, and can lead to improved properties. This field of application is still in its infancy, but amazing properties have already been obtained, *e.g.* in the reinforcement of glass with carbon fibers.

In addition to mechanical reinforcement, another important application of inorganic fibers is thermal insulation at high temperatures. However, since extreme mechanical properties are less important here than resistance to high temperatures, low thermal conductivity, resistance to thermal shock, and low embrittlement, this field is dominated not by polycrystalline inorganic fibers but by the amorphous SiO_2 and alumina silica fibers.

Certain polycrystalline inorganic fibers have special fields of application. The steel filaments produced by Monsanto by melt spinning are intended for tire cord. Fabrics made from polycrystalline oxide filaments can be used as filters for hot corrosive gases, liquids, or molten metals. BN fibers, for example, are suitable for electrical insulation at high temperatures; these fibers are also unaffected by boiling alkalis and acids or by molten Fe or Al, and even withstand an atmosphere of chlorine at 700 °C.

Synthetic resins reinforced with polycrystalline inorganic fibers may be expected in the future to find a spectrum of application similar in breadth to that existing at present for glass-fiber reinforced plastics. The former class of composite materials currently seems particularly attractive in aircraft and space applications, since they allow a reduction of weight without loss of strength and rigidity, and hence greater ranges and lower fuel consumptions. However, the weight saving is economically justifiable only if the cost does not exceed a certain limit. This limit is around \$ 60 per kg of weight saved for conventional light aircraft, and around \$ 600 for supersonic aircraft. The cost of saving 1 kg of structural weight by the use of *e.g.* carbon-fiber reinforced materials is at present between \$ 350 and \$ 1900. By 1975, these costs should have fallen to approximately \$ 90 to \$ 500. A considerable saving would thus be possible in particular for supersonic aircraft[22]. For the near future, the addition of small proportions of polycrystalline inorganic fibers to glass-fiber reinforced plastics may be expected; in this way, their rigidity and their fracture energy can be increased, so that they are better suited to the construction of tanks, silos, pipelines, vehicles, containers, *etc.* Other applications of polycrystalline inorganic fibers will become interesting as prices fall. Conceivable applications include lighter bridges with higher carrying capacities and load-bearing structural components in tall buildings in construction engineering, underwater buildings in the exploitation of the sea, rigid but lighter, corrosion-resistant structural components in shipbuilding and boatbuilding, and corrosion-resistant pressure vessels, tanks, and reactors in chemistry and in reactor engineering. The applications that have already been successful in sports (fiber reinforced components in racing cars, racing canoes, yacht masts, *etc.*) are likely to be extended to skis, boat hulls, golf

clubs, *etc.* In the opinion of many experts we are entering an "age of inorganic fibers".

Received: October 8, 1971 [A 900 IE]
German version: Angew. Chem. *84*, 866 (1972)
Translated by Express Translation Service, London

[1] *P. H. Selden:* Glasfaserverstärkte Kunststoffe. Springer-Verlag, Berlin 1967, p. 181.

[2] *I. E. Campbell* and *E. M. Sherwood:* High-Temperatur Materials and Technology. Wiley, New York 1967, pp. 256ff.

[3] *L. Piatti:* Werkstoffe der chemischen Technik, Vol. 3. Verlag Sauerländer, Aarau 1955, p. 76.

[4] *H. W. Rauch, W. H. Sutton,* and *L. R. McGreight:* Ceramic Fibers and Fibrous Composite Materials. Academic Press, New York 1968.

[5] *C. Z. Carroll-Porczynski:* Advanced Materials. Chemical Publishing, New York 1969.

[6] Chem. Week *108* (Feb. 24), 51 (1971).

[7] *H. P. Blakelock, N. A. Hill, N. Austin, S. A. Lee,* and *C. Goatcher,* Proc. Brit. Ceram. Soc. *1970*, No. 15, 69.

[8] *A. H. Frazer:* High Temperature Resistant Fibers. Wiley, New York 1967, pp. 105ff, 183ff, 267ff.

[9] *W. L. Lachmann* and *J. P. Sterry,* Chem. Eng. Progr. *58* (10), 37 (1962).

[10] *B. H. Hamling, A. W. Naumann,* and *W. H. Dresher,* Polymer Reprints, Atlantic City Meeting *9* (2), 1449 (1968).

[11] *W. T. Gunston,* Sci. *5*, 39 (1969).

[12] *H. M. Hawthorne,* Int. Conf. Carbon Fibres, Composites and Applications, London 1971, Paper No. 13.

[13] *J. Economy, R. V. Anderson,* and *V. I. Matkovich,* Polymer Reprints, Atlantic City Meeting *9* (2), 1392 (1968).

[14] *H. W. Rauch,* Mater. Eng. *66*, 74 (1967).

[15] *J. Nixdorf,* Metall *23*, 887 (1969).

[16] *H. J. Schladitz,* Z. Metallk. *59*, 18 (1968).

[17] *M. Polanyi,* Z. Phys. *7*, 323 (1921).

[18] *E. Orowan,* Z. Phys. *86*, 195 (1933).

[19] *F. P. Knudsen,* J. Amer. Ceram. Soc. *42*, 376 (1959).

[20] *W. Kleber:* Einführung in die Kristallographie. VEB Verlag Technik, Berlin 1961, pp. 114ff.

[21] *H. Grünewald,* DEW (Deut. Edelstahlwerke) Techn. Ber. *8* (4), 271 (1968).

[22] *J. Fray,* Int. Conf. Carbon Fibres, Composites and Applications, London 1971, Paper No. 46.

Cathodic Dimerization[**]

By Fritz Beck[*]

The technical, electrochemical, and preparative aspects of cathodic dimerization, which leads to bifunctional compounds, are reviewed. With the hydrodimerization of acrylonitrile as an example, the effects of the reaction parameters and the mechanism are discussed in detail. In addition to the hydrodimerization of activated compounds, the coupling can also proceed *via* elimination of halide or *via* the discharge of cations. Processes of special preparative interest are those in which two different molecules are coupled, which can yield *e.g.* esters, alcohols, or ketones with cyano groups, as well as asymmetric diols. The reductive dimerizations of acrylonitrile, β-chloropropionitrile, acetone, acetylpyridine, nitrobenzene (→ benzidine), and pyridinium salts have already found industrial use.

1. Introduction

The field of cathodic dimerization has developed particularly rapidly in recent years. This is no accident, since this area of organic electrosynthesis involves aspects of great preparative, technical, and mechanistic interest. The object of this progress report is to present a comprehensive survey, with special emphasis on industrial and electrochemical possibilities. Only recently, *Baizer* (together with *Petrowitsch*), who played an extremely important part in the development of the field, published a brilliant survey of the synthetic and mechanical aspects[1]. This topic is also discussed at length in a recent review on organic electrosynthesis[2]. Overlapping with these publications cannot be entirely avoided, but will be kept to a minimum.

In cathodic dimerization, the organic molecule takes up an electron directly at the electrode. It thus passes through the intermediate stage of a radical-ion. The negative charge is compensated in accordance with Scheme 1 by uptake of protons ("hydrodimerization"), by elimination of halide ions, or by the positive charge on the substrate when the latter is a cation. Each of these cases can in principle be further subdivided into the dimerization of two identical molecules, which yields a symmetrical product, the coupling of two different molecules, and intramolecular reactions leading to cyclic products.

If the monomer contains one or more functional groups, bifunctional or polyfunctional dimers are formed. Cathodic dimerization is therefore a valuable method for the synthesis of such compounds. Since only one electron is taken up per monomer in every case, the energy consumption is comparatively low. This is extremely favorable in industrial uses.

The formation of a symmetrical dimer is only one of several possible reactions. In principle, the molecule could also be

[*] Dr. F. Beck
Badische Anilin- & Soda-Fabrik AG, Hauptlaboratorium
67 Ludwigshafen (Germany)

[**] Based, in part, on a lecture at the 1st EUCHEM Conference on Organic Electrochemistry at Ronneby Brunn, Sweden, on June 9, 1971.

hydrogenated (possibly in several stages), add on an acceptor molecule instead of the second substrate molecule, form oligomers by addition of a third molecule, a fourth *etc.*, or finally form organometallic compounds with the cathode metal. The fact that cathodic dimerization nevertheless often occurs, with extremely high yields in many cases, shows that this reaction is often favored in electrochemistry. An article by *Knunyants* and *Gambarian*[3] on hydrodimerization clearly shows that electrochemical reduction (or the equivalent reduction with Na amalgam, Zn/glacial acetic acid, or the like) generally leads to hydrodimers,

$2X + 2H^{\oplus} + 2\ominus \longrightarrow HX{-}XH$
hydrodimerization of two molecules of the same type

$X + X' + 2H^{\oplus} + 2\ominus \longrightarrow HX{-}X'H$
hydrodimerization of two different molecules

$X{-}X' + 2H^{\oplus} + 2\ominus \longrightarrow HX{-}X'H$
cyclizing hydrodimerization

$2X\text{-Hal} - 2Hal^{\ominus} + 2\ominus \longrightarrow X{-}X$
dimerization with elimination of halogen

$2X^{\oplus} + 2\ominus \longrightarrow X{-}X$
dimerization of cations

Scheme 1. Survey of cathodic dimerization. (Strictly speaking the second and third variants are not dimerizations.)

whereas catalytic hydrogenation yields such products only in exceptional cases. This may be connected with the strong adsorption of the intermediate products on the catalyst surface, which is unfavorable for the dimerization step. In the electrochemical method, on the other hand, the intermediate products generally interact only weakly with cathodes having high hydrogen overvoltages (exceptions: formation of organolead, organomercury, or organozinc compounds).

2. General Mechanistic Considerations

What intermediates are involved in cathodic hydrodimerization? Scheme 2 shows all the possibilities that are found on application of the following conditions:

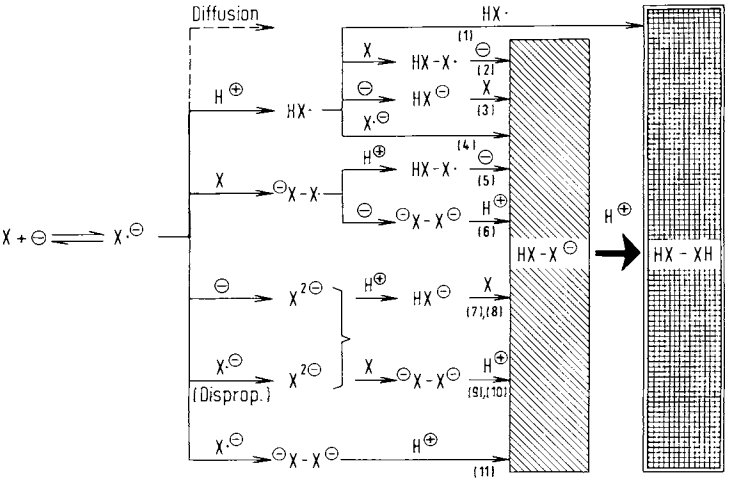
a) The primary step is the transfer of an electron to the substrate X with formation of the radical-anion. This reaction is reversible in most cases; surprisingly high exchange current densities are found for this primary process, *e. g.* for aromatic compounds[4]. In exceptional cases, this primary electron transfer may be preceded by a chemical reaction, such as the protonation in strongly acidic solution that has been proposed for ketones[5,6] or for acrylonitrile[7] The unusual increase in basicity is attributed to a field effect[8].

b) The second protonation can occur only *after* the dimerization step, since the hydrogenated monomer would otherwise result.

c) A total of two electrons and two protons is taken up.

The initially formed radical-anion, in (rare) cases in which its stability is high, will diffuse in part into the interior of the solution, where it can be detected *e. g.* by ESR spectroscopy[9]. In general, however, it will react where it is formed, *i. e.* in the electrochemical double layer in front of the electrode. In this case, it reacts in a strong electric field ($\approx 10^7$ V/cm); the subsequent reactions are therefore generally different from those of the same radical-ion formed, *e. g.* by a homogeneous redox process. However, it should be noted that the electric field strengths in the atomic range, *e. g.* in the vicinity of a (small) ion or a dipole, could quite easily be of the order of magnitude mentioned above.

According to Scheme 2, the second reaction step (proceeding toward the hydrodimer) may be the uptake of a proton or combination with a second substrate molecule, *i. e.* the radical-*anion* reacts as a nucleophile. The *free-radical* nature of the primary product becomes evident in the uptake of a second electron or in the (electrostatically improbable) reaction with a second radical anion, which



Scheme 2. Reaction paths in cathodic dimerization. For the figures under the reaction arrows see also Scheme 3.

can also lead to disproportionation. The possibility that the free-radical function directly causes the abstraction of a hydrogen atom, *e. g.* from the solvent, is not shown in Scheme 2.

The secondary intermediates formed can react further as shown in Scheme 2. The intermediate product HX· (or $HX^{\ominus}$) cannot *e. g.* be protonated since this would be contrary to rule b). The intermediate product $^{\ominus}X{-}X^{\ominus}$ or $^{\ominus}X{-}X\cdot$ cannot take up further monomer, and the intermediate $X^{2\ominus}$ has already taken up both possible electrons.

In this way one obtains eleven reaction paths to the hydrodimer, which are summarized once again in abbreviated form in Scheme 3 (in the same order as in Scheme 2). (The actual dimerization step in practically every case is the formation of a C—C bond.) It can be seen that the first reaction step, as required (rule a), is an electron transfer, and the last [except in case (1)] is a protonation; in (1), (4), and (11), the dimerization follows a free-radical course. For electrostatic reasons all mechanisms involving doubly negatively charged dimeric and particularly monomeric

particles are relatively unlikely [(6)–(11)]. Of the remaining first five possibilities (1) and (4) are free-radical, (3) and (5) are ionic, and in (2) the monomer reacts with a free radical. (1) occurs *e. g.* in the hydrodimerization of ketones, and (3)

e p } d	(1)
e p }	
e p d e p	(2)
e p e d p	(3)
e p } d p	(4)
e }	
e d p e p	(5)
e d e p p	(6)
e e p d p	(7), (8)
e e d p p	(9), (10)
e } d p p	(11)
e }	

Scheme 3. Reaction path in cathodic dimerization (see Scheme 2); abbreviated notation: e = electron transfer, p = protonation, d = dimerization.

or (5) in the hydrodimerization of activated olefins. According to *Bard*[272], however, two radical-ions dimerize to give the dimeric dianion in the case of dimethyl fumarate.

3. The Cathodic Hydrodimerization of Acrylonitrile

3.1. Industrial Importance

The cathodic dimerization of acrylonitrile (AN) leads directly in one step to adiponitrile (ADN), which is an important intermediate for 6,6 nylon. The fact that the monomer could be obtained relatively cheaply by a new petrochemical process (Sohio process = ammonoxidation of propylene) drew the attention of the polyamide manufacturers to this electrochemical process about a decade ago. This process had the fundamental advantage that it requires one step less than the conventional industrial syntheses.

cyclohexane $\xrightarrow{O_2}$ cyclohexanol $\xrightarrow{HNO_3}$ adipic acid $\xrightarrow{NH_3}$ ADN

butadiene $\xrightarrow{Cl_2}$ 1,4-dichloro-2-butene $\xrightarrow[-NaCl]{NaCN}$ 1,4-dicyano-2-butene $\xrightarrow{H_2}$ ADN

The hydrodimerization carried out by *Knunyants*[10–12] in the 1950's with Na amalgam initially gave the desired product in a material yield of only 65% and in an amalgam yield of 35%. It was the work of *Baizer* at Monsanto[13–15], who was able to obtain almost quantitative material and current yields, that gave the decisive thrust that led to the construction of an industrial plant at Monsanto. The outstanding purity of the product was a strong argument in favor of the polyamide synthesis. Another advantage was the absence of stoichiometric by-products.

This development helped to bring about an unexpected renaissance in the field of organic electrochemistry, which appeared even around the turn of the century[16,17] to be on the way to becoming an established chemical reaction technique. The earlier view that the use of organic electrosynthesis in industry was to be expected at most for valuable products on a fairly small scale had thus turned out to be wrong. An early review on the hydrodimerization of acrylonitrile was published by *Tomilov et al.*[18].

3.2. Electrolysis Conditions

The choice of the optimum electrolysis conditions will be discussed for the case of acrylonitrile, since data on this reaction is particularly abundant because of its technical importance, and since these considerations can be applied to the hydrodimerization of other compounds. The problem is to optimize the numerous important parameters for the electrosynthesis so that under acceptable industrial conditions of temperature, pressure, *etc.*, the desired reaction

$$\underset{\text{AN}}{2CH_2{=}CH{-}CN} + 2H_2O + 2\ominus \longrightarrow \underset{\text{ADN}}{NC(CH_2)_4CN} + 2OH^{\ominus} \quad (12)$$

clearly predominates over electrochemical side reactions such as

$$CH_2{=}CH{-}CN + 2H^{\oplus} + 2\ominus \longrightarrow CH_3{-}CH_2{-}CN \quad (13)$$

$$2H^{\oplus} + 2\ominus \longrightarrow H_2 \quad (14)$$

$$n\,CH_2{=}CH{-}CN + H_2O + 2\ominus \longrightarrow \text{oligomers} \quad (15)$$

$$2CH_2{=}CH{-}CN + 2H^{\oplus} + 2\ominus + Sn \longrightarrow Sn(CH_2CH_2CN)_2 \quad (16)$$

and chemical side reactions such as the hydrolysis of the nitrile group (in acidic media), cyanoethylation of water to form β-hydroxypropionitrile and β,β'-dicyanoethyl ether (in alkaline media), and free radial initiated polymerization.

3.2.1. Cathode Material

Figure 1 shows the polarographic current-voltage curve of acrylonitrile in aqueous solution. The half-wave potential is strongly negative (−1.96 V against the saturated calomel electrode). This has two immediate consequences. Cathodes with high hydrogen overvoltages are required to suppress the simultaneous liberation of hydrogen in accordance with reaction (14). Furthermore, the discharge potential of the cation of the carrier electrolyte must be as negative as possible. Quaternary ammonium salts satisfy this condition, as has been known for some time from polarography. Mercury and above all lead have proved to be excellent cathode metals. Cadmium is unsuitable, since it is attacked with formation of bis(cyanoethyl)-cadmium[19]. Carbon is also a good cathode material, which differs in important respects from Pb and Hg (see below). The hydrodimer is formed even on platinum, though in poor yields[20]. This is probably due to substantial inhibition of (14) by adsorbed organic products.

3.2.2. Acrylonitrile Concentration

The number of electrons found from the wave height of the polarographic current-voltage curve (Fig. 1) with the aid of the Ilkovič equation is 2. At low acrylonitrile concentrations, therefore, only propionitrile is formed. *Baizer*

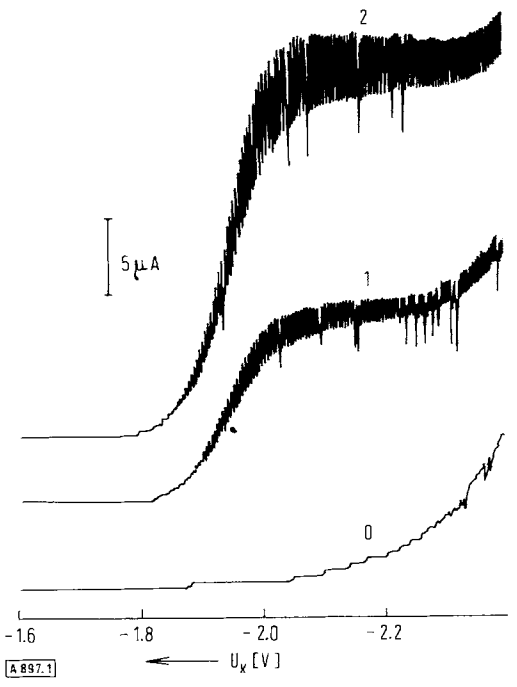


Fig. 1. Polarographic current-voltage curves of acrylonitrile in the presence of 0.1 mol/l of tetramethylammonium chloride. The numbers by the curves indicate the content of acrylonitrile (in mmol/l). For conditions see text.

emphasized in his first reports that ADN is formed in high yields only if the acrylonitrile concentration is higher than 10%[13,15]. The yield of ADN was almost quantitative at an initial AN concentration of 20%, but decreased to 7% with 10% AN and to 2% with 5% AN. At the same time, the yield of propionitrile increased. The reaction mixture also contained a high concentration of quaternary ammonium salt and water. The cathode consisted of mercury.

We have reacted mixtures of 28% of isopropanol, 16% of water, 1% of tetraethylammonium ethyl sulfate,

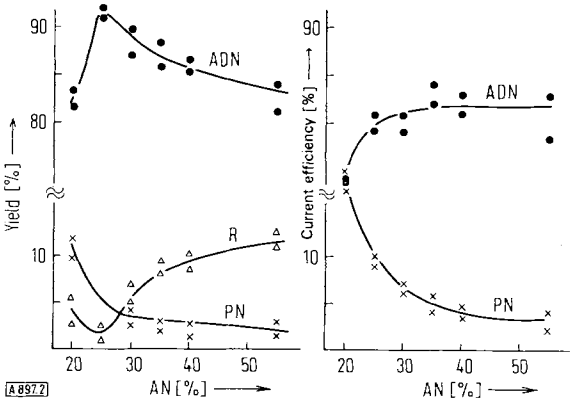


Fig. 2. Dependence of the yield on the acrylonitrile concentration. PN = propionitrile, R = oligomer. For conditions see text.

remainder AN + acetonitrile on graphite cathodes in undivided cells (cf. Fig. 10)[21]. As can be seen from Figure 2, the AN concentration has a strong influence on the ADN yield. An optimum is found for an initial AN concentration of 25 wt.% (the formation of oligomer R has decreased to a minimum). At lower AN concentrations, as in *Baizer*'s experiments, the yield decreases because of the formation of increasing quantities of propionitrile PN. The current yield shows a corresponding decrease[22].

The decrease in the formation of ADN at low monomer concentrations is reasonable in itself. The point beyond which an appreciable decrease occurs depends on the reaction conditions. *Tomilov et al.*[23] obtained high yields of ADN on an Hg cathode at AN concentrations as low as about 2.5% when the ratio of water to dimethylformamide in the reaction mixture was adjusted to an optimum value. It was also shown later[24,25] that high yields of ADN are obtained on lead cathodes in 2 to 5% solutions of acrylonitrile in the presence of *non*-lyotropic carrier salts such as tetramethylammonium sulfate. These carrier salts reduce the solubility of acrylonitrile in water, which is around 7% (at 25°C), by the salting-out effect.

These observations can be best explained if one considers that the solution compositions in the bulk of the electrolyte and at the interface are quite different. Salt effects in particular play an important part here, as is shown in Section 3.2.8.

3.2.3. Current Density

The current density plays a minor part in the hydrodimerization of acrylonitrile. Thus constant yields of ADN were observed in the range between 1 and 30 A/dm²[26] and even in the range between 14 and 128 A/dm²[27]. This suggests that the reaction does not have a free-radical mechanism, in which the yields should decrease greatly at low current densities. Since hydrogenation and hydrodimerization cannot be distinguished in the current-voltage curve in the case of acrylonitrile (both processes have the same rate-determining step), there is no prospect of increasing the selectivity by electrolysis at a constant potential (or indirectly with the aid of the current density). To obtain a good space-time yield in industry, one should not use excessively low current densities[28].

3.2.4. Water Concentration

If the water concentration is too high, the formation of proprionitrile increases, while at excessively low water concentrations, the oligomerization[29,30] becomes very pronounced. Figure 3 shows some examples for Hg cathodes from the literature[23,31], together with our own results (obtained on vibrating lead mesh cathodes, cf.[27,32]). It can be seen that the optimum water concentration depends on the AN concentration, and increases with the latter. The nature of the second solvent, on the other hand, is of minor importance.

3.2.5. pH

The pH should have a considerable influence on the yield of ADN, since excessively low pH values lead to propionitrile formation and liberation of hydrogen at the cathode, as well as to hydrolysis of the nitrile group, while excessively high pH values lead to cyanoethylation. It is therefore recommended in the first Monsanto patents that weakly alkaline solutions should be used.

It can be seen from Figure 4, in fact, that the ADN yield at an Hg cathode greatly decreases even in the weakly acidic range[13]. The situation changes when a graphite cathode

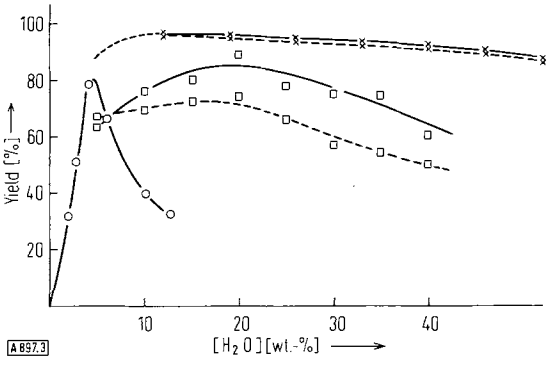


Fig. 3. Dependence of the ADN yield on the water concentration. (——) material yield, (----) current efficiency. Conditions:

	○ [23]	× [31]	□
AN [%]	≈ 3	15	50
NR_4X [%]	≈19	33	1
Auxiliary solvent	Dimethyl-formamide	Acetonitrile	Isopropanol
j [A/dm²]	1	30	20

is used, practically no change in yield being observed in this case over a wide pH range down to pH 1[22]. In conjunction with a "wick cell", electrolysis is possible even in up to 5.5 M H_2SO_4[33]. It is also possible to work at pH values above 14 if the cyanoethylation is sufficiently retarded by cooling to 0 °C[34].

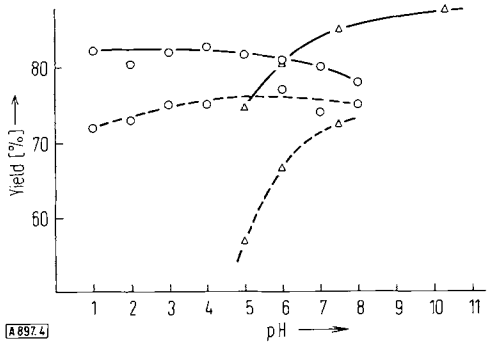


Fig. 4. Dependence of the ADN yield on the pH. (——): material yield, (---) current efficiency. Conditions: (△) 40% AN, 26% H_2O, 34% NR_4X, mercury cathode. (○) 55% AN, 16% H_2O, 28% isopropanol, 1% NR_4X, graphite cathode.

We now know that the pH can no longer be regarded as critical in this electrosynthesis. During optimization, it should be noted that a pronounced increase in pH may occur in the diffusion boundary layer in front of the cathode, particularly where convection is inadequate.

3.2.6. Temperature

The conductivity of the electrolyte increases with rising temperature, and the dissipation of the Joule heat becomes technically easier. However, the rates of chemical side reactions and the vapor pressure also increase. The range between 30 and 40 °C may be regarded as a good compromise. As was mentioned, electrolyses have been carried out even at 0 °C[34]. We have also electrolyzed acrylonitrile on Pb and Hg cathodes (in water/McKee salt[*]) at 20—50 and 80 °C (boiling point of the catholyte), and found that the yield and the current efficiency decrease rapidly with rising temperature; increasing quantities of cyanoethylation products and propionitrile are formed[35].

3.2.7. Second Solvent

A solubilizing agent is necessary in order to obtain higher acrylonitrile concentrations without excessively low water concentrations. Suitable solubilizing agents include lyotropic supporting electrolyte, *e.g.* tetraethylammonium ethyl sulfate[36,37]. Additional solvents such as acetonitrile (which is present in any case in crude AN from the Sohio process), dimethylformamide, or isopropanol have also been used. The use of acrylonitrile-in-water emulsions has also been suggested[38,25].

3.2.8. Supporting Electrolyte

As can be seen from Table 1, optimum material yields and current yields are obtained only with supporting electrolytes containing higher quaternary ammonium ions[15,39]. A decrease in the yields occurs even with tetramethylammonium salts, and this decrease becomes more pronounced with the use of tertiary ammonium salts and in particular of alkali metal salts. This cannot be due to an

Table 1. Dependence of the ADN yield on the cation of the carrier electrolyte. Anion: tosylate. The solution contains 40% of AN, 26% of H_2O, and 34% of carrier electrolyte. The deposition potential is based on a current density of 10 mA/cm².

Cation	ADN Current Efficiency [%]	ADN Yield [%]	U_K [V]
$N(C_4H_9)_4^{\oplus}$ $N(C_2H_5)_4^{\oplus}$	90	87.5	−2.89
$N(CH_3)_4^{\oplus}$ [a]	≈55	≈75	−2.72
$N(C_2H_5)_3H^{\oplus}$	16	34.3	−2.39
$Li^{\oplus}$	6	15	−2.28
$P(C_6H_5)_3CH_3^{\oplus}$	75	87.5	−1.80
$CH_2{=}CH{-}CN$	—	—	−1.80

[a] Calculated from experiments with low salt concentrations.

[*] In this case McKee salt is NEt_4 tosylate.

excessively positive deposition potential of the cations, since even $Li^{\oplus}$ is reduced only at a potential about 0.5 volts more negative than that at which acrylonitrile is reduced. On the other hand, triphenylmethylphosphonium salts give good material yields with only slightly depressed current yields, though the cation is partly discharged on electrolysis.

These observations can be readily explained as "double-layer effects". The ions of the supporting electrolyte not only serve for the transport of current and possibly for the solubilization of the substrate, but also produce many important effects at the phase boundary, which are indicated schematically in Figure 5. They influence the course of the potential in the rigid and diffuse parts of the double layer, and hence indirectly the rate of the electrode reaction. They can also compete as adsorbents for the substrate molecule. As counterions to the ionic intermediates formed, they influence the reactivity of the latter in the subsequent reactions. Thus the ionic function of a radical-anion can be so extensively shielded by a *small* cation (ion-pair formation) that it behaves as a free radical, whereas with a large cation the anionic function has a chance to act as a nucleophile. *Baizer* recently studied these relationships with the aid of cyclic voltammetry[40].

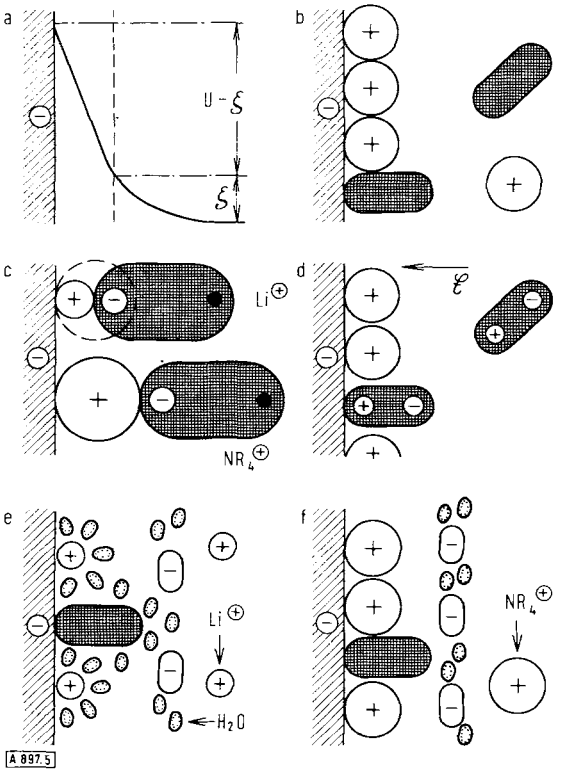


Fig. 5. Salt effects at the phase boundary, schematic. a) Influence on the rate of the electrode reaction, b) adsorption, c) action of counterions, d) orientation and polarization, e), f) action of water at the phase boundary.

Moreover, an organic molecule with a dipole moment may be oriented in the high electric fields at the phase boundary, and the dipole moment may also be considerably increased by polarization. Finally, the rate of the proton-consuming steps is extremely strongly dependent on the water concentration in the double layer. This in turn is determined by the hydration sheath of the cations, so that larger quantities of water reach the vicinity of the phase boundary in the case of alkali metal ions, but practically none in the case of the hydrophobic higher quaternary ammonium ions. This immediately explains the results in Table 1[23,41,39].

Current-voltage measurements as a function of the concentration of quaternary ammonium salt clearly show that the cations influence mainly the ζ potential (Fig. 6a), whereas they have practically no action as competing adsorbents[39]. The hydrodimerization proceeds in high yields even at very low carrier salt concentrations; the electrolysis can be carried out at industrial current densities with a carrier salt concentration of only 0.1% in special cells with a short distance between the electrodes[22,27,39]. Even in these dilute electrolyte solutions, the carrier salt cations are accumulated in the rigid part of the double layer. However, acrylonitrile has also been electrolyzed in concentrated carrier salt solutions (*e.g.* 55 wt.% of tetramethylammonium methyl sulfate)[13]. In the presence of high concentrations of lyotropic salts, the separation of the components is complicated, and requires a multi-stage extraction and distillation process[42].

In the presence of a mixture of tetramethylammonium and tetraethylammonium salts, the hydrodimer is formed in higher yields than in the presence of either of the components alone[43]. Hydrodimerization of acrylonitrile is also possible in the presence of alkali metal salts such as $NaClO_4$ or KSCN if the water concentration is kept below 10% and the reaction is carried out in the presence of high concentrations of aprotic solvents such as DMF or DMSO[44]. Under these conditions, the alkali metal ions appear to be largely resolvated.

3.2.9. Convection

As in any electrolysis, convection must be so strong that transport processes cannot become rate-determining. Moreover, the diffusion boundary layer in front of the electrode must not become too thick, since the phase boundary concentration of acrylonitrile otherwise becomes too low, and that of $OH^{\ominus}$ ions too high (Fig. 6). Particularly strong stirring is necessary in the emulsion procedure[23,38], in order to accelerate the mass transport at the AN/solution

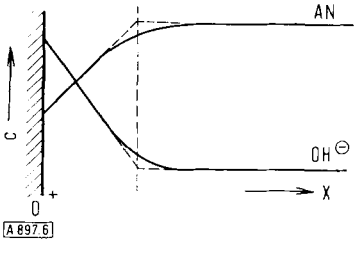


Fig. 6. Diffusion layer in the hydrodimerization of acrylonitrile, schematic. c: concentration; x: space coordinate.

and solution/electrode phase boundaries. The increased power required for stirring in this case may be of the same order of magnitude as the electrolysis power.

3.3. Mechanism

There has been a great deal of speculation on the mechanism of the hydrodimerization of acrylonitrile; however, few measurements of kinetic value have so far been carried out. Measurements at low acrylonitrile concentrations are of limited value (polarography, cyclic voltammetry), since only the hydrogenation occurs under these conditions.

Knunyants originally tried to explain his observations in the reduction with amalgam by a free-radical mechanism of the type (1) (see Schemes 2 and 3)[11].

Exclusively free-radical mechanisms are also discussed in an earlier article on electrochemical dimerizations[45]. Strong adsorption of the intermediates is suggested in an attempt to explain why free-radical initiated polymerization does not occur.

Systematic current-voltage measurements with variation of the principal parameters[26] led to a result that could not be reconciled with this free-radical mechanism, which was also opposed by the fact that the yield of hydrodimer is independent of the current density[26,27]. Figure 7

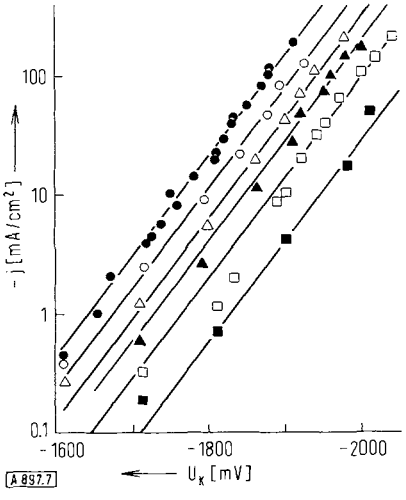


Fig. 7. Tafel lines at various acrylonitrile concentrations [26]. Electrolyte (25 °C, pH = 0): x % AN, (40 − x)% acetonitrile, 26% H_2O, 34% NR_4 tosylate. Concentration of acrylonitrile: ● 40%, ○ 20%, △ 10%, ▲ 5%, □ 1%, ■ 0.2%.

shows a semilogarithmic current-voltage plot for a series of measurements with solid cathodes, in which the acrylonitrile concentration was varied by more than two orders of magnitude. At a constant potential, the current density, *i.e.* the reaction rate at the phase boundary, increases with increasing acrylonitrile concentration. The following relation is also valid at a constant potential in the electrochemical kinetics:

$$j = k \cdot c_{AN}^{\nu}; \quad \log j = \log k + \nu \log c_{AN}$$

where ν is the reaction order with respect to acrylonitrile. A corresponding evaluation (Fig. 8) gives a reaction order $\nu_{AN} \approx 1$. Similar measurements at various water concentrations also lead to a reaction order $\nu_{H_2O} \approx 1$.

It follows from the slope of the "Tafel lines" of 120 mV, assuming a value of 0.5 for the transfer coefficient[46], that one electron is transferred in the rate-determining step.

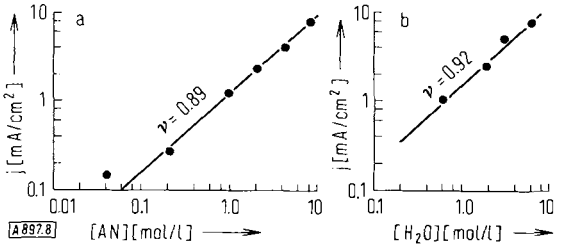
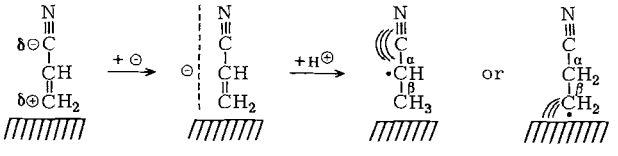


Fig. 8. Reaction order ν with respect to a) acrylonitrile and b) water [28]. Potential against saturated calomel electrode: −1.750 V, 25 °C carrier salt: tetraethylammonium tosylate. a) 26% H_2O, 34% carrier salt, acetonitrile; b) 40% acrylonitrile, 34% carrier salt, acetonitrile.

These kinetic observations were later fully confirmed by other workers[47]. Since it is not possible, as was mentioned earlier, to decide from the current-voltage curve whether hydrogenation or hydrodimerization has occurred, the slow step must be the same for both reaction paths. The only possibility was

$$CH_2{=}CH{-}CN + \ominus + H_2O \xrightarrow{\text{slow}} \cdot CH_2{-}CH_2{-}CN + OH^{\ominus}$$

The initially formed radical-anion is thus simultaneously protonated. Controversy exists regarding the site of the protonation (or of the unpaired electron). LCAO calculations for the free radical-anion show[48] that the protonation should occur on the β-C atom rather than on the α-C atom; the α radical would then be stabilized by the π system of the nitrile group.



However, these considerations ignore the fact that the reaction steps take place at the phase boundary, with the dipole oriented as illustrated. The stabilization of the β radical by the π-electron system of the metal should be much more effective than the stabilization of the α radical by the nitrile group (cf. Ref. [41]). The protonation of the radical-anion in the α position is also indicated by the argument that the proton migrates first to the position of maximum basicity, with intermediate formation of $\cdot CH_2{-}CH{=}C{=}\ddot{N}H$, which then undergoes prototropic rearrangement to form the β-C radical[15].

The cyanoethyl radical is rapidly reduced further at the prevailing potential[*], so that the steady-state free-radical concentration is extremely low. This explains why a free radical initiated polymerization does not occur.

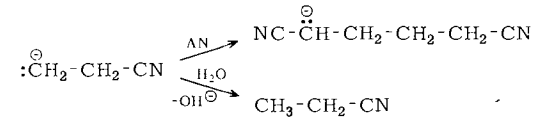
$$^{\bullet}CH_2{-}CH_2{-}CN + \ominus \xrightarrow{\text{rapid}} [{:}CH_2{-}CH_2{-}CN]^{\ominus}$$

[*] If the cyanoethyl radical is produced by cathodic dehalogenation of β-iodopropionitrile

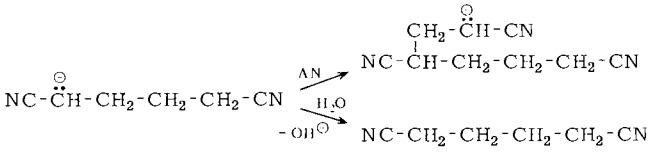
$$I{-}CH_2{-}CH_2{-}CN + \ominus \rightarrow I^{\ominus} + \cdot CH_2{-}CH_2{-}CN$$

the reduction proceeds at a much more positive potential [49].

The carbanion formed either combines with a second acrylonitrile molecule to form the anion of the dimer or is protonated to form propionitrile.



The anion of the hydrodimer is less reactive than the anion of the monomer, since the negative charge is distributed over the α-C atom and the nitrile group[50]; oligomers are therefore formed only in systems with very low water concentrations.



The first protonation step may even fail to occur at very low water concentrations, an anionic polymerization being initiated by the resulting radical anion[30].

The two other possible anionic mechanisms, starting from the radical-anion $[CH_2{=}CH{-}CN]^{\bullet\ominus}$[48,51] or from the dianion $[CH_2{=}CH{-}CN]^{2\ominus}$[7,13,23,52,53] do not agree with our kinetic findings. With increasing lifetime of the radical anion, the probability of direct dimerization of this species should increase. Some diactivated olefins form relatively long-lived radical-anions, and appear to favor this reaction path[54]. Two possibilities are available: a free-radical mechanism of type (11) or an ionic mechanism of type (5) or (6) (cf. Schemes 2 and 3); the free-radical mechanism should be favored if the anionic function is shielded by a small cation[40]. *Bard*[272] found this mechanism for dimethyl fumarate; in the case of acrylonitrile, the lifetime of the intermediates is too short for the measuring methods used. In the cathodic hydrocyclization of diactivated olefins, a "concerted" mechanism of type (5) has been proposed, *i.e.* the electron transfer and the formation of the C—C bond are closely coupled[55].

The mechanism *via* the dianion of the monomer, which has been considered by a number of authors (see above), is relatively improbable for energetic reasons. However, the two charges may move as far apart as possible after the dimerization step.

3.4. Processes in Divided Cells

The first process in divided cells that allowed the direct electrohydrodimerization of acrylonitrile to adiponitrile in high yields was developed by Monsanto[13]. A diaphragm was necessary, since lyotropic quaternary ammonium salts (such as tetraethylammonium ethyl sulfate), which undergo oxidative degradation at the anode, were used in high concentrations. An example of a typical catholyte composition is as follows: 40% of acrylonitrile, 34% of tetraethylammonium tosylate, 26% of H_2O; the anolyte consists of dilute sulfuric acid. The industrial cells have a cross section of about one square meter, and are of the filter press type.

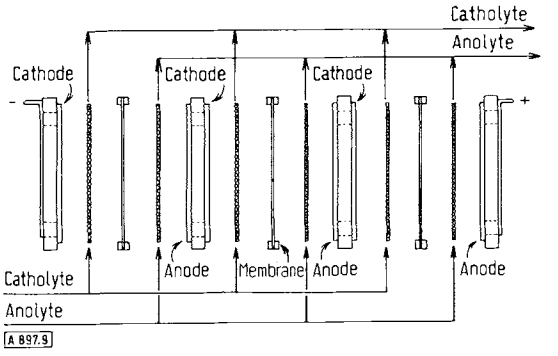


Fig. 9. Filter press cell [58].

Figure 9 shows a diagram of a cell block. The (internally cooled) bipolar electrodes consist of lead on the cathode side and lead alloy on the anode side, the latter becoming passive during operation through the formation of a PbO_2 layer. An ion exchange membrane based on polystyrenesulfonic acid is used as the diaphragm[56]. Membranes of this type have been steadily improved since the development of this industrial organic electrosynthesis, so that they now have a satisfactory lifetime[57]. The advantages over a porous diaphragm are less mixing of the anolyte with the catholyte and an improved acid/base balance in the cell. The catholyte and the anolyte are circulated separately; the Joule heat is eliminated internally *via* the internally cooled bipolar plates. The entire process was described in detail some years ago[58].

The plant in Decatur, Alabama (USA), has been in operation since 1965, and was expanded in 1969 (for economic data see Ref. [59]). The industrial importance of the process is underlined by a series of patents on technological details such as the separation of the quaternary ammonium salt from the material removed from the cell[42] (the salt must be recirculated as quantitatively as possible to maintain economy), the production of the quaternary ammonium hydroxide used for pH control in the catholyte by electrodialysis[60], the preparation of quaternary ammonium salts[61], the separation of by-products[62], the removal of traces of metal from the catholyte (these may reduce the hydrogen overvoltage of the lead cathodes during continuous operation)[63], the removal of oligomers of acrylonitrile[64], the extraction of nitriles from the anolyte by higher amines to reduce corrosion of the anode[65], the improvement of the ion exchange membrane[66], and the stabilization of the anode by lead alloys[67].

The Japanese company Asahi Chemical Industries, which, like Monsanto, has large acrylonitrile plants, has also developed a process having divided cells; a plant of this type is soon to be put into operation[68]. The company's experience in the field of ion exchange membranes proved very useful in this development[69]. The main difference from the Monsanto process is that the concentration of dissolved acrylonitrile in the aqueous phase is kept low (<5%) by nonlyotropic salts such as tetramethylammonium

sulfate[24]. Excess of AN forms an emulsion[25]. The solubility of the reaction products in the organic phase is good, while that of the salt is low, so that subsequent treatment is relatively simple. A typical catholyte composition (aqueous phase) is as follows: 5% of AN, 10% of salt, 85% of H_2O[24]. Here again, numerous patent applications, *e.g.* on problems of working up[70, 71] and on the removal of metallic impurities by carbonate precipitation[72], are indicative of the industrial development.

The Badische Anilin- & Soda-Fabrik has proposed the use of very low concentrations of quaternary ammonium salts in homogeneous solutions[73]. To be able to operate with industrial current densities under these conditions, special cells were developed, in which the liquid-permeable electrodes (meshes, sieves, or expanded sheet) are in direct contact with the ion exchange membrane. The low carrier salt concentrations facilitate working up. An additional solvent is used to homogenize the catholyte, a typical composition of which is: 77% of AN, 10% of H_2O, 10% of DMF, 3% of tetraethylammonium tosylate. It would be possible, in principle, to omit the use of carrier salts in these cells; however, low concentrations are favorable because of the salt effects, which are already pronounced. It has also been suggested[74] that these salt effects should be produced by introduction of insoluble compounds containing $-\overset{\oplus}{N}R_3$ groupings into the pores of the graphite cathode.

The Belgian Company UCB has shown[44] that good yields are also possible in the presence of Na or K salts (in divided or undivided cells) if mixtures containing low water concentrations are used. A typical reaction mixture, which is treated at 20 °C with graphite cathodes, has the composition 39% of DMSO, 27% of AN, 26% of $NaClO_4$ and 8% of H_2O.

Despite the progress in the technology of ion exchange membranes, an electrosynthesis is technically easier to carry out in a diaphragm-free cell. The better the yields and the qualities of the products, therefore, the more this process will be able to compete with the processes discussed in Section 3.4.

It has been shown that the supporting electrolyte is preferentially decomposed at the anode in the McKee system[22]. Cells with very small distances between the electrodes ($d \approx 0.2$ mm) in the form of liquid-permeable stationary[75] or vibrating[32] pairs of electrodes and capillary gap cells[21] enabled the electrolysis to be carried out at BASF at industrial current densities, despite a carrier salt concentration of only 0.5 wt.%. The product was formed in yields of 90%, with current yields of 80%. The cell voltages were so favorable that the energy consumption was less than 3 kWh per kg of product. A typical electrolyte composition is 55% of AN, 28.5% of isopropanol, 16% of H_2O, and 0.5% of tetraethylammonium ethyl sulfate. The isopropanol completely protects the acrylonitrile, which is itself fairly stable, against oxidation at the PbO_2 anode, and is itself oxidized to acetone, CO, and CO_2. The isolation of the product is greatly facilitated by the small quantities of carrier salt.

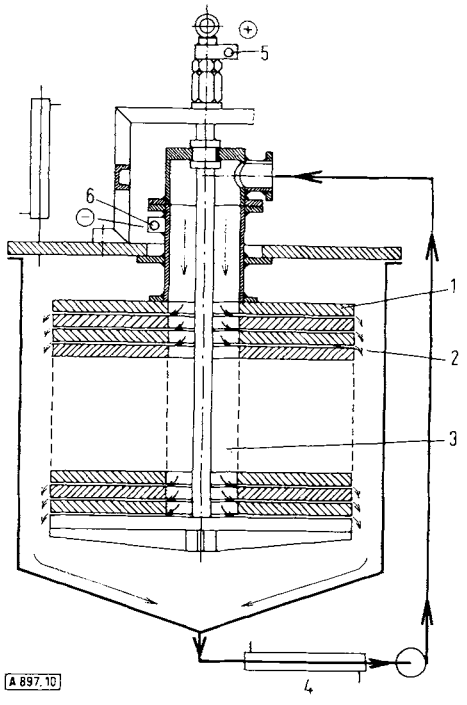


Fig. 10. Capillary gap cell. 1) Bipolar circular electrode plates; 2) capillary gap; 3) bore in the center of the stack; 4) heat exchanger; 5), 6) current leads.

Figure 10 shows one form of the capillary gap cell. It consists of a stack of circular graphite disks, which are connected bipolarly in series. The anode side is covered with PbO_2. The distance between the disks is 0.2 mm. The reaction mixture is pumped in a loop, and flows radially through the capillary gaps. The Joule heat is removed in an external heat exchanger. (The development of these cells is described in[22, 27].) The isolation of the product is simple, and consists essentially of distillation steps. Processes for the production of quaternary ammonium hydroxides[76], the improvement of the yields by the use of carrier salt mixtures[43] or by the addition of small quantities of polyacids[77], and the production of PbO_2/Ti composite electrodes[100] may be mentioned in this connection.

Knunyants has proposed the electrolysis of AN on graphite cathodes in aqueous sodium hydroxide solution[34]. The cyanoethylation of water[78] which, at 35 °C has a half-life of 20 minutes at pH = 14 and of 40 hours at pH = 12[79], is strongly retarded by the use of an electrolysis temperature of 0 °C. The yield of ADN is less than 80%, even when a neutral electrolyte (Na_2SO_4) is used[80].

Tomilov et al.[38] emulsified acrylonitrile in an aqueous phosphate buffer (1 M K_2HPO_4) containing approximately 1% of quaternary ammonium salt. The emulsion was pumped turbulently through a cell with graphite cathodes and magnetite-covered iron anodes. Despite the high water concentration and the low acrylonitrile concentration, the dimer was formed in a yield of about 90%. The process was developed further by the Belgian Company

UCB. The internal surfaces of a drilled graphite block were used as graphite cathodes, the cylindrical magnetite anodes being inserted coaxially in the drillings[51]. The corrosion of the anode was reduced by a factor of 10 on addition of polyphosphates[81]. The isolation of the product appears to be greatly simplified in this process and consists essentially of distillation of the organic phase. The electrolysis temperature must be kept at the relatively low level of 18—20 °C to minimize corrosion of the magnetite anode.

Rhône-Poulenc solved the problem of the supporting electrolyte in the undivided cell by the use of quaternary ammonium salts with anions that are stable at the anode[82]. Examples are sulfates, borates and carbonates.

3.6. Processes with Alkali Metal Amalgam

As was mentioned earlier, the industrial development in this field was started by the pioneering work of *Knunyants*[10-12], who was able to show that an approximately 10% solution of acrylonitrile in dilute mineral acid can be hydrodimerized with Na amalgam to adiponitrile in material yields of 65% and with "amalgam yields" of 35%. Though these results were not good enough to allow the process to be carried out economically, they showed the fundamental possibility of the reaction.

Katchalskii was later able to increase the yield to 75% by the addition of polymerization inhibitors[83]. This value was regarded for a long time as the maximum obtainable, until it was shown in the middle 1960's, mainly through work carried out at ICI, that yields and current efficiencies of more than 90% are quite feasible if the reaction with amalgam is carried out under the following conditions: buffering with CO_2 instead of with mineral acid[84], addition of quaternary ammonium or phosphonium salts[85], of dimethyl sulfoxide, *etc.*[86], and of hexamethylphosphoroamide[87]. Particularly good results were obtained when solutions strongly diluted with acetonitrile were used[88]. It was suggested that the actual reducing agent was not the Na amalgam but quaternary ammonium amalgam formed as an intermediate[89, 90]. The quantitative separation of the very finely divided sodium hydrogen carbonate formed proved to be very difficult on the industrial scale. Elimination of Hg from the products was also a problem. These investigations have not yet progressed beyond the pilot-plant scale.

A series of further patent applications by other workers all claim certain additives as "catalysts". They probably all act by producing an optimum water concentration in the double layer. Examples are dimethylurea[91, 92], biuret[93], diethylacetamide[94], hexamethylenetetramine[95], and tetraalkylarsonium salts[96]. It has also been suggested that the reaction should be carried out in liquid ammonia[97] or in DMSO/H_2O without buffering with acid, so that alkali metal hydroxide is obtained at the same time[98]. In a process developed by UCB to the semi-industrial scale, a mixture of AN/H_2O/formamide is allowed to react with K amalgam[99]. Dilute H_2SO_4 is added for buffering. The K_2SO_4 formed appears to be easier to separate than Na_2SO_4, and is a commercial product.

Regarding amalgam processes in general, they have the disadvantage with respect to the direct process that they are two-step processes. Large quantities of dilute (0.1%) alkali metal amalgam must be circulated. The separation of the alkali metal salt and of the mercury from the organic compounds can be problematic. We shall not discuss here whether these disadvantages can be offset by the advantage that it is industrially easier to construct an amalgam reactor than an electrolytic cell for a direct electrosynthesis. From the point of view of mechanism, the direct synthesis at an Hg cathode is substantially equivalent to the indirect synthesis with Na amalgam.

3.7. Chemical and Catalytic Processes

Attempts have been made to carry out the industrially important synthesis of ADN by catalytic hydrogenative dimerization with the addition of molecular hydrogen. Ru catalysts (at 100—200 °C and 400—500 atm) appear to be the most suitable, but the yields are still low at present because of the predominant hydrogenation to form propionitrile[101, 102].

The catalytic hydrogenation generally proceeds by a free-radical mechanism, and the surface concentration of the intermediate HX· is very low[103, 104]. Its dimerization is therefore unlikely. Ionic mechanisms have also been suggested, *e.g.* for polar substances such as nitrobenzene or quinone[105, 106]. Moreover, with decreasing coverage with H_{ad}, the mechanism is reported to change into an ionic mechanism[107], in which dimerization should be more likely.

The homogeneously catalyzed hydrodimerization of AN in the presence of carbonylmetal compounds[108, 109], in some cases with exposure to light[110], also does not proceed very selectively. The by-products include the head-to-tail dimer 1-methyleneglutaronitrile.

The hydrogenolysis of the cyclic dimer 1,2-dicyanocyclobutane, which is formed in high yields in the thermal dimerization of acrylonitrile to form adiponitrile has not yet been achieved with satisfactory yields[111]. The hydrodimerization with metals as reducing agents is of no industrial importance, owing to the stoichiometric formation of heavy metal salts. Almost quantitative yields have been obtained with Mn in DMF[112].

4. Preparative Aspects

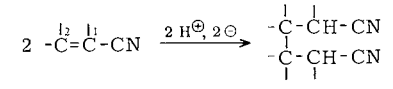
Following the classification shown in Scheme 1, this section presents the preparative aspects. Though it is not possible to go into experimental details, the essential conditions are briefly indicated, and the result is given, if possible, as the current efficiency (quantity of product as a fraction of the quantity to be expected according to *Faraday*'s law), which is more important to the electrochemist, and the yield (based on the quantity of monomer that has reacted).

4.1. Activated Olefins[113]

4.1.1. α,β-Unsaturated Nitriles

A number of results are shown in Table 2. Acrylonitrile itself was discussed very fully in Section 3. Because of the industrial importance of the reaction, this dimerization has probably been investigated more thoroughly by many authors than any other. It can nowadays be carried out with almost quantitative yields, even under industrial conditions. In other reactions, which have not been so thoroughly investigated, a poorer reported yield may be due to failure to optimize. In comparison with the direct dimerization on an Hg cathode investigated by *Baizer* and *Anderson*[114], the indirect amalgam method described by *Knunyants*[10-12] appeared to give much poorer yields. However, these results have now been optimized and good results are also obtained in the presence *e.g.* of quaternary ammonium salts[96].

Table 2. Cathodic dimerization of α,β-unsaturated nitriles. The numbers in brackets refer to the amalgam method.

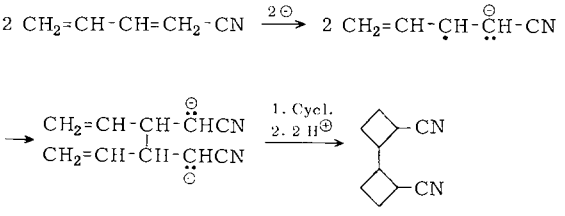


Reaction	Compound	Current Efficiency [%]	Yield [%]
(17)	$CH_2=CH-CN$	90	95 (65)
(18)	$CH_2=C(CH_3)-CN$	75 (0) [a] +10 [b]	
(19)	$(CH_3)_2C=CH-CN$	90	(37)
(20)	$CH_3-CH=CH-CN$	90 [a] + 1 [b]	
(21)	$CH_2=CH-CH_2-CN$	—	
(22)	$CH_2=CH-CH=CH-CN$		70
(23)	$NC-CH=CH-CH_2-CH_2-CN$		
(24)	$C_6H_5-CH=CH-CN$		18 [a] +50 [b]
(25)	$C_6H_5-CH=C(C_6H_5)-CN$		15 [c]
(26)	$C_6H_5-CO-CH=CH-CN$	55	

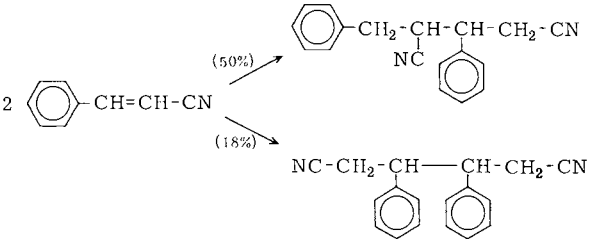
[a] 2,2-linked product.
[b] 1,2-linked product.
[c] 15% of 2,2-linkage; main product: 2-amino-1,3,4,5-tetraphenyl-2-cyclopentene-1-carbonitrile.

In the case of methacrylonitrile [reaction (18)], the dimerization does not proceed exclusively in the 2,2 position, 10% of 1,2-dimerization also taking place[115]. In the case of crotononitrile [reaction (20)] this fraction is only 1%. A patent has been granted for the hydrodimerization of allyl cyanide[116]; the reaction [(21)] is inhibited, since in the presence of 10% of crotononitrile, only the hydrodimer of the latter is formed[117]. The hydrodimerization of allylamine, which would lead directly to hexamethylenediamine, has not been achieved in H_2O/tetraethylammonium tosylate on Hg cathodes[118]. 1-Cyano-1,3-butadiene, the vinylog of acrylonitrile, has been dimerized *via* position 4 in good yields [reaction (22)] to form the dinitrile, which gave sebacic dinitrile on hydrogenation of the two remaining C=C double bonds[119,120]. Polarographic findings led to a different interpretation of the dimerization[121], according to which 2,2'-dicyanobicyclobutyl is formed.

Tetranitriles were formed by hydrodimerization of 1,4-dicyano-1-butene [reaction (23)][122,123].

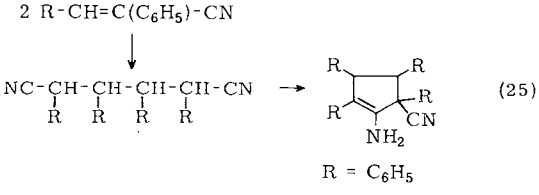


1,2-Diactivated olefins exhibit a number of peculiarities. Cinnamonitrile [reaction (24)] reversibly takes up an electron on polarography in DMF to form a stable radical-anion[121], which, according to investigations by *Baizer et al.*[54b], dimerizes mainly in the 1,2-position.



(24)

The substituents on the C=C double bond stabilize the radical-ion formed in the following order[54a]: $C_6H_5 < COOC_2H_5 < CN < C_6H_5CO$, so that this intermediate is formed at potentials that become increasingly positive in the above order. However, the species containing nitrile groups are much more reactive than any others in the subsequent reactions[54a]. Benzoylacrylonitrile dimerizes exclusively in the 1,1 position [reaction (26)]. 1-Phenylcinnamonitrile gives the 2,2-dimer (2,3,4,5-tetraphenyladiponitrile) only as a by-product, while the main product is the cyclization product, which occurs in the enamine form [reaction (25)][124]. The course of the dimerization again depends on the size of the counterion[40].



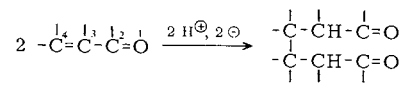
(25)

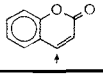
The nitrile group is generally stable to reduction; in acrylonitrile, however, selective reduction to allylamine has been observed under certain conditions (Pb, sulfuric acid solution)[125,126]. The dimerization on the C=C double bond appears to proceed best in the presence of quaternary ammonium salts, possibly with the addition of an auxiliary solvent.

4.1.2. α,β-Unsaturated Carbonyl Compounds

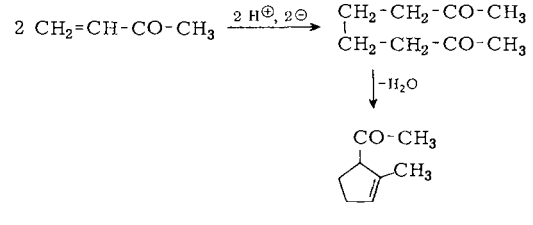
Table 3 shows some representative examples of the hydrodimerization of α,β-unsaturated ketones, esters, acids, and amides (for other ketones and aldehydes, see Section 4.2.). Though reduction of the C=O group cannot be entirely ruled out here, coupling in the 4,4-position, corresponding to the normal scheme, occurs in most cases; coupling in the 2,2 or even the 2,4 position occurs only to a small extent. *Pasternak*[127] pointed this out at an early date on the basis of polarographic results. The "pinacones" found for these compounds in the earlier literature were therefore 1,6-diketones in most cases.

Table 3. Cathodic dimerization of α,β-unsaturated carbonyl compounds.



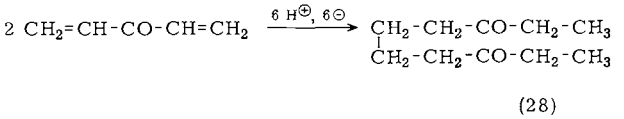
Reaction	Compound	Current Efficiency [%]	Yield [%]
(27)	$CH_2=CH-CO-CH_3$		80
(28)	$CH_2=CH-CO-CH=CH_2$		45
(29)			80
(30)	$(CH_3)_2C=CH-CO-CH_3$		up to 90
(31)	$C_6H_5-CH=CH-CO-CH_3$		74
(32)	$CH_2=CH-COOC_2H_5$	87	
(33)	$H_5C_2OCO-CH=CH-COOC_2H_5$	62	
(34)	$C_6H_5-CH=CH-COOH$		70
(35)			93
(36)	$CH_2=CH-CON(C_2H_5)_2$		73
(37)	$C_6H_5-CH=CH-CON(CH_3)_2$		40

In the past, the electrolysis was often carried out in acidic solution, and followed a free-radical course. More recently, the use of a neutral solution with quaternary ammonium salts has again been found to be advantageous, but the difference in the yields is much smaller than in the cases of nitriles[128]. *Wiemann* and *Bouguerra*, for example, found[129] that on reduction of methyl vinyl ketone on Hg cathodes at approx. —1.4 V (against the saturated calomel electrode), the diketone was formed as the main product [reaction (27)], irrespective of whether the reaction was

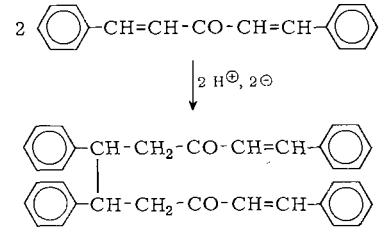


carried out in aqueous-alcoholic alkali metal acetate buffer or with tetraethylammonium tosylate in acetonitrile/water. Under these last conditions, the diketone partly cyclized to give a cyclopentene derivative.

Simonet has suggested the intermediate formation of Hg compounds[130]. Divinyl ketone with Zn/acetic acid yields 3,8-decanedione as the main product, *i.e.* the second vinyl group is hydrogenated[131]. In the case of the analogous dibenzylideneacetone, two double bonds are retained[132, 133].

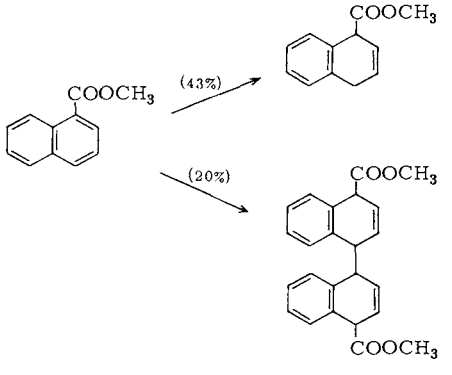


(28)



The reductive dimerization of cyclohexenone [reaction (29)][134a] or of 4,4-dimethylcyclohexenone[134b] also proceeds predominantly by the 4,4 scheme, as does the hydrodimerization of mesityl oxide[130, 135b–135d], which has been known since the work of *Law* (1912)[135a]. *Wiemann* and *Bouguerra*[135b] were also able to isolate furan derivatives in large quantities. Benzylideneacetone [reaction (31)][135a, 127] and dibenzoylethylene[54b] are further examples.

Ethyl acrylate [reaction (32)][114, 136a, 136b] and methyl acrylate[136c] have been hydrodimerized in high yields to the esters of adipic acid. The dimerization of acrylic acid has now also been achieved[137]. The reaction of free cinnamic acid [reaction (34)] was achieved in good yields in acidic aqueous alcoholic solution as early as 1943 by *Wilson* and *Wilson*[138, 139]. Coumarin, as an unsaturated lactone, dimerizes almost quantitatively in the 4,4 position [reaction (35)][140, 141]. *Misono*[142, 143] has reported on the dimerization of α,β-unsaturated aldehydes, which proceeded relatively nonuniformly. The reaction of α,β-unsaturated amides, such as diethylacrylamide [reaction (36)][114], cinnamic acid dimethylamide [reaction (37)][154b], or cyclohexenecarboxamide[144], proceeded selectively in the 4,4 position.



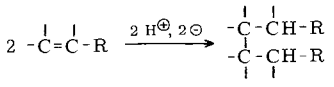
(38)

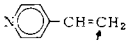
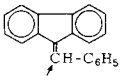
An example of a vinylogous reaction is the reaction of methyl 1-naphthoate [reaction (38)]. In addition to the 1,4-dihydro compound, the 4,4 hydrodimer is formed on reduction with Na amalgam[145].

4.1.3. α,β-Unsaturated Hydrocarbons

Unsaturated hydrocarbons are generally reduced only at very strongly negative potentials. The radical-anions formed are extremely strong bases, so that even when the proton activity of the solvent is very low, protonation to give the hydrogenation product is favored over dimerization. There are consequently only a few known examples in this series (Table 4).

Table 4. Cathodic dimerization of α,β-unsaturated hydrocarbons.



Reaction	Compound	Current Efficiency [%]	Yield [%]
(39)	C_6H_5—CH=CH—C_6H_5		30
(40)		82	
(41)		66	

Wawzonek[146] was able to hydrodimerize stilbene in a yield of 30% in DMF [reaction (39)] (but not in acetonitrile) on Hg cathodes in the presence of tetrabutylammonium iodide. The hydrodimerization of phenanthrene was also achieved under similar conditions[147]. *Baizer*[148] dimerized 9-benzylidenefluorene in accordance with reaction (41) in a yield of 66%; only 8% of hydrodimer could be obtained with 2-phenyl-1,3-butadiene. 2-Vinylpyridine and 4-vinylpyridine can again be converted into dimers in high yields[149]. The electrolytic dimerization product of *N*-vinylcarbazole is formulated as a cyclobutane derivative[150].

4.2. Ketones and Aldehydes

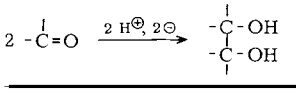
The hydrodimerization of ketones and aldehydes, which has been known for some time, leads to pinacols, *i.e.* derivatives of ethylene glycol. As can be seen from Table 5, there is a considerable difference even in the yield between the aliphatic and the aromatic series (for α,β-unsaturated carbonyl compounds see Section 4.1.2).

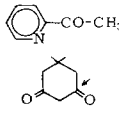
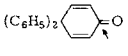
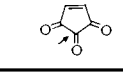
4.2.1. Aliphatic Ketones and Aldehydes

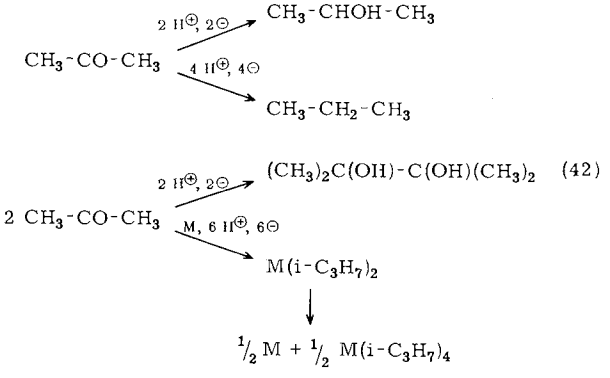
Despite many investigations, some of which were carried out a long time ago, no clear picture has yet emerged regarding the hydrodimerization of acetone. The reason for this may lie in the large number of possible reaction paths.

A free radical mechanism is certain on the basis of polarographic measurements, which have been carried out in particular on aromatic ketones. A central intermediate is the radical anion of the ketyl type, which is formed in acidic solution at relatively positive potentials, and which arises *via* e p or p e, depending on the pH value. A comprehensive description of the complicated situation has

Table 5. Cathodic dimerization of ketones and aldehydes.

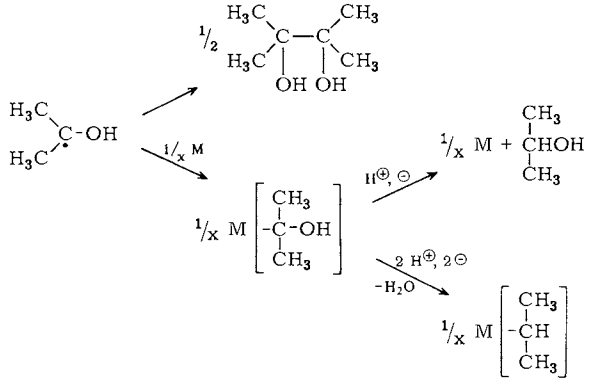


Reaction	Compound	Cathode	Current Efficiency [%]	Yield [%]
(42)	CH_3—CO—CH_3	Pb/Sn, Pb/Cu, C(H_2SO_4)	13	60
(43)	C_2H_5—CO—CH_3	Zn (NaOH)	8	25
(44)	$(CH_3)_2$CH—CO—CH$(CH_3)_2$	Zn		11
(45)		Pb		30
(46)	CH_3—CH_2—CHO	Hg	20	60
(47)	CH_2OH—CHOH—CHO	Zn		82
(48)	C_6H_5—CO—CH_3	Pb, Hg, Zn	97	96
(49)	C_6H_5—CO—C_6H_5	Hg	95	
(50)		Hg, Cu		98
(51)		Hg	70	
(52)	C_6H_5—CO—CH_2—CO—C_6H_5	Hg		90
(53)		Hg		95
(54)		Hg		≈50
(55)	C_6H_5—CHO	Hg		80



(42)

been published by *Zuman et al.*[6] (see also[5, 127]). It has been suggested that isopropanol is formed on Hg or Pb mainly *via* the organometallic compound, since the quantities of the two by-products are interdependent[151].



A characteristic feature is the extremely strong dependence of the results on the nature and state of the cathode material. The most suitable materials for pinacol formation appear to be Hg, Pb, Pb/Cu[151] and Pb/Sn alloys[152], which were recommended even in early patents[153]. However, the current efficiencies are poor, with values of 13%[151, 152]; the high values reported in the early publications could not be reproduced. Graphite is also suitable[154, 155]; this material has the advantage that the formation of organometallic compounds is impossible. A patent on the synthesis of pinacols with Na amalgam (80% material yield) actually describes an electrolysis on graphite, since carbon is in simultaneous contact with the Na amalgam and with the alkaline reaction mixture[156]. A yield of 60% was also found on Hg in alkaline media[157].

The strong interaction of acetone with the cathode can be seen from Figure 11. The cathodic current-voltage curve in the base electrolyte has been recorded for several metals. Evolution of hydrogen is observed. After the addition of acetone at a constant current density, the potential is displaced in the negative direction in most cases, and the evolution of H_2 stops. After a few minutes, a new steady-state value is reached. This unexpected displacement of the current-voltage curve, which has also been observed by Japanese authors[158], can be explained by strong adsorption of intermediates, which completely blocks the evolution of hydrogen and allows the further reactions of the intermediates to proceed only at negative potentials.

Slotterbeck[159] was able to obtain a material yield of 60% with a current yield of 50% for short periods on copper electrodes freshly electroplated with lead, but these values decreased considerably after only one day. It was found[160] that with cathodes electroplated with zinc, the result depends on the support; this may be due to orientation effects.

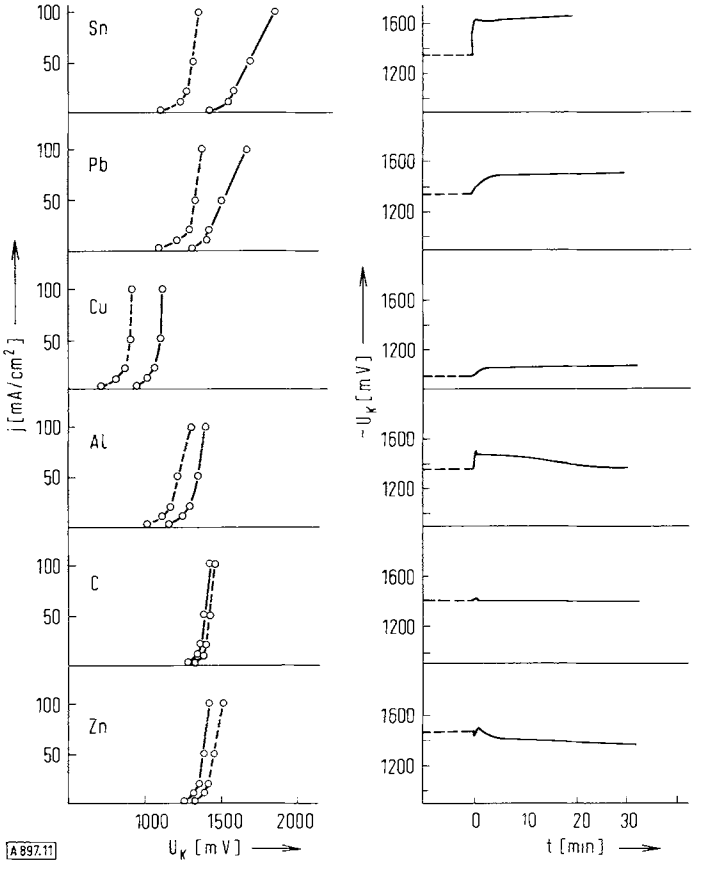


Fig. 11. Electroreduction of acetone in aqueous sulfuric acid. Left: current-voltage curves, right: voltage-time curves. (---) 1 N H_2SO_4; (——): 1 N H_2SO_4 + 1 mol/l of acetone. Current density $j = 50$ mA/cm².

The electrosynthesis of pinacol was of industrial interest for some decades, since it allowed direct access to 2,3-dimethyl-1,3-butadiene, an intermediate for the production of methyl rubber. The many early patents testify to the development work carried out. An original cell with an overlayered catholyte, in which no diaphragm is needed, is the subject of one of these patents[161]. Other aliphatic ketones such as methyl ethyl ketone [reaction (43)][162], diethyl ketone[163], diisopropyl ketone [reaction ((44)][164], or cyclohexanone [reaction (45)][165] also give the pinacols only in moderate yields.

This is also true of aliphatic aldehydes such as acetaldehyde and propionaldehyde [reaction (46)][166]; according to a Russian patent[167], however, glyceraldehyde can be hydrodimerized in high yields to the hexitol [reaction (47)]. Glyoxylic acid (which can be obtained electrochemically from oxalic acid) can be converted into tartaric acid[168].

4.2.2. Aromatic Ketones and Aldehydes

In the aromatic series, the ketyls formed as intermediates in the reduction are stabilized by the aromatic system. The tendency to form organometallic compounds is much smaller than in the aliphatic series, but the reactivity is just high enough for the dimerization to proceed preferentially. The ketyl of benzophenone can be readily detected and followed kinetically by ESR spectroscopy[169], with the rotating ring-disk electrode[170], by cyclic voltammetry, and even polarographically[171].

Almost quantitative yields are obtained for acetophenone [reaction (48)][172-174], propiophenone[175,176], and the higher alkylphenones[176]. *Stocker et al.*[174] investigated the stereoselectivity of the pinacol formation for acetophenone. In alkaline media, it was possible to increase the DL/*meso* ratio to 3, irrespective of the cathode material. Further examples are 2-acetylfuran[177], 2-acetylthiophene[178], and 2- and 3-acetylpyridine[179][*], which has also been synthesized industrially as a pharmaceutical intermediate[180]. The same is true of *p*-hydroxypropiophenone[181,182], which has been dimerized industrially to the glycol with a material yield of 50%.

Diketones, such as dimedone [reaction (51)][183], 1,3-diphenyl-1,3-propanedione [reaction (52)][184] and phenyl glyoxylate[185] are also dimerized smoothly because of the mutual activation of the CO groups. Keto groups in crossed conjugated systems such as cyclohexadienone[186] or croconic acid [reaction (54)][187] (cf. Table 5) also react to give the pinacol in high yields. Because of the double activation of the CO group, the dimerization takes place in the 2,2 position and not in the 4,4 position.

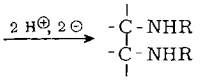
Benzaldehyde gives hydrobenzoin, which is also formed on reduction of the product obtained by chemical condensation. The DL/*meso* ratio can be as high as 3.25[188]. With vanillin as the starting material, the pure *meso* form of hydrovanilloin is obtained for steric reasons[189]. Salicylaldehyde also gives the pinacol[190]. The yield increases with increasing substrate concentration.

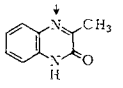
4.3. Azomethines

The cathodic hydrodimerization of azomethines leads to derivatives of ethylenediamine (cf. Table 6). The hydrolysis of the monomer must be suppressed by the use of low temperatures and neutral or alkaline solution[191]. *N*-Benzylideneaniline gives medium yields on Hg cathodes [reaction (56)][192] but almost quantitative yields on reduction with alkali metal[193]. Asymmetric optical induction was observed in the reduction of *N*-(α-methyl benzylidine)-benzylamine on Hg cathodes in the presence of chiral supporting electrolyte [reaction (57)][194]. On lead cathodes, the hydrodimer is formed above all in alkaline solution[195]. Quinazoline is a cyclic compound with an activated C=N bond[196]. The 4,4-dimer formed [reaction (58)] can be readily cleaved again by oxidation. In the case of quinoxalones alkylated in position 3, the dimerization occurs by formation of an N—N bond [reaction (59)], which can also be readily broken again[197].

[*] For 2-acetylpyridine, unlike for acetophenone, the DL/*meso* ratio is found to depend on the electrode material.

Table 6. Cathodic dimerization of azomethines.

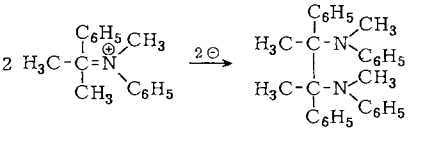


Reaction	Compound	Yield [%]
(56)	$C_6H_5-\underset{\uparrow}{CH}=N-C_6H_5$	99
(57)	$C_6H_5-\underset{\uparrow}{C}(CH_3)=N-C_6H_5$	
(58)		
(59)		

4.4. Cations

4.4.1. Immonium Ions

The hydrodimerization of immonium ions is similar to the hydrodimerization of azomethines. *Andrieux* and *Savéant*[198,199] have investigated this field very thoroughly.



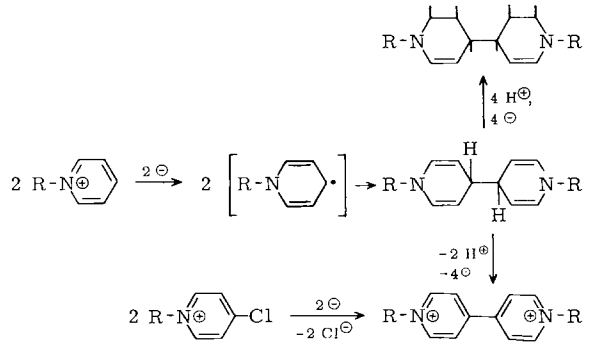
(60)

On discharge, free radicals are formed, and can be detected by cyclovoltammetry[199] and ESR spectroscopy[200]. In most cases, *e.g.* in reaction (60), the primary electron transfer is irreversible, and a free radical mechanism leads to the dimer. Cations highly substituted with aromatic groups are reversibly discharged to form stable radicals. The electrolysis must be carried out in acetonitrile owing to the ease of hydrolysis of the immonium ions.

4.4.2. Pyridinium (Quinolinium) Ions

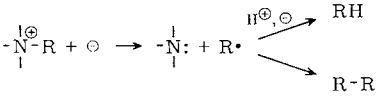
This type of cathodic dimerization is also similar to the reaction with azomethines. *Emmert* was able to show that in the reduction of pyridinium or quinolinium salts on lead in sulfuric acid solution, tetrahydrobipyridyl or tetrahydrobiquinolyl is formed[201], the reaction proceeding *via* deeply colored radicals as intermediates. The dimerization takes place in the 4,4 and 2,2 positions, and to a small extent in the 2,4 position. Tetrahydrobipyridyl can be reduced further to the octahydro product, but can also be oxidized *e.g.* with air to the dication; because of the herbicidal activity of these compounds, both the reduction of pyridinium salts with alkali metal amalgam or cathodic

reduction on lead in alkaline solution[202,203] and the oxidation to the dication[204] have been subjects of recent development work. By reversible uptake of an electron, the dication can be reduced to a radical-cation[205,206]. It has also been obtained in one step, by reduction of 4-chloro- or 4-cyanopyridinium salts; the substituents are eliminated as anions[207,208].



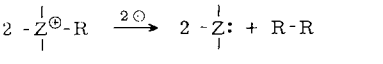
4.4.3. Other Cations

The reductive cleavage of quaternary ammonium ions was discovered by *Emmert*[209]. *Horner* later constructed a cleavage series for the groups removed[210]. Only the hydrogenated product is formed in aqueous solution[210].



In DMF[211] and hexamethylphosphoramide[212], on the other hand, the formation of dimers was observed (cf. Table 7). Ylides are also obtained with phosphonium-[213]

Table 7. Cathodic dimerization of ammonium, phosphonium, and sulfonium ions.

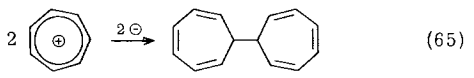


Reaction	Compound	Yield [%]
(61)	$C_6H_5-\overset{\oplus}{N}(CH_3)_2-\underset{\uparrow}{CH_2}-C_6H_5$	35
(62)	$(CH_3)_3\overset{\oplus}{N}-\underset{\uparrow}{CH}(CH_3)-C_6H_5$	30
(63)	$(C_6H_5)_3\overset{\oplus}{P}-\underset{\uparrow}{CH_2}-C_6H_5$	31
(64)	$(CH_3)_2\overset{\oplus}{S}-\underset{\uparrow}{CH_2}-C_6H_4-NO_2(p)$	

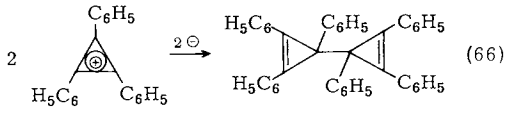
and sulfonium salts[214]. The cleavage of the dimethyl-*p*-nitrobenzylsulfonium ion occurs at such positive potentials (0.7 V) that the nitro group is not attacked, and the dimeric product *p,p'*-dinitrobibenzyl can be isolated[215].

4.4.4. Cyclic Cations

As can be seen from reactions (65) and (66), cyclic cations such as the tropylium ion[216,217] and the triphenylcyclopropenylium ion[218,219] dimerize quantitatively when discharged cathodically or with reducing agents.



(65)

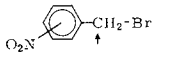


(66)

4.5. Halogen Compounds

The electrochemical reduction of halogen compounds can lead, with elimination of halide ions, to dimeric products. The frequently observed formation of organometallic compounds points to a free-radical mechanism. The industrially important dimerization of β-chloropropionitrile [reaction (67)] to form adiponitrile either with Na amalgam[220,221] or cathodically[222,223] is the subject of several patents. One disadvantage is the chloride that is always formed. The dimerizations of benzyl bromide[224] and of nitrobenzyl bromide [reaction (68)][225] have also been intensively studied. The latter reaction was carried out in acetonitrile with tetraethylammonium perchlorate.

Table 8. Cathodic dimerization of halogen compounds.

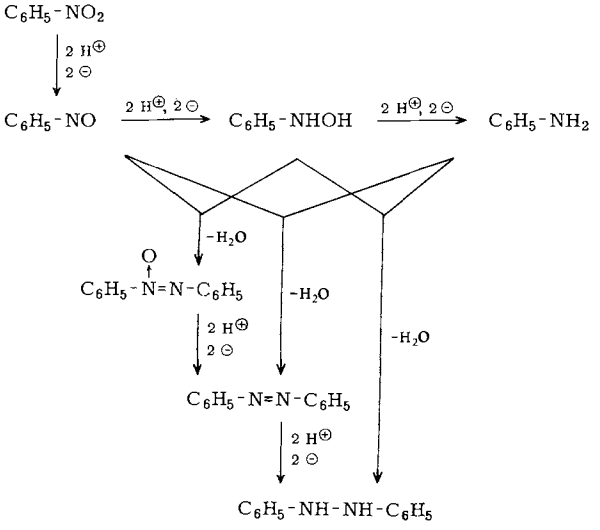
Reaction	Compound	Yield [%]
(67)	$NC-\underset{\uparrow}{CH_2}-CH_2-Cl$	90
(68)		
(69)	$R-CO-\underset{\uparrow}{CH_2}-CH_2-Cl$	
(70)	$(p\text{-}H_3C-C_6H_4)_2CH-\underset{\uparrow}{CH_2}-Cl$	

In earlier work[226], the dimer of 1,1-di-*p*-tolyl-2-chloroethane was obtained [reaction (70)] (cf. Table 8). β-Chloro ketones give diketones[227].

4.6. Nitroaromatic Compounds

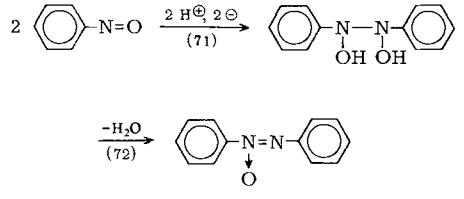
The classical reductive dimerization of aromatic nitro compounds[228] to form azoxybenzene, azobenzene, and hydrazobenzene derivatives (cf. Scheme 4) can be formally regarded as a condensation of the intermediates. The best yields are obtained in alkaline solution; the intermediate azoxybenzene can be intercepted in aqueous solution, since it is sparingly soluble, and is therefore withdrawn from the further reduction. However, as was shown by *Haber* in his fundamental investigation[229], azoxybenzene is also formed in alcoholic aqueous solution (with a current yield of 76%) if the electrolysis is carried out at a constant potential ($U_K = -0.84$ V). Hydroxylamine reacts very

rapidly with nitrosobenzene to form azoxybenzene. An electrochemical mechanism, *e.g.* in accordance with reactions (71) and (72), thus does not seem to be ruled out. Trifluoronitrosomethane can be dimerized cathodically[273]. The formation of an N—N bond *via* the hydrodimerization of a C=N bond was mentioned in Section 4.3.



Scheme 4. Cathodic dimerization of nitroaromatic compounds, with nitrobenzene as the example.

Hydrazobenzene has been produced on the industrial scale with a current efficiency of 90% as an intermediate for the production of benzidine. The divided cells were fitted with steel cathodes covered with spongy lead[230–232].



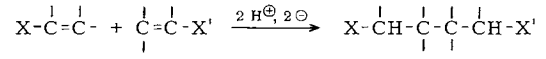
4.7. Mixed Dimers with Identical Activated Groups

The mixed dimerization of two activated olefins or two ketones A and B should lead preferentially to the mixed dimer AB if the reaction is carried out close to the potential of the more easily reducible component (A), with introduction of a large excess of the other component (B)[233]. In most cases, an ionic mechanism appears to occur. A reacts at the cathode to form an anionic intermediate ($A^{\bullet\ominus}$, $AH^{\ominus}$), which reacts as a nucleophile with the acceptor molecule B. Free-radical mechanisms cannot be ruled out, *e.g.* in the case of the ketones.

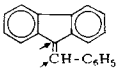
Some characteristic examples are shown in Table 9. Ethyl acrylate and acrylonitrile, whose reduction potentials differ by only 0.1 volt, react to give the cyano ester in a material yield of 60% [reaction (73)] at a cathode[222, 234], or with sodium amalgam[235]. This electrolysis has also been carried out in undivided cells[236]. In the coreduction of diethyl maleate and acrylonitrile, whose reduction potentials differ considerably (0.5 V), *Baizer* made the interesting observation that the yield of mixed dimer increases rapidly as the potential becomes more negative [reaction (74)][237]. This observation has been confirmed by other examples[238]. Even when the reaction was carried out at the potential of the less easily reducible compound, a large quantity of mixed product was obtained. To explain this, it is assumed that the reactivity of the acceptor increases with increasing potential as a result of a field effect. The concentration of the acceptor in the diffusion layer is also much higher than that of the electroactive particle, which can react even at the limiting current density. The specific adsorption of the acceptor may also play some part.

Other examples are the reaction of acrylonitrile with 1,4-dicyano-1-butene[239], vinylpyridine[240], and mesityl oxide [reaction (76)][241]; with the last of these combinations, several cyclic products are also formed[242]. With 9-benzylidenefluorene [reaction (77)][243], acrylonitrile acts as the donor; an interesting feature here is the double addition, in which 9,10-dicyanoethylbenzylidenefluorene is formed.

Table 9. Cathodic codimerization of compounds with identical activated groups.



Donor (A) Acceptor (B)

Reaction	Donor	Acceptor	Yield [%]
(73)	$H_5C_2OCO—CH=\underset{\uparrow}{C}H_2$	$\underset{\uparrow}{C}H_2=CH—CN$	60
(74)	$H_5C_2OCO—CH=\underset{\uparrow}{C}H—COOC_2H_5$	$\underset{\uparrow}{C}H_2=CH—CN$	23
(75)	$NC—\underset{\uparrow}{C}H=CH—CH=CH_2$	$\underset{\uparrow}{C}H_2=CH—CN$	55
(76)	$CH_3—CO—CH=\underset{\uparrow}{C}(CH_3)_2$	$\underset{\uparrow}{C}H_2=CH—CN$	
(77)	$NC—CH=\underset{\uparrow}{C}H_2$		
(78)	$(CH_3)_2N$-C6H4-$CO-CH_3$	CH_3O-C6H4-$CO-CH_3$	35
(79)	$C_6H_5—CO—C_6H_5$	$CH_3—CO—CH_3$	18

In series of ketones, *Allen* mentioned a number of mixed hydrodimerizations, *e.g.* of *p*-dimethylaminoacetophenone and *p*-methoxyacetophenone [reaction (78)][244]. *Nicolas* and *Pallaud* recently combined acetone with benzophenone [reaction (79)][245].

4.8. Mixed Dimers with Different Activated Groups

Most investigations in this field are concerned with the reaction of acetone with an activated olefin (cf. Table 10). As was shown earlier, acetone itself dimerizes only with poor yields. As early as 1965, *Sugino* and *Nonaka* reported that acetone and acrylonitrile give the mixed hydrodimer in good yields in sulfuric acid solution [reaction (80)][246,247]. *Brown* and *Lister* were able to detect a free-radical mechanism by kinetic measurements[248]; even at $U_K = -1.3$ V, ketyls are formed, and these add to the acrylonitrile.

In neutral solution in the presence of quaternary ammonium salts, *Baizer* recently obtained the mixed hydrodimer in a material yield of 85%[238]. Since unprotonated acetone is reduced only at $U_K = -2.4$ V, the roles are reversed in this case.

Nicolas and *Pallaud* coelectrolyzed acetone with hydrocarbons such as styrene [reaction (81)], butadiene, and cyclohexene, and obtained tertiary alcohols in moderate yields[236,249]. Similar coelectrolyses of acetone with pyridine [reaction (82)][250] and benzophenone[240] have been described. Reaction with allyl alcohol leads to very good yields of 4-methyl-1,4-pentanediol, which is cyclized with dilute sulfuric acid to 2,2-dimethyltetrahydofuran[251,252].

The mixed dimerization of acrylonitrile with halogen compounds such as β-chloropropionitrile (→ adiponitrile) [reaction (85)][220,253] or chloro ketones[254] has already been examined in detail.

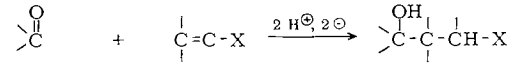
The intermediates formed on cleavage of quaternary phosphonium ions [reaction (86)][255,256] and tertiary sulfonium ions[257] can add to acrylonitrile and similar compounds.

The mixed coupling of activated olefins with azomethines or azo compounds leads to cyclic products[113,258].

A Japanese patent describes the mixed dimerization of acrylonitrile and acetonitrile to form glutaronitrile[259].

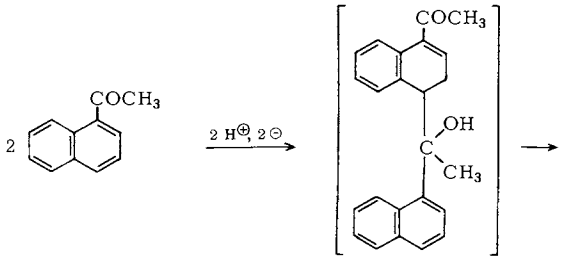
Two examples that prove only on closer inspection to belong to this section are the hydrodimerization of 1-acetylnaphthalene [reaction (87)][260] and the hydrodimerization of methacrolein [reaction (88)][261].

Table 10. Cathodic codimerization of compounds with different activated groups.

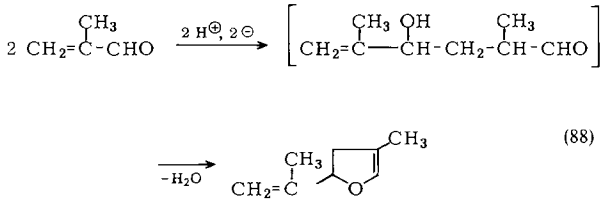


Donor (A) Acceptor (B)

Reaction	Donor	Acceptor	Current Efficiency [%]	Yield [%]
(80)	$CH_3-CO-CH_3$	$CH_2=CH-CN$	70	70
(81)	$CH_3-CO-CH_3$	$CH_2=CH-C_6H_5$	25	42
(82)	$CH_3-CO-CH_3$			73
(83)	$CH_3-CO-CH_3$	$CH_2=CH-CH_2OH$	70	95
(84)	$C_6H_5-CO-C_6H_5$	$CH_2=CH-CN$		15
(85)	$Cl-CH_2-CH_2-CN$	$CH_2=CH-CN$	90	90
(86)	$(C_6H_5)_3\overset{\oplus}{P}-CH_2-CH_2-CN$	$CH_2=CH-C_6H_5$		10



(87)

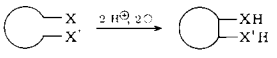


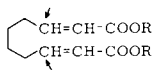
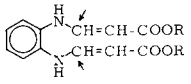
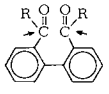
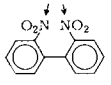
(88)

4.9. Cyclizations

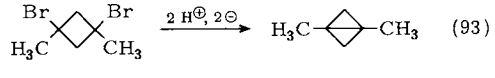
In electrochemical cyclizations, any of the dimerization reactions discussed so far can in principle proceed *intramolecularly* if the steric conditions in the molecule allow this. Some examples are shown in Table 11; a detailed review of this subject was published in 1969[262].

Table 11. Cathodic cyclizations. R = alkyl.

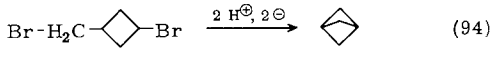


Reaction	Compound	Current Efficiency [%]	Yield [%]
(89)		90	
(90)		86	
(91)			50
(92)			95

The ring closure can be carried out on some activated bisolefins with high yields [cf. reaction (89) and (90)][263-265]. The pinacol formation between two keto groups has also been used for cyclization [reaction (91)][266]. It was similarly shown at a very early date that the dinitro compound gives the cinnoline (N=N linkage) in accordance with reaction (92)[267].



(93)



(94)

The cathodic elimination of halogen has often been used for ring closure reactions; whereas dibromodimethylcyclobutane can be smoothly reduced to the bicyclic compound (material yield 94%) in accordance with reaction (93)[268-270], bicyclo[1.1.1]pentane is formed from bromo(bromomethyl)cyclobutane [reaction (94)] in a material yield of only 4%. The main product is 1,4-pentadiene, which is formed by ring cleavage[271].

5. Concluding Remarks

Whereas the investigation of electrochemical "homodimerizations" has been brought to some sort of conclusion through the rapid developments of the past ten years, the investigation of the "heterodimerizations" is just beginning (cf. Sections 4.7 and 4.8). The number of possible variations is immense. The use of the principle of "coelectrolysis", in which at least two organic substrates are allowed to react together in an electrolytic cell, one of these substrates being converted at the electrode into reactive intermediates, which react further with the second component, will lead to many valuable preparative results in the future. Specific electrochemical factors such as supporting electrolyte effects, concentration profiles in the diffusion layer, and adsorption will lead in this work to unexpected products. Together with the undeniable technological advantages of this reaction technique, this will help greatly toward the advance of organic electrosynthesis.

Received: July 13, 1971 [A 897 IE]
German version: Angew. Chem. *84*, 798 (1972)
Translated by Express Translation Service, London

[1] *M. M. Baizer* and *J. P. Petrowitsch*, Progr. Phys. Org. Chem. *7*, 189 (1970).
[2] *L. Eberson* and *H. Schäfer*, Fortschr. Chem. Forsch. Vol. 21 (1971).
[3] *I. L. Knunyants* and *N. P. Gambarian*, Usp. Khim. *23*, 781 (1954).
[4] *M. E. Peover* in *A. J. Bard*: Electroanalytical Chemistry. Marcel Dekker Inc., New York 1967, Vol. 2, p. 1.
[5] *P. J. Elving* and *J. T. Leone*, J. Amer. Chem. Soc. *80*, 1021 (1958).
[6] *P. Zuman, D. Barnes*, and *A. Rivolova-Kejharowa*, Discuss. Faraday Soc. *45*, 87 (1968).
[7] *Y. Arad, M. Levy*, and *D. Vofsi*, J. Org. Chem. *34*, 11 (1969).
[8] *P. H. Given* in *H. Berg*: Tagungsberichte zum 1. Jenaer Symposium (1962) über Polarographie in Chemotherapie, Biochemie und Biologie. Akademie-Verlag, Berlin 1964.
[9] *B. Kastening*, Chem.-Ing.-Tech. *42*, 190 (1970).
[10] *I. L. Knunyants et al.*, UdSSR-Pat. 105286 (1954).
[11] *I. L. Knunyants* and *N. S. Wjasankin*: Report on the 4th Electrom. Congress Moscow 1956. Nauka Moscow 1959, p. 227.
[12] *I. L. Knunyants* and *N. S. Wjasankin*, Izv. Akad. Nauk SSSR, Ot. Khim. Nauk *1957*, 238.
[13] *M. M. Baizer*, Belg. Pat. 623657 and 623691 (1962), cf. US-Pat. 3193480/81, Monsanto.
[14] *M. M. Baizer*, Tetrahedron Lett. *1963*, 973.
[15] *M. M. Baizer*, J. Electrochem. Soc. *111*, 215 (1964).
[16] *W. Löb*, Z. Elektrochem. *1*, 293 (1895).
[17] *F. Fichter*: Organische Elektrochemie. Steinkopff, Leipzig 1942.
[18] *A. P. Tomilow, V. A. Klimow*, and *S. L. Warschawskii*, Khim. Prom. SSSR *1966*, 12.
[19] US-Pat. 3332970 (1964), Shell; *I. N. Brago, L. V. Kabaak*, and *A. P. Tomilow*, Zh. Vses. Khim. Obshchest. *12*, 472 (1967).
[20] Belg. Pat. 649625 (1963), Du Pont.
[21] Belg. Pat. 729856, DOS 1804809 (1968).
[22] *F. Beck*, Lecture at the Conference of the Electrochemical Society, Los Angeles 1970; cf: J. Appl. Electrochem. *2*, 59 (1972).
[23] *L. G. Feoktistow, A. P. Tomilow*, and *I. G. Sewastjanowa*, Elektrokhimiya *1*, 165 (1965).
[24] French Pat. 1503244 (1965), Asahi.
[25] Dutch Pat. 6708254—56 (1966), Asahi.
[26] *F. Beck*, Chem.-Ing.-Tech. *37*, 607 (1965).
[27] *F. Beck* and *H. Guthke*, Chem.-Ing.-Tech. *41*, 943 (1969).
[28] *F. Beck*, Chem.-Ing.-Tech. *42*, 153 (1970).
[29] *M. M. Baizer* and *J. D. Anderson*, J. Org. Chem. *30*, 1351 (1965).
[30] *F. Beck* and *H. Leitner*, Angew. Makromol. Chem. *2*, 51 (1968).
[31] Jap. Pat. 26489/68 (1965), Asahi.
[32] DBP 1298087 (1966), BASF.
[33] US-Pat. 3492209 (1966), Hooker.
[34] *I. L. Knunyants, S. L. Warschawskii, A. P. Tomilow*, and *L. V. Kabaak*, French Pat. 1401175 (1963).
[35] *F. Beck* and *J. Floss*, unpublished.
[36] *R. H. McKee et al.*, Trans. Electrochem. Soc. *62*, 203 (1936); *65*, 301, 327 (1934); *68*, 229 (1935).

[37] *A. Dobry-Duclaux*, Chem.-Ztg. *76*, 805 (1952).

[38] *A. P. Tomilow et al.*, Dutch Pat. 6610378 (1965).

[39] *F. Beck*, Ber. Bunsenges. Phys. Chem. *72*, 380 (1968).

[40] *J. P. Petrowitsch* and *M. M. Baizer*, J. Electrochem. Soc. *118*, 447 (1971).

[41] *I. Gillet*, Bull. Soc. Chim. Fr. *1968*, 2919; cf. Chem.-Ing.-Tech. *40*, 573 (1968).

[42] DOS 1543196 (1964), Monsanto.

[43] Belg. Pat. 726519 (1968), BASF.

[44] Dutch-Pat. 6704123 (1966), UCB.

[45] *M. Ja. Fioschin* and *A. P. Tomilow*, Khim. Prom. SSSR *40*, 649 (1964).

[46] *K. J. Vetter:* Elektrochemische Kinetik. Springer-Verlag, Berlin 1961.

[47] *H. Rösler*, Diplomarbeit, Technische Hochschule München 1966.

[48] *M. Figeys* and *M. P. Figeys*, Tetrahedron *24*, 1097 (1968).

[49] *L. G. Feoktistow* and *S. I. Schadanow*, Dokl. Akad. Nauk SSSR, Otd. Khim. Nauk *1962*, 2127; Electrochim. Acta *10*, 657 (1965).

[50] *O. R. Brown* and *J. A. Harrison*, J. Electroanal. Chem. *21*, 387 (1969).

[51] *C. van Eygen*, *A. Hendrickx*, *J. Ramioulle*, *J. Walravens*, and *A. Verheyden*, Chim. Ind. Belg. *104*, 71 (1971).

[52] *T. Asahara*, *M. Seno*, and *T. Arai*, Bull. Chem. Soc. Jap. *42*, 1316 (1969).

[53] *A. P. Tomilow* and *V. A. Klimow*, Elektrokhimiya *3*, 232 (1967).

[54] a) *J. P. Petrowitsch*, *M. M. Baizer*, and *M. R. Ort*, J. Electrochem. Soc. *116*, 743 (1969); b) *116*, 749 (1969).

[55] *J. P. Petrowitsch*, *J. D. Anderson*, and *M. M. Baizer*, J. Org. Chem. *31*, 3897 (1966).

[56] Belg. Pat. 643247 (1964), Monsanto; Dutch-Pat. 6707472 (1966), Monsanto.

[57] *M. Ja. Fioschin* in: Der Fortschritt auf dem Gebiet der Elektrochemie von organischen Verbindungen. Nauka, Moscow 1969, Vol. 1, p. 250.

[58] *J. H. Prescott*, Chem. Eng. *72*, 238 (1965).

[59] Eur. Chem. News vom 1. 5. 1970.

[60] Brit. Pat. 1911265 (1968), Monsanto.

[61] US-Pat. 3193510 (1961), Monsanto.

[62] Dutch-Pat. 6601722 (1965), Monsanto.

[63] Dutch-Pat. 6607654 (1965), Monsanto.

[64] Dutch-Pat. 6801294 (1967), Monsanto.

[65] Dutch-Pat. 6610248 (1965), Monsanto.

[66] Brit. Pat. 1906545 (1968), Monsanto.

[67] DOS 1903656 (1969), Monsanto.

[68] Chem. Eng. News *45*, No. 42, p. 58 (1967).

[69] *M. Seko*, Dechema Monograph. *47*, 575 (1962).

[70] Jap. Pat. 10106/66 (1966), Asahi.

[71] Dutch-Pat. 6715362 (1966), Asahi.

[72] Brit. Pat. 1932037 (1968), Asahi.

[73] French-Pat. 1476162 (1965), BASF.

[74] *A. P. Tomilow*, Belg. Pat. 739354 (1969), UCB.

[75] DOS 1518570 (1965), BASF.

[76] French-Pat. 1546227 (1966), BASF.

[77] DOS 1643700 (1967), BASF.

[78] Cf. *O. Bayer*, Angew. Chem. *61*, 229 (1961).

[79] *F. Beck* and *J. G. Floss*, unpublished.

[80] *I. L. Knunyants et. al.*, USSR-Pat. 178807 (1963).

[81] DOS 1928748 (1968), UCB.

[82] French-Pat. 1491516 (1966), Rhône Poulenc.

[83] *A. Katchalskii et. al.*, French-Pat. 1289071 (1961).

[84] Brit. Pat. 1182248 (1966), ICI.

[85] Dutch-Pat. 6515603 (1964), ICI.

[86] Dutch-Pat. 6515216 (1964), ICI.

[87] Dutch-Pat. 6615188 (1965), ICI.

[88] French-Pat. 1555206 (1967), ICI.

[89] French-Pat. 1554242 (1967), ICI.

[90] *J. D. Littlehailes* and *B. J. Woodhall*, Discuss. Faraday Soc. *45*, 187 (1968).

[91] Jap. Pat. 8648/69 (1966), Mitsui Toatsu.

[92] *F. Matsuda*, Tetrahedron Lett. *1966*, 6193.

[93] Jap. Pat. 2966/69 (1966), Mitsui Toatsu.

[94] Jap. Pat. 8844/69 (1966), Mitsui Toatsu.

[95] Belg. Pat. 716833 (1968), BASF.

[96] French-Pat. 1541272 (1966), Toyo Koatsu.

[97] Dutch-Pat. 6803625 (1967), UCB.

[98] Dutch-Pat. 6702922 (1966), UCB.

[99] Belg. Pat. 683650 (1966), UCB.

[100] French-Pat. 1534453 (1966), BASF.

[101] French-Pat. 1451443 (1965), Rhône Poulenc.

[102] Dutch-Pat. 6704251 (1966), Du Pont.

[103] *F. Beck* and *H. Gerischer*, Z. Elektrochem. *65*, 504 (1961).

[104] *F. Beck*, Ber. Bunsenges. Phys. Chem. *69*, 199 (1965).

[105] *F. Nagy*, Acta Chim. (Budapest) *37*, 295 (1963).

[106] *C. Wagner* and *Z. Takehara*, Elektrochim. Acta *15*, 987, 999 (1970).

[107] *T. C. Franklin* and *M. Naito*, Tetrahedron Lett. *1968*, 5723.

[108] French-Pat. 1377425 (1963), Rhône Poulenc.

[109] *A. Misono*, *Y. Uchida*, *K. Tamai*, and *M. Hidai*, Bull. Chem. Soc. Jap. *40*, 931 (1967).

[110] Jap. Pat. 22287/68 (1965), Toyo Rayon.

[111] Patents by Du Pont and by BASF.

[112] *G. Agnes et. al.*, Chem. Commun. *1968*, 1515.

[113] *M. M. Baizer*, *J. D. Anderson*, *J. H. Wagenknecht*, *M. R. Ort*, and *J. P. Petrowitsch*, Elektrochim. Acta *12*, 1377 (1967).

[114] *M. M. Baizer* and *J. D. Anderson*, J. Electrochem. Soc. *111*, 223 (1964).

[115] *G. C. Jones* and *T. H. Ledford*, Tetrahedron Lett. *1967*, 615.

[116] French-Pat. 1446919 (1964), Monsanto.

[117] *M. R. Ort* and *M. M. Baizer*, J. Org. Chem. *31*, 1646 (1966).

[118] *F. Beck* and *J. G. Floss*, unpublished.

[119] Dutch-Pat. 332916 (1963), Monsanto.

[120] *M. M. Baizer* and *J. D. Anderson*, J. Electrochem. Soc. *111*, 226 (1964).

[121] *J. G. Sewastianowa* and *A. P. Tomilow*, Sov. Electrochem. *3*, 494 (1967).

[122] *A. P. Tomilow*, *J. D. Smirnow*, *S. K. Smirnow*, and *S. L. Warsavskii*, Zh. Org. Khim. *3*, 954 (1967); *J. D. Smirnow*, *S. K. Smirnow*, and *A. P. Tomilow*, *ibid. 4*, 216 (1968).

[123] *A. P. Tomilow*, USSR-Pat. 213021 (1966).

[124] *S. Wawzonek*, *A. R. Zigman*, and *G. R. Hansen*, J. Electrochem. Soc. *117*, 1351 (1970).

[125] *S. L. Warschawskii*, USSR-Pat. 181656 (1965).

[126] *T. Nonaka* and *K. Sugino*, J. Electrochem. Soc. *114*, 1255 (1967).

[127] *R. Pasternak*, Helv. Chim. Acta *31*, 753 (1948).

[128] *A. P. Tomilow*, *E. V. Kryukowa*, *V. Aklimow*, and *J. N. Brago*, Elektrokhimiya *3*, 12 (1967).

[129] *J. Wiemann* and *M. L. Bouguerra*, Ann. Chim. (Paris) [14] *3*, 215 (1968).

[130] *J. Simonet*, C. R. Acad. Sci. *C 267*, 1548 (1968).

[131] *J. Wiemann* and *M. Bouyer*, C. R. Acad. Sci. *C 262*, 1271 (1966).

[132] *J. Simonet*, C. R. Acad. Sci. *C 263*, 685 (1966).

[133] *M. Bouyer*, C. R. Acad. Sci. *C 263*, 1072 (1966).

[134] a) *E. Touboul*, *F. Weisbuch*, and *J. Wiemann*, Bull. Soc. Chim. Fr. *1968*, 4291; b) *J. Wiemann*, *S. Risse*, and *P. F. Calsals*, *ibid. 1966*, 381.

[135] a) *H. D. Law*, J. Chem. Soc. *101*, 1016, 1544 (1912); b) *J. Wiemann* and *M. L. Bouguerra*, Ann. Chim. (Paris) [14] 2, 35 (1967); French-Pat. 1532273 (1966), CNRS; c) *P. Martinet* and *J. Simonet*, Bull. Soc. Chim. Fr. *1967*, 3533; d) US-Pat. 3274084 (1962), Monsanto.

[136] a) US-Pat. 3193482 (1964), Monsanto; b) *M. L. Bouguerra* and *J. Wiemann*, C. R. Acad. Sci. *C 263*, 782 (1966); c) *I. N. Brago*, *L. V. Kaabak*, and *A. P. Tomilow*, Zh. Prikl. Khim. *42*, 1194 (1969).

[137] Belg. Pat. 718211 (1968), UCB.

[138] *C. L. Wilson* and *K. B. Wilson*, Trans. Electrochem. Soc. *84*, 153 (1943).

[139] *C. L. Wilson* and *K. B. Wilson*, Brit. Pat. 553765 (1943), ICI.

[140] *R. N. Gourley*, *J. Grimshaw*, and *P. G. Millar*, Chem. Commun. *1967*, 1278.

[141] *L. N. Lawrischewa*, *T. A. Volodina*, and *V. N. Bolow*, Tr. Mosk. Khim.-Tekhnol. Inst. *57*, 106 (1968).

[142] *A. Misono*, *T. Osa*, and *T. Ueno*, Nippon Kagaku Zasshi *88*, 1182 (1967).

[143] *A. Misono*, *T. Osa*, and *T. Yamagishi*, Kogyo Kagaku Zasshi *69* (5), 945 (1966).

[144] US-Pat. 3193475 (1962), Monsanto.

[145] *G. T. Mondodoev, N. M. Przijalgovskaja,* and *V. N. Belov,* Zh. Org. Khim. *1*, 2008 (1965).

[146] *S. Wawzonek, E. W. Blaha, R. Berkey,* and *M. E. Runner,* J. Electrochem. Soc. *102*, 235 (1955).

[147] *S. Wawzonek* and *D. Wearring,* J. Amer. Chem. Soc. *81*, 2067 (1959).

[148] *M. M. Baizer* and *J. D. Anderson,* J. Org. Chem. *30*, 1348 (1965).

[149] *J. D. Anderson, M. M. Baizer,* and *E. J. Prill,* J. Org. Chem. *30*, 1645 (1965).

[150] *J. W. Breitenbach, O. F. Olaj,* and *F. Wehmann,* Monatsh. Chem. *95*, 1007 (1964).

[151] *A. P. Tomilow* and *B. L. Kljuew,* Sov. Electrochem. *3*, 1042 (1967).

[152] *A. P. Tomilow* and *B. L. Kljuew,* Sov. Electrochem. *2*, 1284 (1966); Elektrokhimiya *2*, 1405 (1966).

[153] *Fr. Müller* in *Houben-Weyl:* Methoden der Organischen Chemie. Thieme, Stuttgart 1955, 4 Edit., Vol. 4/2, p. 499.

[154] DRP 113719 (1899), Merck.

[155] DRP 324920 (1918/1920), Bayer.

[156] DBP 890643 (1953), Bayer.

[157] *C. L. Wilson* and *K. B. Wilson,* Trans. Electrochem. Soc. *80*, 151 (1941).

[158] *T. Sekine, A. Yamura,* and *K. Sugino,* J. Electrochem. Soc. *112*, 439 (1965).

[159] *O. Slotterbeck,* Trans. Electrochem. Soc. *92*, 11 (1947).

[160] *A. P. Tomilow, B. L. Kljuew, J. D. Smirnow,* and *E. L. Gal'perin,* Elektrochimiya *5*, 1307 (1969).

[161] DRP 310023 (1920), Bayer.

[162] *A. P. Tomilow* and *M. I. Kalitina,* Zh. Prikl. Khim. *38*, 1574 (1965).

[163] *A. P. Tomilow* and *L. A. Ignat'eva,* Zh. Prikl. Khim. *38*, 2715 (1965).

[164] *S. Swann jr., D. K. Eads,* and *L. H. Krone jr.,* J. Electrochem. Soc. *113*, 274 (1966).

[165] *T. Arai,* Denki Kagaku *30*, 31 (1962); Chem. Abstr. *62*, 15760 (1965).

[166] *V. G. Chomjakov, A. P. Tomilow, B. G. Soldatov,* and *I. P. Tkaceva,* Elektrochimiya *6*, 1094 (1970).

[167] *S. L. Varshavskii,* USSR-Pat. 167847 (1961).

[168] *A. Cox,* Brit. Pat. 12467 (1912); Chem. Abstr. *7*, 3719 (1913).

[169] *K. Umemoto,* Bull. Chem. Soc. Japan *40*, 1058 (1967).

[170] *L. N. Nekrasov* and *A. D. Korsun,* Elektrokhimiya *6*, 1753 (1970).

[171] *S. Wawzonek* and *A. Gundersen,* J. Electrochem. Soc. *107*, 537 (1960).

[172] *B. E. Conway, E. J. Rudd,* and *L. G. M. Gordon,* Discuss. Faraday Soc. *45*, 87 (1968).

[173] *J. H. Stocker* and *R. M. Jenevein,* J. Org. Chem. *33*, 294 (1968).

[174] *J. H. Stocker, R. M. Jenevein,* and *D. H. Kern,* J. Org. Chem. *34*, 2810 (1969).

[175] *S. Piekarski, F. Meziou,* and *P. Federlin,* Bull. Soc. Chim. Fr. *1968*, 4063.

[176] *I. A. Avruckaja, S. F. Belevskij, M. J. Fiosin,* and *Nguyen Van Tchan,* Elektrokhimiya *6*, 683 (1970).

[177] *C. Caullet, M. Salaün,* and *M. Hèbert,* C. R. Acad. Sci. *C 264*, 2006 (1967); *J. P. Morizur* and *J. Wiemann,* Bull. Soc. Chim. Fr. *1964*, 1619.

[178] *C. Caullet, M. Salaün,* and *M. Hèbert,* C. R. Acad. Sci. *C 264*, 228 (1967).

[179] *J. H. Stocker* and *R. M. Jenevein,* J. Org. Chem. *34*, 2807 (1969).

[180] US-Pat. 3200053 (1961), Ciba; French-Pat. 1312848 (1961), Ciba.

[181] *J. E. Slager* and *P. W. Staal,* Lecture at the ECS-Meeting, Dallas 1967.

[182] *M. J. Fiosin, I. A. Avruckaja, L. E. Gerasimova,* and *Nguyen Van Tchan,* Elektrokhimiya *5*, 1371 (1969).

[183] *E. Kariv, J. Hermolin,* and *E. Gileadi,* J. Electrochem. Soc. *117*, 342 (1970).

[184] *D. H. Evans* and *E. C. Woodbury,* J. Org. Chem. *32*, 2158 (1967); *R. C. Buchta* and *D. H. Evans,* Anal. Chem. *40*, 2181 (1968).

[185] *A. P. Timolow, E. A. Mordvinceva,* and *E. V. Krjukova,* Zh. Prikl. Khim. *41*, 2524 (1968); *J. Armand, G. Dana,* and *F. Valentini,* Bull. Soc. Chim. Fr. *1968*, 4581; *J. Armand, P. Souchay,* and *F. Valentini,* C. R. Acad. Sci. *C 265*, 1267 (1967).

[186] *A. Mazenga, D. Lomnitz, J. Villegas,* and *C. J. Polowczyk,* Tetrahedron Lett. *1969*, 1665.

[187] *M.-B. Fleury, P. Souchay, M. Gouzerh,* and *P. Gacian,* Bull. Soc. Chim. Fr. *1968*, 2562.

[188] *J. H. Stocker* and *R. M. Jenevein,* J. Org. Chem. *33*, 2145 (1968).

[189] *J. Grimshaw* and *J. S. Ramsey,* J. Chem. Soc. *C 1966*, 653.

[190] *L. N. Lavrisceva, T. A. Volodina,* and *V. N. Belov,* Zh. Org. Khim. *2*, 2167 (1966).

[191] US-Pat. 3410769 (1965), Monsanto.

[192] *L. Horner* and *D. H. Skaletz,* Tetrahedron Lett. *1970*, 1103.

[193] *J. J. Eisch, D. D. Kaska,* and *C. J. Peterson,* J. Org. Chem. *31*, 453 (1966).

[194] *L. Horner* and *D. H. Skaletz,* Tetrahedron Lett. *1970*, 3679.

[195] *M. Matsuoka, M. Imaki,* and *T. Shirakura,* Denki Kagaku *36*, 369 (1968).

[196] *H. Lund,* Acta Chem. Scand. *18*, 1984 (1964).

[197] *P. Pflegel* and *G. Wagner,* Z. Chem. *8*, 179 (1968).

[198] *C. P. Andrieux* and *J. M. Savéant,* Bull. Soc. Chim. Fr. *1968*, 4671.

[199] *C. P. Andrieux* and *J. M. Savéant,* J. Electroanal. Chem. Interfacial Electrochem. *26*, 223 (1970).

[200] *C. P. Andrieux* and *J. M. Savéant,* J. Electroanal. Chem. Interfacial Electrochem. *28*, 448 (1970).

[201] *B. Emmert,* Ber. dtsch. chem. Ges. *42*, 1997 (1909); *46*, 1716 (1913); *52*, 1351 (1919); *53*, 376 (1920); *Fr. Müller* in *Houben-Weyl:* Methoden der Organischen Chemie. Thieme, Stuttgart 1955, Vol. 4/2, p. 502.

[202] Brit. Pat. 1073082, Dutch-Pat. 6604612, Belg. Pat. 679246, alle (1965), ICI; US-Pat. 3478042 (1966), ICI.

[203] *J. N. Burenett* and *A. L. Underwood,* J. Org. Chem. *30*, 1154 (1965).

[204] Dutch-Pat. 6904975 (1968), ICI.

[205] *C. S. Johnson jr., R. E. Visco, H. S. Gutowsky,* and *A. M. Hartley,* J. Chem. Phys. *37*, 1580 (1962).

[206] *J. Volke* and *V. Volkova,* Collect. Czech. Chem. Commun. *34*, 2037 (1969).

[207] Brit. Pat. 1913149 (1968), ICI; Dutch-Pat. 6903978 (1968), ICI.

[208] *E. M. Kosower* and *J. L. Cotter,* J. Amer. Chem. Soc. *86*, 5524 (1964).

[209] *B. Emmert,* Ber. dtsch. chem. Ges. *42*, 1507 (1909).

[210] *L. Horner* and *A. Mentrup,* Liebigs Ann. Chem. *646*, 49 (1961).

[211] *S. D. Ross, M. Finkelstein,* and *R. C. Petersen,* J. Amer. Chem. Soc. *82*, 1582 (1960).

[212] *J. E. Dubois, A. Monvernay,* and *P. C. Lacaze,* Electrochim. Acta *15*, 315 (1970).

[213] *J. H. Wagenknecht* and *M. M. Baizer,* J. Org. Chem. *31*, 3885 (1966).

[214] *T. Shono* and *M. Mitani,* Tetrahedron Lett. *1969*, 687.

[215] US-Pat. 3480527 (1967), Dow Chemical.

[216] *R. W. Murray* and *M. L. Kaplan,* J. Org. Chem. *31*, 962 (1966).

[217] *A. M. Khopin* and *S. J. Zhadanow,* Elektrokhimiya *4*, 228 (1968).

[218] *T. Shono, T. Toda,* and *R. Oda,* Tetrahedron Lett. *1970*, 369.

[219] *R. Breslow, W. Bahary,* and *W. Reinmuth,* J. Amer. Chem. Soc. *83*, 1763 (1961).

[220] Belg. Pat. 618095 (1961), Knapsack-Griesheim.

[221] Jap. Pat. 13448/67 (1965), Toyo Rayon.

[222] US-Pat. 3475298 (1966), Du Pont.

[223] French-Pat. 1489206 (1966), Solvay.

[224] *J. Grimshaw* and *J. S. Ramsey,* J. Chem. Soc. *B 1968*, 60.

[225] *J. G. Lawless, D. E. Bartak,* and *M. D. Hawley,* J. Amer. Chem. Soc. *91*, 7121 (1969).

[226] *K. Brand* and *M. Matsui,* Ber. dtsch. chem. Ges. *46*, 2939 (1913).

[227] *J. K. Mogto, J. Kossanyi,* and *J. Wiemann, C. R.* Acad. Sci. *C 267*, 779 (1968).

[228] *W. H. Harwood, R. M. Hurd,* and *W. H. Jordan jr.,* Ind. Eng. Chem., Proc. Des. Develop. *2*, 72 (1963).

[229] *F. Haber,* Z. Elektrochem. *4*, 506 (1898).

[230] *M. J. Fiosin* and *A. P. Tomilow,* Khim. Pm. SSSR *43*, 243 (1967).

[231] *K. Udupa, G. Subramanian,* and *H. Udupa,* J. Electrochem. Soc. *108*, 373 (1961).

[232] *T. D. Balakrishan, K. S. Udupa, G. S. Subramanian,* and *H. V. K. Udupa,* Chem.-Ing.-Tech. *41*, 776 (1969).

[233] *M. M. Baizer,* J. Org. Chem. *29*, 1670 (1964).

[234] *K. Sugino, K. Shiray,* and *T. Nonaka,* Bull. Chem. Soc. *37*, 1895 (1964).

[235] *H. Rosen, Y. Arad, M. Levy*, and *D. Vofsi*, J. Amer. Chem. Soc. *91*, 1425 (1969).
[236] *S. M. Makarockina* and *A. P. Tomilow*, Zh. Obshch. Khim. *40*, 3676 (1970).
[237] *M. M. Baizer, J. P. Petrovich*, and *D. A. Tyssee*, J. Electrochem. Soc. *117*, 173 (1970).
[238] *M. M. Baizer* and *J. L. Chruma*, J. Electrochem. Soc. *118*, 450 (1971).
[239] *A. P. Tomilow et al.*, USSR-Pat. 194088 (1966).
[240] US-Pat. 3218245 (1963), Monsanto.
[241] *M. M. Baizer* and *J. D. Anderson*, J. Org. Chem. *30*, 3138 (1965).
[242] *J. Wiemann* and *M. L. Bouguerra*, C. R. Acad. Sci. *C 265*, 751 (1967).
[243] *M. M. Baizer* and *J. D. Anderson*, J. Org. Chem. *30*, 1348 (1965).
[244] *M. J. Allen* and *M. J. Levine*, J. Chem. Soc. *1952*, 254; *M. J. Allen, J. A. Siragusa*, and *W. Pierson*, *ibid. 1960*, 1045; *M. J. Allen et al.*, *ibid. 1961*, 757, 2081.
[245] *M. Nicolas* and *R. Pallaud*, C. R. Acad. Sci. *C 267*, 1834 (1968).
[246] *K. Sugino* and *T. Nonaka*, J. Elektrochem. Soc. *112*, 1241 (1965).
[247] *K. Sugino*, Jap. Pat. 14446/68 (1965).
[248] *O. R. Brown* and *K. Lister*, Discuss. Faraday Soc. *45*, 106 (1968).
[249] *M. Nicolas* and *R. Pallaud*, Acad. Sci. *C 265*, 1044 (1967); *C 267*, 1834 (1968).
[250] *T. Nonaka* and *K. Sugino*, J. Electrochem. Soc. *116*, 615 (1969).
[251] *A. P. Tomilow* and *B. L. Kljuev*, Zh. Obshch. Khim. *39*, 470 (1969).
[252] *A. P. Tomilow et al.*, USSR-Pat. 233 651 (1967).
[253] Jap. Pat. 9658/69 (1965), Asahi Glass Co. Ltd.
[254] Jap. Pat. 9886/69 (1965), Asahi Glass K. K.
[255] US-Pat. 3440154 (1966), Monsanto.
[256] *J. H. Wagenknecht* and *M. M. Baizer*, J. Org. Chem. *31*, 3885 (1966).
[257] *M. M. Baizer*, J. Org. Chem. *31*, 3847 (1966).
[258] US-Pat. 3438877 (1966), Monsanto.
[259] Jap. Pat. 2965/69 (1966), Asahi Chem. Ind. Co. Ltd.
[260] *J. Grimshaw* and *E. J. F. Rea*, J. Chem. Soc. *C 1967*, 2628.
[261] *A. Misono, T. Osa*, and *T. Ueno*, Nippon Kagaku Zasshi *88*, 1184 (1967); Chem. Abstr. *69*, 58794C (1968).
[262] *J. D. Anderson, J. P. Petrovich*, and *M. M. Baizer*, Advan. Org. Chem. *6*, 257 (1969).
[263] *J. D. Anderson* and *M. M. Baizer*, Tetrahedron Lett. *1966*, 511.
[264] *J. D. Anderson, M. M. Baizer*, and *J. P. Petrowitsch*, J. Org. Chem. *31*, 3890 (1966).
[265] US-Pat. 3413202 (1964), Monsanto.
[266] *R. N. Gourley* and *J. Grimshaw*, J. Chem. Soc. *C 1968*, 2388.
[267] *T. Wohlfahrt*, J. Prakt. Chem. [2] *65*, 295 (1902).
[268] *K. Griesbaum* and *P. E. Butler*, Angew. Chem. *79*, 467 (1967); Angew. Chem. internat. Edit. *6*, 444 (1967).
[269] *M. R. Rifi*, J. Amer. Chem. Soc. *89*, 4442 (1967).
[270] *M. R. Rifi*, Tetrahedron Lett. *1969*, 1043.
[271] *K. B. Wiberg* and *D. S. Connor*, J. Amer. Chem. Soc. *88*, 4437 (1966).
[272] *A. J. Bard*, Comments at the EUCHEM Conference in Ronneby (Sweden), June 1971.
[273] *J. L. Gerlock* and *E. G. Janzen*, J. Amer. Chem. Soc. *90*, 1652 (1968).

Organic Syntheses in the Plasma of Glow Discharges and Their Preparative Application

By Harald Suhr[*]

It is only during the last few years that reactions of organic substances as a result of electron collisions in the cold plasma of glow and corona discharges have been developed into a preparatively useful method with a wide range of possibilities. Its basic principles and development prospects are discussed in the present progress report on the basis of the research results that are known at present.

1. Introduction

In the continuous search for new methods of syntheses, the possibility of using the plasma[**] of spark, arc, and glow discharges for this purpose was examined by chemists at an early date[2][***]. However, many of the earlier efforts met with only slight success. This is easy to understand nowadays, since the early experimental techniques were unfavorable, and gave only low yields and nonuniform reaction products. The organic compounds investigated in this way decomposed in the plasma, largely with formation of tarry or polymeric products. Despite the numerous efforts to make preparative use of reactions in plasmas, therefore, the only processes of this type that have achieved any industrial importance are the formation of ozone in silent discharges and the formation of nitrogen oxides and of acetylene in an arc. Apart from these, a few syntheses of inorganic compounds on the laboratory scale[3a] and the modification of oils[3b] have also been developed. It is only in the last few years that organic syntheses on the preparative scale have been successfully carried out in plasma. These results and the possible applications of plasma chemistry with organic compounds form the subject of the present report.

[*] Prof. Dr. H. Suhr
Chemisches Institut der Universität
74 Tübingen, Wilhelmstrasse 33 (Germany)

[**] Plasma = partly ionized gas.

[***] A large number of publications (cf. [1g]) report successful attempts to synthesize fairly complicated systems from very simple starting materials and to break down or isomerize organic compounds by plasma reactions. However, the present review deals only with those that are closely concerned with preparative applications.

2. Forms of Discharge

The various types of electric discharge are best illustrated with the aid of a current-voltage diagram (Fig. 1)[4]. A current flows between two electrodes that project into a vessel having a low gas pressure and that are connected to a source of direct current. Various regions with different types of discharge, depending on the current strength, are clearly discernible. At currents of less than 10^{-12} A, the current flow is unsteady, and occurs only when charged particles are produced in the vessel by cosmic radiation or light quanta. At higher current strengths, the production of electrons by external agencies is no longer necessary. The self-supporting dark discharge occurs in the region of $10^{-12}-10^{-5}$ A, and this is followed by a region in which the passage of current is associated with luminous phenomena. The weakly luminous glow discharge appears first between 10^{-4} and 10^{-1} A, and the bright arc occurs at current intensities of more than 1 A. Whenever the current is switched on, the discharge passes through all the stages in a short time (approx. 1 ms) until the type determined by the magnitude of the resistance is reached. If low-frequency alternating current of up to about 1000 Hz is used instead of direct current, a new discharge builds up in each half cycle. The decay of a discharge takes approximately 0.5 ms. At frequencies of more than 1000 Hz, therefore, the time between two half cycles is no longer sufficient for the ionization to decay completely. Numerous electrons are therefore already available for the ignition process in the next half cycle.

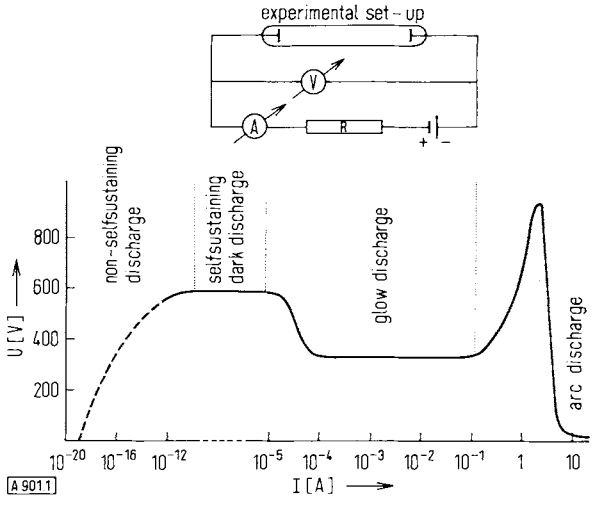


Fig. 1. Plot of a current-voltage curve in a vessel 50 cm long filled with neon at 1 torr. The various types of discharge appear at various resistance values.

At higher frequencies, discharges can be maintained even if the electrodes are situated outside the low-pressure vessel (capacitive coupling). Energy can be equally easily supplied to the plasma by induction if a coil is wound round the vessel and connected to a high-frequency generator.

The elementary processes of electric discharges[4] can be most simply described as follows. Individual electrons, formed *e.g.* by cosmic radiation, are accelerated by the electric field, and can excite or ionize atoms or molecules with which they collide. Since a new electron is released in each ionization, the number of electrons avalanches until it reaches an equilibrium value determined by the rates of the electron-supplying and electron-consuming processes. The main electron-consuming process is recombination in the gas phase or on the wall of the vessel.

The possibilities of using the various forms of discharge in chemistry depend on the thermal stabilities of the starting materials and of the final products, since extremely high temperatures sometimes occur in the discharges. It is necessary here to distinguish between the temperatures of the electrons, of the ions, and of the neutral molecules. A temperature can be formally assigned to each particle on the basis of its velocity:

$$\frac{m}{2}v^2 = \frac{3}{2}kT.$$

In a discharge, electrons and ions acquire additional velocity through the electric field, and hence a higher "temperature" than the neutral particles. Because of their high mobility, the electrons reach a particularly high temperature. In a neon tube, for example, the temperature of the electrons is about 25000 °C, whereas that of the neutral particles and ions differs only slightly from the ambient temperature. Systems of this type in which the temperature of the electrons is much higher than that of the neutral particles and of the ions are known as cold or nonequilibrium plasmas; if the temperatures of the electrons, ions, and neutral particles differ only slightly from one another, one speaks of hot or equilibrium plasmas. Typical examples of cold plasmas are glow discharges and corona discharges, while arcs are typical of hot plasmas.

Arc discharges with gas temperatures above 1000 °C can be used for chemical syntheses only if the reaction products are thermally very stable. Carbides, borides, and nitrides have been prepared in arc discharges. Only a few organic compounds, such as HCN, C_2N_2, C_2H_2, and CO, can withstand such temperatures without decomposing. Larger molecules are broken down under these conditions[5-7].

In glow and corona discharges, the gas temperatures are so low that thermal decomposition of organic substances can be avoided. They should therefore be suitable for many syntheses. Despite intensive efforts, however, only a few syntheses (mainly inorganic) have been achieved with cold discharges[2, 8]. Apart from the formation of ozone, which was mentioned earlier, the most important of these are the syntheses of hydrazine[9-12], sulfur monoxide[13], and halides and hydrides[8] of boron, silicon, germanium, phosphorus, and arsenic. Experiments with organic substances did not lead to any preparatively useful syntheses. Though it was possible to show that most organic compounds undergo chemical changes in cold discharges, the products were mainly polymeric material or low molecular weight decomposition products. The reasons for the earlier failures have been revealed only by recent investigations. Most organic compounds have only a low stability in the plasma, must not be exposed to excessively high energies, and must be removed quickly from the reaction zone to avoid complete decomposition. These facts impose a very narrow

range of experimental conditions in which syntheses can be carried out with preparatively useful yields.

3. Execution of Reactions in Cold Plasmas

Since glow discharges occur only under reduced pressure, all arrangements that make use of this form of discharge show some resemblance to vacuum distillation apparatus (cf. Fig. 2).

A particularly simple arrangement is a glass apparatus with metal electrodes, across which a DC or low-frequency AC voltage of 20—50 V/cm is applied (Fig. 2a). Experimental arrangements of this type are very suitable for the preparation of atomic hydrogen, nitrogen, or oxygen[14,15]. For the reaction of organic compounds, the electrodes must be protected by an inert gas, since they otherwise rapidly become coated with decomposition products[16]. Apparatus of this type is cheap and robust, but is dangerous because of the high voltages required.

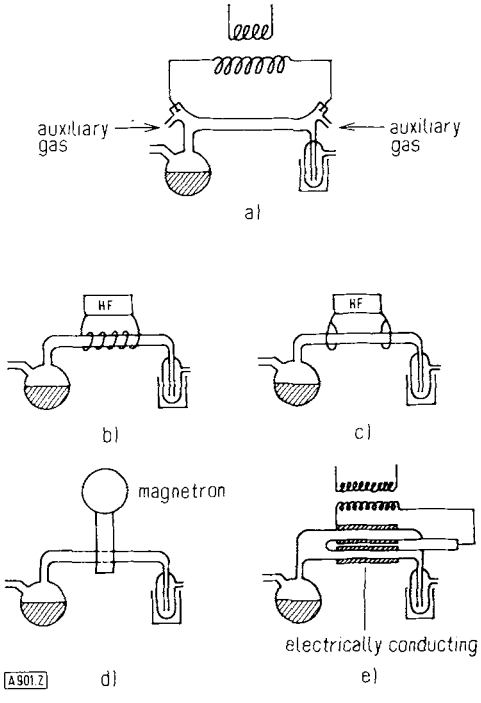


Fig. 2. Simple forms of apparatus for reactions in glow discharges.

No electrode problems arise in short-wave and microwave units. The short-wave energy is coupled inductively or capacitively to the plasma (Fig. 2b and 2c). For microwave discharges (Fig. 2d), quartz[*] reaction tubes are passed through the wave guides or through resonance cavities. Microwave and short-wave generators are commercially available. Short-wave generators can also be constructed in the laboratory at low cost. Even the simplest push-pull oscillators give good results. Multistage oscillators have the advantage of high stability of frequency and power output independent of load conditions. After matching the high-frequency energy in both cases can be easily carried from the oscillator to the reaction vessel by coaxial cables. This separation of the electronic from the chemical apparatus greatly facilitates operation.

For corona or silent discharges, DC or low-frequency AC current flows through a glass wall (Fig. 2e). In this way, one obtains low-current discharges, which are uniformly distributed over the entire surface. The advantage of this form of discharge is that operation at normal pressure is possible. Against this it has the disadvantage that high voltages must be used, and that very large surface areas are necessary for high conversion rates.

Experience gained so far in organic plasma chemistry shows that the result of the reaction depends mainly on the field strength, pressure, and vessel dimensions, so that similar results can be obtained with various types of discharge. Short-wave apparatus is therefore recommended for laboratory work because of the ease of operation, while the simpler high-voltage types of equipment are recommended for larger units.

4. Applications

4.1. Reactions of Atomic Gases with Organic Compounds

Glow discharges are excellently suited for the dissociation of molecular hydrogen, oxygen, or nitrogen into atoms. Since the atoms recombine mainly on the wall, high yields are obtained only if the walls are "poisoned" with certain substances such as water, phosphoric acid, Dryfilm, or Teflon[17-22].

The atomic gases can react with many organic compounds[23-25]. Atomic hydrogen abstracts hydrogen atoms from saturated compounds[26] and adds to unsaturated compounds[27]. In both cases free radicals are formed, and these can give a variety of further products by decomposition, disproportionation, combination, or rearrangement:

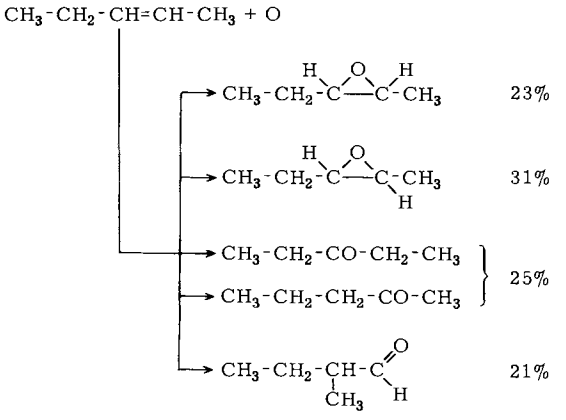
$$\left.\begin{array}{l} H\cdot + H_3C\text{-}CH_3 \rightarrow H_2 + CH_3\text{-}CH_2\cdot \\ H\cdot + H_2C{=}CH_2 \rightarrow CH_3\text{-}CH_2\cdot \end{array}\right\} \rightarrow \text{Products}$$

Atomic oxygen abstracts hydrogen from saturated compounds. With unsaturated compounds, the first reaction step is the formation of an epoxide, which then partly rearranges to form carbonyl compounds[27-30]. Thus 2-pentene gives approximately 50% of *cis-trans*-pentene oxide, 25% of diethyl and methyl propyl ketones, and 20% of 2-methylbutanal. A synthesis of particular industrial interest is that of propylene oxide from propene and atomic oxygen. Mixtures of oxygen and propene give good yields of propylene oxide in silent discharges. With a conversion of 20%, approximately 30% (corresponding to 100 g/kWh) of propylene oxide was obtained[31].

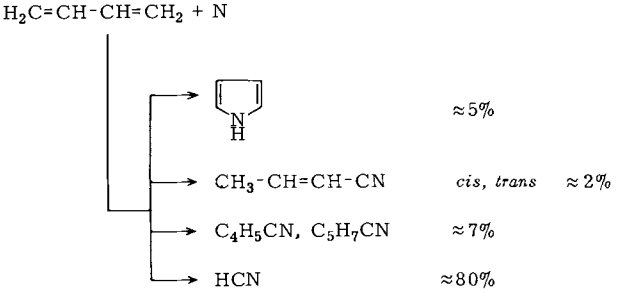
Nitrogen atoms react very vigorously with organic compounds[32-35]. Irrespective of the type of compound, the

[*] Because of the high dielectric losses, glass would heat up too much and might soften.

reaction always yields large quantities of hydrogen cyanide as well as some cyanogen and ammonia. In some cases the yields are so high that the formation of hydrogen cyanide can be used for the determination of atomic nitrogen[36].



Only a few cases are known at present in which active nitrogen was incorporated into organic compounds. In the reaction with butadiene, however, in addition to a large quantity of hydrogen cyanide (about 80%), a mixture of pyrrole, crotononitrile, and cyanobutadiene is formed[37, 38]. Isoprene similarly gives methylpyrrole[39] in yields of about 10%. A reaction was recently achieved between atomic nitrogen and aqueous solutions of organic compounds. However, no products containing nitrogen are formed; the atomic nitrogen merely has a dehydrogenating action, and so converts *e.g.* alcohols into aldehydes[40].



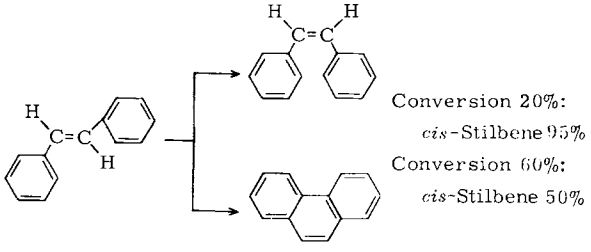
Whereas atomic hydrogen often effects interesting reductions with inorganic compounds, and many substrates can be converted into nitrides with active nitrogen, no preparatively useful syntheses with atomic hydrogen or nitrogen are known as yet for organic compounds.

4.2. Reactions of Organic Compounds

Several hundred organic compounds have already been investigated in glow discharges. The findings are very diverse. The number of results that have been reported so far is not yet sufficient to show any clear patterns, but a typical plasma behavior of certain classes of compounds is already discernible. Some typical plasma reactions of this type will be described in the following sections.

4.2.1. Isomerizations

Olefins can be isomerized even under very mild reaction conditions. Thus *trans*-stilbene is converted into the *cis* form[41]. At high flow rates and a correspondingly low conversion, 95% of the reaction product is *cis*-stilbene. If the distillation rate is reduced to increase the conversion, the content of *cis*-stilbene decreases, while the content of phenanthrene increases. Similar isomerizations have been observed for cinnamonitrile, crotononitrile, and stilbazole[42].



Another typical plasma reaction is the change in the position of substituents. In some cases this is only a side reaction. Xylene, for example, in addition to a large quantity of the synthetic product bixylyl (cf. Table 4), gives about 1% of rearranged xylenes[*]. The migration of the sub-

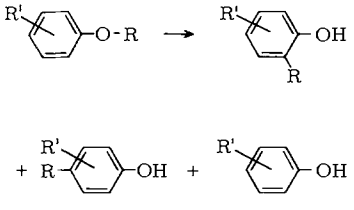


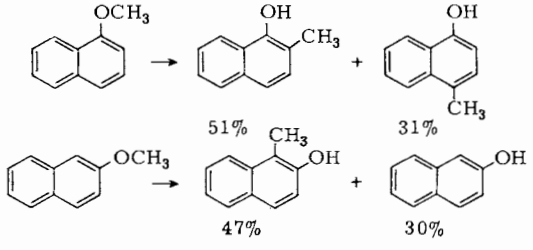
Table 1. Products and yields of rearrangement reactions [45—47].

Starting compound	Yields of rearrangement products [mol.-%]				[g/kWh]
Anisole	*o*-cresol	44	*p*-cresol	27	50
Phenyl isopropyl ether	*o*-isopropylphenol	36	*p*-isopropylphenol	22	25
p-Tolyl methyl ether	2,4-dimethylphenol	59			58
1-Naphthyl methyl ether	2-methyl-1-naphthol	51	4-methyl-1-naphthol	31	55
2-Naphthyl methyl ether	1-methyl-2-naphthol	47			58
Diphenyl ether	2-phenylphenol	53	4-phenylphenol	18	180
N,*N*-Dimethylaniline	*N*-methyl-*o*-toluidine	28	*N*-methyl-*p*-toluidine	15	23

[*] In experiments with *p*-xylene that was free from the *ortho* isomer, the xylene component recovered at conversions of 20—50% contained about 1% of *o*-xylene; small proportions of *m*-xylene could not be separated from the *para* isomer under these conditions. Similarly, about 1% of *o*-xylene is formed from *m*-xylene. *o*-Xylene gives approximately equal quantities of the *meta* and *para* isomers [43].

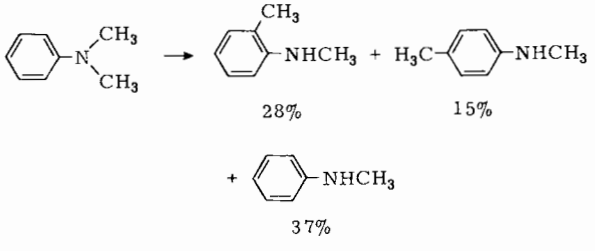
stituents often becomes the main reaction, as in the rearrangement of aryl alkyl ethers to alkylphenols[44]. Methyl ethers and ethers of primary alcohols isomerize as readily as ethers of secondary and tertiary alcohols[45] (Table 1).

Anisole gives a mixture containing 95% of *o*-cresol, *p*-cresol, and phenol. *m*-Cresol, benzene, toluene, and cyclopentadiene are also formed in small quantities. The ratio of *o*-cresol to *p*-cresol can be varied only slightly, whereas the content of phenol in the reaction products is strongly dependent on the experimental conditions. It increases with increasing power, and can ultimately exceed the content of cresol. The rearrangements of other ethers[45, 46] are very similar to those of anisole, but cleavage of the migrating alkyl group sometimes occurs as a side reaction. If the *ortho* or *para* positions are blocked by other substituents in these arrangements, the proportion of the corresponding "phenol" always increases. In the case of the naphthyl methyl ethers[46], the 1-naphthyl derivative gives a mixture of 2- and 4-methyl-1-naphthol, while the 2-naphthyl derivative gives only 1-methyl-2-naphthol.

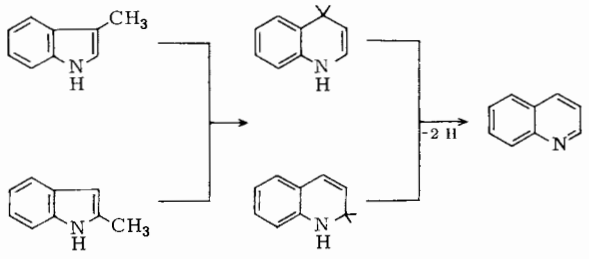


Purely aromatic ethers exhibit similar rearrangements. Diphenyl ether gives a mixture of *o*- and *p*-phenylphenol together with some phenol[47]. The *ortho* compound partly cyclizes to dibenzofuran[47]. Finally, the same reaction can also be detected for vinyl ethers. Ethyl vinyl ether isomerizes to 1-butenal or decomposes to form vinyl alcohol which is isolated as the tautomeric aldehyde[46].

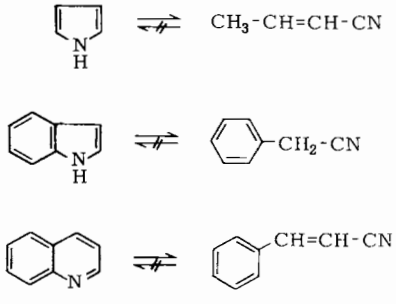
Behavior similar to that of the ethers is shown by the analogous nitrogen compounds[47]. *N, N*-Dimethylaniline gives *o*- and *p*-*N*-methyltoluidine as rearrangement products and *N*-methylaniline as a degradation product (cf. Table 1). When *N*-methylaniline is used as the starting material, *o*- and *p*-toluidine and aniline are found. Other reactions take precedence over the rearrangement in the cases of phenyl esters and acetanilides.



Other types of isomerization in glow discharges are ring contractions, ring expansions, and ring cleavages. Some cycloolefins, such as cycloheptatriene and cyclooctatetraene, rearrange readily in the plasma to form the more stable aromatic compounds toluene and styrene[48]. On the other hand, ring expansions, which are frequently assumed to occur in mass spectroscopy, are unusual in the plasma. The only example observed so far is the rearrangement of 2- or 3-methylindole into quinoline[42].



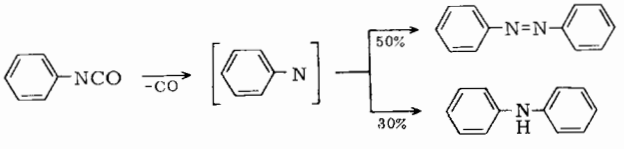
Interesting preparative possibilities are offered by ring-chain isomerizations found for various heterocyclic systems[42]. In glow discharges, pyrrole gives crotononitrile and polymeric material having the same elemental composition. Similarly, indole decomposes to give phenylacetonitrile, and quinoline forms cinnamonitrile. Attempts to



isomerize nitriles to heterocycles, on the other hand, have been unsuccessful[42].

4.2.2. Eliminations

Another type of reaction that proceeds preferentially in glow discharges is elimination. Single atoms or small groups can be removed from many compounds in the plasma without disruption of the rest of the molecule. Eliminations of carbon monoxide, carbon dioxide, and nitrogen proceed particularly smoothly. Thus isocyanates are decarbonylated to nitrenes, which then dimerize or undergo other nitrene reactions. Azobenzene and diphenylamine have been obtained in this way from phenyl isocyanate[49].



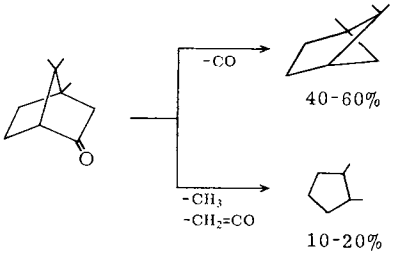
Aldehydes and ketones can also be readily decarbonylated (Table 2). The resulting radicals are stabilized by hydrogen abstraction or by dimerization. Thus benzene and biphenyl are formed from benzaldehyde, thiophenecarbaldehyde is converted almost entirely into thiophene[49], and 2-pyridinecarbaldehyde gives pyridine and 2,2'-bipyridyl[42].

The mildness of this decarbonylation is evident in the case of thiophenecarbaldehyde, since no desulfurization occurs at low conversions. Many ketones are decarbonylated in high yields, and so offer interesting synthetic possibilities.

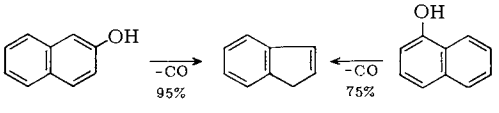
Table 2. Products and yields of some decarbonylation reactions [42, 49, 50].

Starting compound	Conversion [%]	Product	Yield [mol-%]	[g/kWh]
Benzaldehyde	63	benzene	81	93
		biphenyl	16	18
Thiophenecarbaldehyde	4	thiophene	99	24
	40	thiophene	86	46
2-Pyridinecarbaldehyde	25	pyridine	70	
		2,2'-bipyridyl	20	
Benzophenone	68	biphenyl	27	18
		fluorenone	36	24
		biphenylene	36	24
Benzil	18	biphenyl	98	27
Fluorenone	20	biphenylene	99	43
	50	biphenylene	99	63
Camphor	76	trimethylbicyclo-[2.1.1]hexane	76	24

Benzophenone gives biphenyl, and in the decomposition of benzil, the formation of biphenyl is almost quantitative[49]. Fluorenone undergoes ring contraction to form biphenylene[50]. Aliphatic cycloketones react nonuniformly, and give only a small quantity of ring-contraction product. The decarbonylation of bicyclic ketones, such as camphor and norcamphor, on the other hand, leads to very good yields of bicyclic hydrocarbons resulting from ring contraction[43, 49].



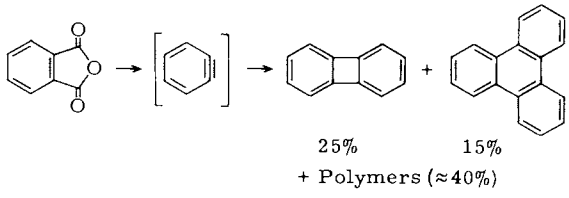
Decarbonylations are also observed for aromatic hydroxy compounds. 10—15% of cyclopentadiene is formed from phenol, while cresols give methylcyclopentadiene in a similar reaction[45]. The yields are considerably higher in the naphthalene series. 1-Naphthol gives up to 75%, and 2-naphthol up to 95%, of indene[51].



The same reaction occurs for 1-nitronaphthalene[48]. This compound decomposes with loss of nitric oxide and subsequent decarbonylation to form the indenyl radical, which is stabilized by formation of indene.

Yields similar to those obtained on decarbonylation are also found on decarboxylation. Carboxylic acids are converted almost quantitatively into the corresponding hydrocarbons. The reaction course is less uniform in the case of esters, but these also preferentially form hydrocarbons[51].

On decomposition of acid anhydrides, carbon dioxide is eliminated first, followed by carbon monoxide. The intermediate carbonyl compounds can be detected in some cases on the basis of the reaction products[51]. The main

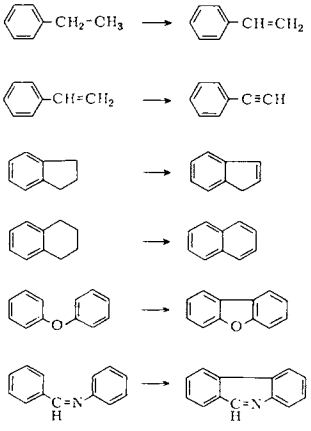


product of the reaction is an unsaturated compound. For example, phthalic anhydride decomposes to give dehydrobenzene, which can react further in various ways. If no other reactant is present, biphenylene, triphenylene, or "polyphenyl" is formed[52, 53].

The decomposition of azo compounds in the plasma has so far been investigated only for azobenzene, which is converted in high yields into biphenyl. The isoelectronic compounds benzylidenaniline and stilbene behave differently; they decompose mainly into benzonitrile or cyclize to form phenanthrene, while the formation of biphenyl is only of minor importance.

Many plasma reactions result in the formation of atomic hydrogen or free radicals[17, 54, 55], which then usually react with other molecules with hydrogen abstraction. For

Table 3. Typical dehydrogenation reactions in the plasma [43, 57].



this reason, dehydrogenations in the plasma are very common. They sometimes occur as side reactions, but can also become preparatively useful principal reactions[57]. Alkanes can be converted into alkenes and alkenes into alkynes in this way. Cycloalkanes and cycloalkenes are aromatized with dehydrogenation (Table 3).

Some aromatic systems form 5- or 6-membered rings in the plasma with elimination of hydrogen[43]. In favorable cases, as in the formation of carbazole[56] or dibenzofuran[47], the yields are so high that they offer interesting preparative possibilities.

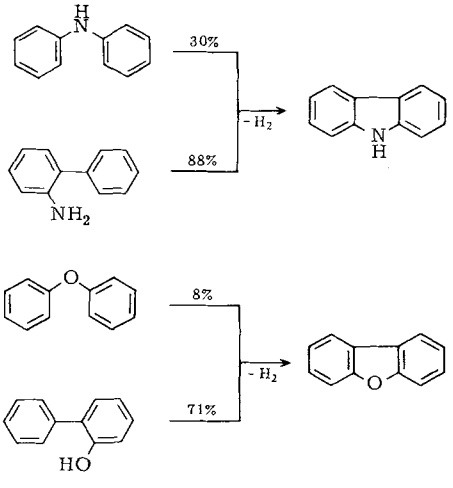
mostly require more elaborate apparatus, and have therefore been investigated in only a few cases.

A bimolecular reaction that very often occurs in the plasma and makes no demands regarding equipment is the dimerization of a compound with removal of hydrogen or other groups. Particularly good yields are obtained with aromatic starting compounds. Thus biphenyl is formed from benzene[44, 58-61], and 1,2-diarylethanes are formed from toluene and other methylaromatic compounds[59, 62-64] and from benzyl halides or benzyl alcohols[43] (Table 4). Substituted ethanes are also formed from aromatic com-

Table 4. Products and yields of dimerization reactions.

Starting compound	Product	Yield [mol-%]	Yield [g/kWh]	Ref.
Benzene	Biphenyl	40	45	[58]
Toluene	Bibenzyl	90	8	[63]
p-Xylene	Bixylyl	90	70	[43]
Durene	Bisdurene	77	43	[43]
Isopropylbenzene	2,3-Diphenylbutane	—	34	[44]
tert-Butylbenzene	2,3-Dimethyl-2,3-diphenylbutane	90	38	[44]
1-Methylnaphthalene	1,2-Di(1-naphthyl)ethane	48	129	[43]
p-Methylbenzonitrile	1,2-Di(4-cyanophenyl)ethane	90	170	[64]

The ease of removal of water or hydrogen halide can also be used for the preparation of olefins[57]. The elimination of other groups has not yet been very extensively studied.



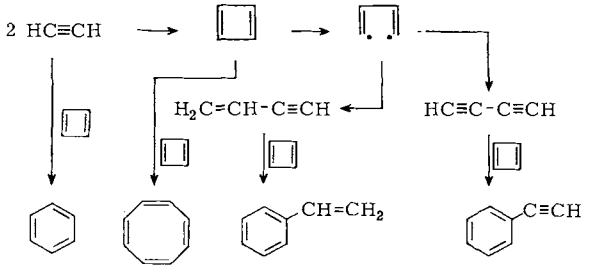
The removal of halogen, hydroxyl, methoxy, or amino groups has been observed in some cases. The yields are mostly low, and the reactions are of little preparative interest.

4.3. Bimolecular Processes

The last section was concerned only with unimolecular reactions, but chemistry in glow discharges is by no means confined to such processes. However, bimolecular reactions

pounds having straight-chain or branched alkyl groups, with C-C bond cleavage in the α position.

Trimerizations and tetramerizations occur only rarely in the plasma. An exception is acetylene, which can also trimerize and tetramerize. Because of its simplicity and its industrial importance, the behavior of acetylene in plasmas has often been investigated[65-67]. In these experiments, in addition to small quantities of vinylacetylene, diacetylene, and benzene, the main product isolated was always a yellow polymer (cuprene). Under certain reaction conditions, however, entirely different results can be obtained[48]. If the surface area of the vessel is greatly increased, the reaction can be stopped at an intermediate stage. Polymer formation can be almost totally suppressed in this way, and compounds containing eight carbon atoms are formed instead, together with vinylacetylene and diacetylene (Table 5). The reaction thus corresponds formally to a tetramerization of acetylene, which can be plausibly explained by the intermediacy of cyclobutadiene:



If the reaction is not stopped at the tetramer, it proceeds to yield high molecular weight compounds. The IR spectra

of the polymerization products from acetylene are very similar to those of polystyrene[60].

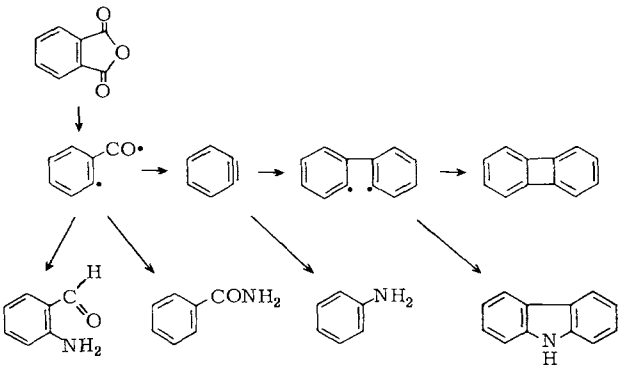
Table 5. Liquid products of the plasma reaction of acetylene [48].

Product	Yield [mol-%]
Styrene	30—70
Phenylacetylene	15—50
Cyclooctatetraene	1
Benzene	5—10
Naphthalene	10—20

Polymerizations are observed much more frequently than oligomerizations in the plasma. In addition to the usual monomers, such as styrene and butadiene, compounds exhibiting no tendency to polymerize under normal conditions can also be polymerized in the plasma[68-73]. For example, under drastic conditions, benzene gives a polymeric material, presumably "polyphenyl", as the only product[59, 60]. A high molecular weight substance, presumably "polyphenyl", is similarly obtained from phthalic anhydride. A series of compounds containing nitrogen, such as pyrrole, pyridine, and aniline, are converted in the plasma into unsaturated nitriles, which can be readily polymerized[42].

In bimolecular reactions of two different components, the range of favorable operating conditions is very narrow. Outside this range, at most only one of the components reacts. Under suitable reaction conditions, propylene oxide has been prepared from propene and oxygen[31], and styrene oxide from styrene and oxygen[48]. Mixtures of benzene and oxygen give phenol[51, 74], and mixtures of benzene and ammonia can be converted into aniline[42, 75]. The yields in such reactions are often unsatisfactory. Systematic attempts to optimize the processes have so far been made only for propylene oxide[31].

Another interesting possibility for carrying out bimolecular reactions is to produce reactive intermediates in the plasma and to intercept these with suitable reactants. This possibility has been investigated in the case of phthalic anhydride[53]. In the first reaction step, the compound loses carbon dioxide, and carbon monoxide is then eliminated to form dehydrobenzene. Two molecules of dehydrobenzene can then combine to form a biphenyl diradical, which cyclizes to biphenylene or reacts with another molecule of dehydrobenzene to form triphenylene. The reaction can be stopped at any of the intermediate stages by means of interceptor reagents. The addition of hydrogen reduces the yields of biphenylene and triphenylene in favor of biphenyl formation. Sulfur atoms also react with the biphenyl diradical to form dibenzothiophene. Dehydrobenzene can be intercepted by the addition of acetylene, and the main reaction product in this case is phenylacetylene. Finally, all the intermediates react with ammonia. The benzoyl radical gives aminobenzaldehyde and benzamide, dehydrobenzene gives aniline, and the biphenyl diradical reacts to form carbazole:



Preparative organic plasma chemistry is still at an early stage of development. The results obtained so far have already shown many possibilities for specific reactions and preparative applications. Most of the investigations have been carried out on simple model compounds, but the results obtained can be readily applied to other, preparatively more attractive systems.

More complicated compounds can often react in several ways, and in such cases the reaction with the lowest energy requirements usually occurs preferentially. To be able to predict the reaction course, the reactivities of the various groups must be known. For this purpose, one still has to rely largely on experience and estimates based on bond energies. If the molecules contain only relatively strong bonds, they react only with difficulty in the plasma. C-C and C-H bonds in aromatic compounds and double and triple bonds are therefore particularly stable. C-C bonds in aliphatic systems are moderately stable, and C-C bonds in benzyl or allyl positions are particularly easily broken. Most functional groups react readily in the plasma. Aldehyde, carboxyl, nitro, and azo groups are most readily attacked. Carbonyl, hydroxyl, alkoxy, amino, and alkyl groups as well as halogens also react under rather more drastic conditions. Only cyano and ethynyl groups and fluorine have been found to be stable substituents.

5. Reaction Mechanisms

In a plasma reaction, the starting materials are known and the end products can be determined by analysis. However, the reaction path is usually unknown. The reaction course can be influenced only by variation of pressure, electron energy, and residence time. Interception reactions or other means for the identification of intermediates are only rarely possible. Views on the mechanisms of organic plasma reactions are therefore largely based on a discussion and critical consideration of the various possible elementary processes and on an interpretation based on the reaction products.

Elementary processes of very different types can occur in the plasma. 1 cm^3 of the plasma zone normally contains about 10^{10}—10^{12} electrons and ions as well as 10^{16} neutral particles. Though the charged particles are present only in a low concentration, it is the presence of these particles that makes the plasma reactions possible. The electrons

absorb energy in the electric field and transfer it to the neutral particles in elastic or inelastic collisions.

The transfer of energy by elastic collisions depends on the relative masses of the colliding particles. On collision of an electron with a molecule of mass 100, only 1/100000 of the energy of the electron is transferred to the larger molecule. In the usual preparative plasma experiments, 0.1—1 mol of starting material is passed through the plasma per hour. Each molecule thus spends only about 0.1 s in the plasma, and the quantity of energy that it receives through elastic collisions during this time is so small that neither chemical reaction nor appreciable heating of the neutral gas occurs. The influence of the elastic collisions is therefore extremely small.

The chemical reactions in the plasma are undoubtedly results of inelastic collisions. Various processes can occur in such collisions, depending on the energy of the colliding electrons. Electrons with low energies may be trapped by the molecules to form negative ions. Somewhat higher electron energies lead to the formation of short-lived collision complexes, whose lifetime is sufficient in many cases for part of the kinetic energy of the electrons to be transferred to the molecules. Vibrationally or electronically excited molecules are formed in this way. If electrons with still higher energies collide with the molecules, they may produce positive ions, possibly in a vibrationally or electronically excited state. Since the kinetic energy in an ionizing collision is distributed over three particles, the probability of the formation of electronically excited positive ions is small.

Vibrationally or electronically excited molecules are undoubtedly crucial intermediates in many plasma processes. The role of the ions is less clear. Despite the low degree of ionization, many of the molecules may be temporarily ionized during their passage through the plasma, since the exchange of charge *via* ion-molecule reactions takes place extremely rapidly[77]. However, it is necessary in every case to investigate whether the structural changes in the molecule take place in the ionic state.

The ions revert to the uncharged state by charge transfer or by neutralization. The recombination of a positive ion with an electron can take place only in a three-body collision or on the wall. Though the energy (approx. 10 eV) is distributed between two particles here, the single molecule receives so much energy that it may decompose. There is less danger of decomposition for larger molecules, since these can absorb more energy through their numerous vibrational modes. Many positive ions form complexes with neutral molecules[78–80]. If such a complex recombines with an electron, or a positive ion with a negative ion, the energy liberated can be distributed over several particles and numerous bonds.

The negative and positive ions and the excited molecules may rearrange or decompose. They or their further reaction products, which are often free radicals, may form new species by reaction with unexcited particles. Only by detailed investigations is it possible to establish which of these numerous possibilities predominates in a given reaction. For this purpose, the electron density and energy distribution and the nature and concentration of the positive and negative ions, the excited molecules, and the intermediates should be determined by sonde measurements or by mass, electron spin resonance, emission, or absorption spectroscopy. Investigations of this nature have already been carried out for simple systems, and have demonstrated the possibilities of determining the elementary processes in the plasma in this admittedly very laborious way[81–87].

A much simpler method is the comparison of the plasma reaction products with the products of related reactions. Some classes of substances, on reaction in the plasma, exhibit similarities to pyrolysis, photolysis, or mass spectroscopy. If analogies are found in the products, it may be assumed that the reaction mechanism is also analogous.

Aliphatic hydrocarbons are converted into a variety of paraffins, olefins, or acetylenes in the plasma by decomposition and degradation reactions[88]. A similar mixture of products is formed on pyrolysis of hydrocarbons, and it can therefore be concluded that the two processes have the same (free-radical) mechanism for this class of compounds. Similarities between glow discharges and pyrolyses occur only occasionally, since the two methods differ in important respects. In pyrolysis, many particles have a high energy, while in the plasma only isolated molecules receive an energy through electron collision that can appreciably exceed the energy involved in pyrolysis. These "hot molecules" react, but are then immediately deactivated again by collisions with the less excited neighboring molecules.

Some plasma reactions yield the same products as photochemical reactions. It cannot be assumed that the reactions in the plasma proceed indirectly *via* photons, since only a small proportion of the photons produced in glow discharges are absorbed by the gas molecules. The "photochemical reactions" in the plasma are due to the fact that the same states can be excited by collision with electrons as by absorption of a photon. Since there are no selection rules and no forbidden transitions for collisions with slow electrons, they can also lead to other states, which are not directly accessible by photochemical processes.

In some classes of compounds, pronounced similarities are found between the behavior in the plasma and in the mass spectrometer. An impressive example is provided by anisole (Table 6). For all the plasma products of anisole[45], there are decomposition paths leading to similar products in the mass spectrum[89]. The only difference is that reactions requiring large amounts of energy, such as the elimination of formaldehyde or of $CH_3 + CO$, are important in the mass spectrometer, whereas the reaction with the lowest energy requirement, *i.e.* the rearrangement to the cresols, is particularly favored in the plasma. The analogy between plasma chemistry and mass spectroscopy is not surprising, since the reactions are induced in both cases by collisions with electrons. However, there are differences with respect to the electron energies and the pressure. Because of the higher pressures in the plasma, bimolecular processes such ion-molecule reactions can readily proceed, whereas these reactions occur only rarely if at all in the mass spectrometer.

Reactions are occasionally found in the plasma for which no analogies are known. One such case is that of nitro-

benzene[90]. In the plasma, this compound gives numerous products, which are almost without exception derived from three intermediates, *i.e.* the phenyl radical, the phenoxyl radical, and dehydrobenzene. The decomposition of nitrobenzene to form the phenyl radical requires 57 kcal/mol, and the elimination of nitric oxide presumably

Table 6. Comparison of the reaction products of anisole (H_5C_6—O—CH_3 = M) in the plasma with the fragmentation processes in the mass spectrometer.

Plasma products	[mol-%]	Mass spectra	Rel. intensities
		M^+	100
Phenol	22—26	$M^+ - CH_3$	15
Benzene	0.4—4	$M^+ - CH_2O$	56
		$M^+ - H—CH_2O$	16
Cyclopentadiene	1—3	$M^+ - CH_3—CO$	63
Cresols	62—70	$M^+ - H$	2 [a]
		$M^+ - H - CO$	10 [a]

[a] Typical cresol band.

requires rather less energy. Both reactions also occur in photolysis[91], pyrolysis[92], and mass spectroscopy[93]. It is surprising that in addition to these readily occurring reactions, the energetically much less favorable elimination of HNO_2 (energy requirement approx. 200 kcal/mol) plays such an important part in the plasma. This surprising observation suggests that an appreciable proportion of the nitrobenzene molecules have been ionized, and the energy of approx. 10 eV liberated on recombination has allowed aryne formation.

The mechanisms of plasma reactions have so far been thoroughly investigated in only a few cases. The results obtained are extremely interesting, but the picture of the organic plasma that can be drawn on the basis of these findings is still too incomplete for any pattern to emerge.

6. Possibilities and Limitations of Organic Plasma Chemistry

The preparative use of a plasma reaction depends on the conversion (in %) and the yield (in g/kWh). Other decisive factors are whether the reaction leads uniformly to the desired product and what trouble is involved in the separation of any by-products, whether the reaction product is also obtainable by another route, and whether the value of the product justifies the outlay on equipment.

The yield and the selectivity of a plasma reaction depend on the experimental conditions, and can be optimized by series of experiments. Figure 3 shows such a dependence for the formation of biphenyl from benzene[47]. With increasing field strength, the total yield increases, but the percentage of biphenyl in the reaction products decreases.

With increasing pressure, the yield of biphenyl passes through a maximum. The first result is due to the fact that secondary processes and fragmentations also occur to an increasing extent with increasing energy. As to the pressure dependence, an increase in the bimolecular reaction rate is opposed here by the decrease in the average electron energy and hence in the number of chemically effective collisions[94]. In many reactions, the selectivity increases with increasing pressure because of the lower electron energy.

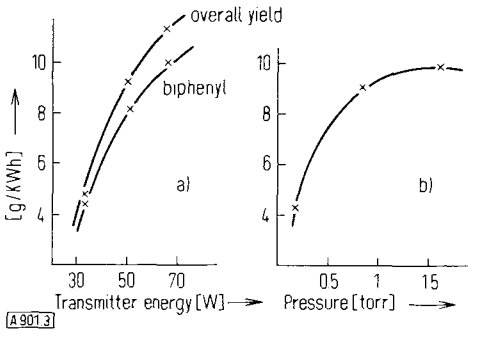


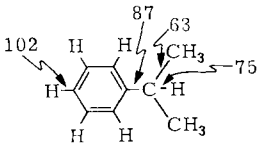
Fig. 3. Yields of biphenyl in the plasma reaction of benzene [47]: a) at constant pressure (0.8 torr) and with varying transmission energy; b) at constant transmission energy (52 W) and with varying pressure.

The rules for the control of plasma reactions are not yet sufficiently known, and it is therefore necessary to determine the optimum conditions experimentally for each new reaction by variation of the pressure, field strength, tube diameter, and flow rate. Moreover, the transfer of experimental data from one plasma apparatus to another is often not directly possible, and a number of further optimization experiments are then necessary. A direct transfer of data will become possibly only when the plasma properties required for a given reaction have been established[95].

The yields of plasma products vary widely. Rearrangements give approx. 1 mol/kWh and dimerizations approx. 1—2 mol/kWh; eliminations usually proceed with yields of 0.1—0.5 mol/kWh. These data relate to experiments in which the field strength, the pressure, and the flow rate have been optimized. If the tube diameter is also varied and the high-frequency coupling optimized, it should be possible to increase the yields further.

Plasma chemistry is confined to the gas phase, and for preparatively useful mass throughputs it requires a vapor pressure of 1 torr or more. In principle, therefore, all compounds that can be distilled without decomposing at pressures of at least 1 torr should be suitable for use in plasma reactions. However, the number of preparatively useful reactions is much smaller, since product mixtures can occur with molecules for which several energetically equivalent reactions are possible. Only if one of the possible reactions has a much lower energy requirement than any of the others can the reaction be controlled in such a way that only a single product is formed. In the case of isopropylbenzene, in which the bond energies differ by almost 30 kcal/mol[96] the reaction can be carried out in such a way as to obtain 2,3-diphenylbutane almost quantitatively by the use of mild conditions. Reactions that require the cleavage of a stronger bond become important only at higher electron energies, but are then accompanied by the formation of 2,3-diphenylbutane.

The mass throughput is decisive to the economy of plasma reactions. The laboratory equipment developed so far operates at pressures of 1—5 torr and distillation rates of



Bond energies in kcal/mol

about 0.1 mol/h. If the pressure is increased to raise the throughput, the field strength must be simultaneously increased, since the ratio of the two quantities should be kept approximately constant. However, this often leads to such high gas temperatures that starting compounds or final products undergo thermal decomposition. It may be possible to overcome these difficulties with pulsed plasmas, in which there is no excessive heating of the neutral gas up to the region of about 50 torr[95].

7. Future Developments

The transformation of organic substances by collision with electrons, which has been known for some time, has been developed in recent years into a preparative method offering a wide range of possibilities. Many technological problems still have to be solved before the processes elaborated so far on the laboratory scale can be applied to industrial production. Owing to the considerable cost of plasma equipment, plasma chemistry is not very likely to be considered for large-scale syntheses. Its future use will presumably lie in the production of compounds that are unobtainable or obtainable only with difficulty by other methods. Though organic plasma chemistry is still in the early stages of development, it is likely, from the very recent preparative successes, that plasma-chemical methods of synthesis will be introduced into laboratory chemistry and industrial production in the near future.

Received: December 28, 1971 [A 901 IE]
German version: Angew. Chem. *84*, 876 (1972)
Translated by Express Translation Service, London

[1] a) *Th. Rummel*: Hochspannungsentladungschemie und ihre industrielle Anwendung. R. Oldenbourg u. H. Reich Verlag, München 1951; b) Ion-Molecule Reactions in the Gas Phase. Advan. Chem. Ser. n 58 (1966); c) *N. S. Pechuro*: Organic Reactions in Electrical Discharges. Russian original, Nauka Press, Moskau 1966; English Translation, Consultants Bureau, New York 1968; d) *F. K. Taggart*: Plasmachemistry in Electrical Discharges. Elsevier, Amsterdam 1967; e) *R. F. Baddour* and *R. S. Timmins*: The Application of Plasmas to Chemical Processing. Pergamon, Oxford 1967; f) Chemical Reactions in Electrical Discharges. Advan. Chem. Ser. n 80 (1969); g) *B. D. Blaustein* and *Y. C. Fu*: Organic Reactions in Electrical Discharges, in *A. Weissberger* and *B. W. Rossiter*: Techniques of Chemistry in Physical Methods of Chemistry, Part II. Interscience, New York; Reactions under Plasma Conditions, *M. Venugopalan* (Editor), Vol. I, II, Wiley-Interscience. New York 1971.
[2] *M. Berthelot*, C. R. Acad. Sci. Paris *67*, 1141 (1869); *82*, 1283 (1876); Ann. Chim. Phys. *7* (Ser. 16), 31 (1899); *S. M. Losanitsch*, Ber. Dtsch. Chem. Ges. *42*, 4394 (1909); *R. W. Wood*, Proc. Roy. Soc. (London) *A 97*, 455 (1920); *K. F. Bonhoeffer*, Z. Phys. Chem. *113*, 199 (1924).
[3] a) *W. L. Jolly*, [1f], p. 156; b) cf. [1a], p. 229, 262.
[4] For details, see: *S. Flügge*: Handbuch der Physik, Vol. XXI and XXII. Springer-Verlag, Berlin 1956; *G. Franzis*: Ionisation phenomena in gases. Butterworths, London 1960; *D. R. Bates*: Atomic and Molecular Processes. Academic Press, New York 1962; *A. v. Engel*: Ionized Gases, 2nd. Edit. Clarendon Press, Oxford 1965; *F. Llewellyn-Jones*: Ionisation and Breakdown in Gases. Methuen, London 1966; *R. Papoular*: Electrical Phenomena in Gases. Iliffe Books, London 1965; *S. C. Brown*: Basic Data of Plasma Physics 1966. The MIT Press, Cambridge, Mass. 1967; *H. S. W. Massey*, *E. H. S. Burhop*, and *H. B. Gilbody*: Electronic and Ionic Impact Phenomena, 2nd Edit. Clarendon Press, Oxford 1969.
[5] *E. N. Borsova*, *E. N. Eremin*, *D. T. Il'in*, *N. S. Pechuro*, *et al.* in [1c].
[6] *M. P. Freeman*, [1f], p. 406.
[7] *B. R. Bronfin*, [1f], p. 423.
[8] Cf. [1d], pp. 202—212.
[9] *J. C. Devins* and *M. Burton*, J. Amer. Chem. Soc. *76*, 2618 (1954).
[10] *K. Uochi*, J. Electrochem. Soc. Japan *20*, 381 (1952).
[11] *H. Schüler* and *V. Degenhart*, Z. Naturforsch. *8a*, 251 (1953).
[12] *J. D. Thornton*, *W. D. Charlton*, and *P. L. Spedding*, [1f], p. 165.
[13] *D. J. Meschi* and *R. J. Meyers*, J. Amer. Chem. Soc. *78*, 6220 (1956).
[14] Cf. [1d], Chapters 5—9.
[15] *K. R. Jennings*, Quart. Rev. Chem. Soc. *15*, 237 (1961).
[16] *H. Schüler* and *L. Reinbeck*, Z. Naturforsch. *5a*, 657 (1950).
[17] *F. Kaufman*, [1f], p. 29.
[18] *W. V. Smith*, J. Chem. Phys. *11*, 110 (1943).
[19] *J. W. Linnett* and *D. G. H. Marsden*, Proc. Roy. Soc. (London) *A 234*, 489, 504 (1956).
[20] *J. C. Greaves* and *J. W. Linnett*, Trans. Faraday Soc. *54*, 1323 (1958).
[21] *R. A. Young*, J. Chem. Phys. *34*, 1292, 1295 (1961).
[22] *P. R. Rony* and *D. N. Hanson*, J. Chem. Phys. *44*, 2536 (1966).
[23] Cf. [1g], Chapter 5.
[24] *H. Gg. Wagner* and *J. Wolfrum*, Angew. Chem. *83*, 561 (1971); Angew. Chem. internat. Edit. *10*, 604 (1971).
[25] *K. H. Geib* and *P. Harteck*, Ber. Dtsch. Chem. Ges. *66*, 1815 (1933).
[26] *B. A. Thrush*, Progr. React. Kinet. *3*, 63 (1965).
[27] *R. J. Cvetanovic*, Advan. Photochem. *1*, 115 (1963).
[28] *R. J. Cvetanovic*, J. Chem. Phys. *25*, 376 (1956).
[29] *R. J. Cvetanovic*, Can. J. Chem. *36*, 623 (1958).
[30] *R. J. Cvetanovic*, J. Chem. Phys. *30*, 19 (1959).
[31] *R. Weisbeck* and *R. Hüllstrung*, Chem. Ing. Tech. *42*, 1302 (1970).
[32] *G. G. Mannella*, Chem. Rev. *63*, 1 (1963).
[33] *A. N. Wright* and *C. A. Winkler*: Active Nitrogen. Academic Press, New York 1968.
[34] *O. K. Fomin*, Russ. Chem. Rev. *36*, 725 (1967).
[35] *P. T. Hinde* and *N. N. Lichtin*, [1f], p. 250.
[36] *A. N. Wright*, *R. L. Nelson*, and *C. A. Winkler*, Can. J. Chem. *40*, 1082 (1962).
[37] *A. Tsukamoto* and *N. N. Lichtin*, J. Amer. Chem. Soc. *82*, 3798 (1960).
[38] *A. Fujino*, *S. Lundsted*, and *N. N. Lichtin*, J. Amer. Chem. Soc. *88*, 775 (1966).
[39] *T. Hanafusa* and *N. N. Lichtin*, Can. J. Chem. *44*, 1230 (1966).
[40] *C. C. T. Chen* and *N. N. Lichtin*, J. Amer. Chem. Soc. *92*, 7506 (1970).
[41] *H. Suhr* and *U. Schücker*, Synthesis *1970*, 431.
[42] *H. Suhr* and *U. Schöch*, to be published.
[43] *H. Suhr et al.*, unpublished.
[44] *H. Suhr*, *G. Rolle*, and *B. Schrader*, Naturwissenschaften *55*, 168 (1968).
[45] *H. Suhr* and *R. I. Weiss*, Z. Naturforsch. *25b*, 41 (1970).
[46] *H. Suhr* and *R. I. Weiss*, Liebigs Ann. Chem., in press.
[47] *H. Suhr* and *R. I. Weiss*, Liebigs Ann. Chem., in press.
[48] *H. Suhr* and *G. Rosskamp*, to be published.
[49] *H. Suhr* and *G. Kruppa*, Liebigs Ann. Chem. *744*, 1 (1971).
[50] *H. Suhr* and *R. I. Weiss*, Angew. Chem. *82*, 295 (1970); Angew. Chem. internat. Edit. *9*, 312 (1970).
[51] *H. Suhr* and *A. Szabo*, to be published.
[52] *E. K. Fields* and *S. Meyerson*, Chem. Commun. *1965*, 474.
[53] *H. Suhr* and *A. Szabo*, Liebigs Ann. Chem. *752*, 37 (1971).
[54] *A. M. Buss* and *H. P. Broida*: Stabilization of Free Radicals at Low Temperatures. NBS Monograph 12, US. Dept. Comm., Washington D.C. 1960.
[55] *E. W. R. Steacie*: Atomic and Free Radical Reactions. Reinhold, New York 1954, Vol. 1, p. 32.
[56] *H. Suhr*, *U. Schöch*, and *G. Rosskamp*, Chem. Ber. *104*, 674 (1971).
[57] *H. Suhr* in *Houben-Weyl*: Methoden der Organischen Chemie V/1b. Thieme Verlag, Stuttgart 1972, in press.
[58] *R. Weisbeck*, Chem. Ing. Tech. *43*, 721 (1971).
[59] *M. W. Ranney* and *W. F. Connor*, [1f], p. 297.
[60] *D. D. Neiswender*, [1f], p. 338.
[61] *J. K. Stille*, *R. L. Sung*, and *J. van der Kooi*, J. Org. Chem. *30*, 3116 (1965).
[62] *C. Boelhouwer* and *E. H. I. Waterman*, Research (London) *9*, 11 (1956).

[63] *H. Suhr*, Z. Naturforsch. *23b*, 1559 (1968).
[64] *H. Suhr, U. Schöch*, and *U. Schücker*, Synthesis *1971*, 426.
[65] Cf. [1d], p. 196.
[66] *E. K. Fields* and *S. Meyerson*, Tetrahedron Lett. *6*, 571 (1967).
[67] *M. Tsakuda* and *S. Shida*, J. Chem. Phys. *44*, 3130 (1966).
[68] *J. R. Hollahan* and *R. P. McKeever*, [1f], p. 272.
[69] *P. M. Hay*, [1f], p. 350.
[70] Cf. [1d], p. 196.
[71] *P. L. Spedding*, Nature *214*, 124 (1967).
[72] *V. M. Kolotyrkin, A. B. Gilman*, and *A. K. Tsapuk*, Russ. Chem. Rev. *36*, 579 (1967).
[73] *A. R. Denaro, P. A. Owens*, and *A. Crawshaw*, Eur. Polym. J. *5*, 471 (1969).
[74] *S. Inone*, J. Chem. Soc. Japan *71*, 518 (1950); Chem. Abstr. *45*, 9499 (1950).
[75] *S. Inone* and *K. Odo*, J. Chem. Soc. Japan *71*, 343 (1950).
[76] *O. I. Zakharov-Nartissov* and *N. G. Pilyugina*, Khim. Vys. Energ. *3*, 3, 5267 (1969).
[77] *J. L. Franklin, P. K. Gosh*, and *S. Studniarz*, [1f], p. 59.
[78] *F. H. Field, P. Hamlet*, and *W. F. Libby*, J. Amer. Chem. Soc. *89*, 6035 (1967).
[79] *C. Lifschitz* and *B. G. Reuben*, J. Chem. Phys. *50*, 951 (1969).
[80] *F. H. Field, P. Hamlet*, and *W. F. Libby*, J. Amer. Chem. Soc. *91*, 2839 (1969).
[81] *E. D. Morris, D. H. Stedman*, and *H. Niki*, J. Amer. Chem. Soc. *93*, 3570 (1971).
[82] *M. Yamane*, J. Chem. Phys. *49*, 4624 (1968).
[83] *E. E. Daby, H. Niki*, and *B. Weinstock*, J. Phys. Chem. *75*, 1601 (1971).
[84] *K. Hoyermann, H. Gg. Wagner*, and *J. Wolfrum*, Ber. Bunsenges. Phys. Chem. *72*, 1004 (1968).
[85] *K. Hoyermann, H. Gg. Wagner, J. Wolfrum*, and *R. Zellner*, Ber. Bunsenges. Phys. Chem. *75*, 22 (1971).
[86] *M. A. Contineanu, D. Mihelcic, R. N. Schindler*, and *P. Potzinger*, Ber. Bunsenges. Phys. Chem. *75*, 426 (1971).
[87] *K. G. Mothes* and *R. N. Schindler*, Ber. Bunsenges. Phys. Chem. *75*, 938 (1971).
[88] Cf. [1g], Chapter 5 and 6.
[89] *F. Meyer* and *A. G. Harrison*, Can. J. Chem. *46*, 2008 (1968).
[90] *H. Suhr* and *G. Rasskamp*, Liebigs Ann. Chem. *742*, 43 (1970).
[91] *R. Hurley* and *A. C. Testa*, J. Amer. Chem. Soc. *88*, 4330 (1966).
[92] *E. K. Fields* and *S. Meyerson*, J. Amer. Chem. Soc. *89*, 3224 (1967).
[93] *H. Budzikiewicz, C. Djerassi*, and *E. H. Williams*: Mass Spectroscopy of Organic Compounds. Holden Day, San Francisco 1967, p. 515.
[94] *W. G. Burns* and *W. R. Marsh*, Trans. Faraday Soc. *65*, 1827 (1969).
[95] *K. G. Müller*, Chem.-Ing.-Tech., in press.
[96] *T. L. Cottrell*: The Strength of Chemical Bonds. Butterworth, London 1958.

Energy Metabolism in Mitochondria

By Hans Walter Heldt[*]

Mitochondria are separate metabolic compartments within the cell. The functional boundary of the mitochondrial compartment is the inner membrane. This membrane contains the enzymatic apparatus for the electron transport and oxidative phosphorylation. The substrate breakdown cycles are localized in the mitochondrial matrix space. Specific carriers are responsible for the exchange of ADP, ATP, phosphate, and intermediates of the citric acid cycle between the matrix space and the extramitochondrial space. The particular importance of the adenine nucleotide transport to the regulation of the energy metabolism of the cell is discussed in detail.

Mitochondria occur in the cytoplasm of all aerobic eukaryotic cells. They are the site of cell respiration, and have therefore been referred to as the "power plant of the cell". The energy liberated on oxidation of the substrate hydrogen drives the endergonic synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and orthophosphate (P). This process is known as oxidative phosphorylation[**]. The energy liberated on hydrolysis of ATP to ADP and phosphate covers the energy-consuming processes of the cell (*e.g.* mechanical, chemical, osmotic, and electric work).

There are two important metabolic compartments in the animal cell, *i.e.* the extramitochondrial compartment, which comprises the ground cytoplasm and the nuclear space, and the mitochondrial compartment. Coordination of the metabolic processes requires the specific transport of substrates and products through the membranes that separate the two compartments. The present report is concerned with the structure of the mitochondrial compartment. Details of specific transport processes between the two compartments should provide an insight into the regulation of the oxidative metabolism.

[*] Priv.-Doz. Dr. H. W. Heldt
Institut für Physiologische Chemie und Physikalische Biochemie der Universität
8 München 2, Pettenkoferstrasse 12—14a (Germany)
The author's own work in this field was supported by the Deutsche Forschungsgemeinschaft.

[**] A comprehensive article on the mechanism of oxidative phosphorylation has been published in this journal by *Schatz* [1].

1. Morphological Structure of Mitochondria

Mitochondria were observed with the aid of the optical microscope in the middle of the last century[2–5], but a precise elucidation of their structure (Fig. 1) became possible only with the advent of electron microscopy[6–8]. A particularly striking feature of mitochondria is the high membrane fraction. They have two types of membrane (Fig. 2), which differ in their fine structure, lipid composition, and protein content. The *outer membrane* surrounds the mitochondrion. The *inner membrane* extends more or less densely packed in an endlessly folded or in a tubular arrangement in the interior of the mitochondria. It has a very large surface. The mitochondrial matrix that it sur-

rounds consists of a dense protein gel. Apart from the membrane phases, therefore, there are two compartments in the mitochondria, *i.e.* the *intermembrane space* between the outer and the inner membranes and the matrix space.

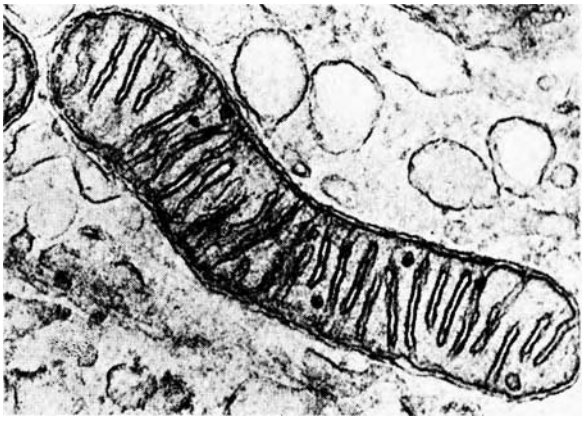


Fig. 1. Mitochondrium from the epididymal epithelium of the mouse. 61000-fold magnification [9].

With the aid of the electron-microscope technique of negative staining[***], characteristic round "knobs" having a diameter of about 90 Å were observed on the side of the

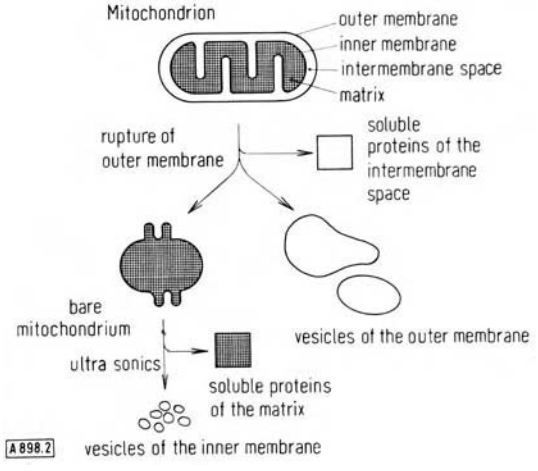


Fig. 2. Scheme of the structure and the fractionation of mitochondria.

inner membrane turned toward the matrix[10]. The outer membrane does not show these knobs. There is now evidence that these knob-shaped subunits are identical with the cold-labile ATPase, an enzyme that catalyzes a step of the oxidative phosphorylation[11]. However, it is doubtful whether these subunits that can be seen in the electron-micrograph are also evident in the intact membrane. It is possible that they were formed from a pre-existing structure on treatment with the reagent. The fact that these structures are observed only on the inside of the inner membrane points to the asymmetric structure of this membrane.

[***] In "negative staining", the sample is spread on a liquid film by surface tension. Phosphotungstate is then applied to the layer. On examination in the electron microscope, cell structures give a negative contrast.

Characteristic differences between the two membranes are also found in the lipid composition (Table 1). Thus cholesterol is found mainly in the outer membrane, while cardiolipin occurs almost only in the inner membrane[12-14]. The inner membrane also contains more protein than the outer membrane. In its lipid composition the inner membrane resembles a bacterial membrane, and the outer membrane resembles the plasma membrane.

Table 1. Composition of the outer and inner membranes of mitochondria from guinea pig liver [12, 13].

	Outer membrane	Inner membrane
Density	1.13	1.21
Protein : Lipid	1 : 0.829	1 : 0.275
Protein : Cholesterol	1 : 0.030	1 : 0.0051
Percentage of individual phospholipids in the entire phospholipid:		
cardiolipin	3.2%	21.5%
phosphatidylinosite	13.5%	4.2%
phosphatidylethanolamine	25.3%	27.7%
lecithin	55.2%	44.5%

Mitochondria multiply by division[15-17]. All the mitochondria of an organism are thus descended from the mitochondria of the egg cell. The deoxyribonucleic acid (DNA) present in the mitochondria[18-21] differs from the DNA in the cell nucleus; like bacterial DNA, it has a cyclic structure. However, the mitochondrial DNA determines only a few proteins that are essential to the genesis of mitochondria[22]. The synthesis of most of the mitochondrial proteins is controlled by the cell nucleus. It has been speculated that the aerobic cells arose from symbiosis between anaerobic cells and aerobic bacteria phagocytized by them[23]. According to this hypothesis, the mitochondrial outer membrane is derived from the cell membrane, which has been turned inward by phagocytosis, while the mitochondrial inner membrane is derived from a bacterial membrane.

2. Permeation Behavior of Mitochondria

Investigations with isolated mitochondria showed that part of the mitochondrial compartment is freely accessible to low molecular weight substances, such as inorganic ions, nucleotides, amino acids, and sucrose. This space is not accessible, however, to large molecules such as polymeric sugars or proteins. The size of the space that is accessible to sucrose can be influenced by the tonicity of the medium. Under isotonic conditions the sucrose-accessible space roughly corresponds to one third of the total mitochondrial solution space. If the isotonic medium is replaced by a hypotonic medium, the sucrose-inaccessible space increases at the expense of the sucrose-accessible space. In electron microscope studies carried out in parallel with this work, swelling of the matrix space (see Fig. 2) was observed, with a simultaneous decrease in the intermembrane space. A comparison of size between the functionally measured and the morphologically observed spaces showed that the sucrose-accessible space is identical with the intermembrane

space, and the sucrose-inaccessible space with the matrix space[24, 25]. It can be seen from the result that the outer membrane is permeable to low molecular weight substances, while the inner membrane is the osmotically active membrane.

3. Localization of Mitochondria Enzymes

Enzymes contained in the mitochondria may be present in the matrix space or in the intermembrane space. They can also be structure-bound components of the inner or outer membrane. An enzyme of the inner membrane may be directed toward the matrix space or toward the intermembrane space.

Two methods are used for the assignment of one of these positions to a mitochondrial enzyme, *i.e.* functional investigations on intact and disrupted mitochondria, and fractionation of the mitochondria with subsequent measurement of the enzyme activities in the fractions.

The functional investigations are based on the fact that the intermembrane space is freely accessible to substrates and nucleotides. The matrix space, which is not freely accessible, contains the mitochondrial nucleotides and Mg^{2+} ions, among other things. The inner membrane is impermeable to nucleotides, apart from a specific transport for adenine nucleotides, which will be discussed later. This transport is inhibited by atractyloside (Section 7). The localization of an enzyme inside the mitochondria can be determined *e.g.* by measurements of the reactivity with intramitochondrial or extramitochondrial nucleotides, sensitivity to atractyloside, and dependence on added Mg^{2+} ions.

The fractionation of the mitochondria is based on specific opening of the outer membrane. The soluble enzymes of the intermembrane space are liberated and are found in the supernatant. A scheme of this process is shown in Figure 2. One method for selective rupture of the outer membrane is treatment of the mitochondria with hypotonic media[12, 24]. Since the inner membrane is osmotically active, the matrix space swells in the hypotonic medium, and the inner membrane presses against the outer membrane and bursts it open.

Another method of rupturing the outer membrane selectively makes use of the fact that cholesterol occurs mainly in the outer membrane. It is well known that cholesterol forms a compound with digitonin. The addition of digitonin to mitochondria binds the cholesterol of the outer membrane and causes the membrane to break open[26–28]. The fragments of the outer membrane, which are mostly in the form of vesicles, can be separated by centrifugation in a density gradient. The bare mitochondria, consisting of the inner membrane and the matrix enclosed by it, remain behind. In these bare mitochondria the folds of the membrane turn outward. Treatment with ultrasonic radiation leads to destruction of the inner membrane. The membrane fragments form small vesicles, which can be separated from the soluble proteins of the matrix space by centrifugation.

The broad lines of the organization of the mitochondrial metabolism are recognized from the localization of some important mitochondrial enzymes, which are listed in Table 2. The oxidation of the substrates and the associated ATP synthesis take place on or in the inner membrane. The substrate breakdown processes (citric acid cycle, degradation of fatty acids) are localized in the matrix space. The reduction equivalents resulting from these processes (in the form of NADH, succinate, or acyl coenzyme A) diffuse to the inside of the inner membrane, where they are oxidized. The ATP synthesis coupled with the respiratory chain takes place on the inside of the inner membrane, and the ATP formed passes into the matrix space. Carefully prepared bare mitochondria accordingly exhibit all the essential properties of intact mitochondria[26]. On the other hand, the enzyme activities of the intermembrane space (some of which also occur outside the mitochondria) and the membranes of the outer membrane appear to have more of an accessory importance.

Table 2. Localization of mitochondrial enzymes [24, 26—41].

Site	Enzyme
Inner membrane	Respiratory chain NADH-oxidase Succinate-dehydrogenase Fatty acyl CoA dehydrogenase Glycerophosphate-oxidase Pyridine nucleotide-transhydrogenase ATP-synthetase
Matrix	Dehydrogenases of the citrate cycle β-Hydroxyacyl-CoA-dehydrogenase Succinate-thiokinase GTP-dependent fatty acid activation ATP-dependent fatty acid activation (for short-chain fatty acids) GTP-AMP phosphate-transferase Transaminases Citrulline-synthetase Pyruvate-carboxylase
Intermembrane space	Adenylate-kinase Creatine-kinase Nucleoside diphosphate-kinase
Outer membrane	ATP-dependent activation of long-chain fatty acids Phospholipase Enzymes of the lecithin synthesis Monoamine-oxidase

4. Properties of the Inner Membrane

From the functional standpoint, the intermembrane space may be regarded as belonging to the extramitochondrial compartment. The partition separating the mitochondrial and the extramitochondrial metabolic compartments is the inner membrane. Through this membrane the substrates of the mitochondrial oxidation, mainly pyruvic acid and fatty acids, as well as orthophosphate and ADP must pass into the matrix space, and the product ATP must be released from the mitochondria.

Closed membranes are fundamentally impermeable both to cations and to anions. Membranes present much less hindrance to the penetration of undissociated acids or bases, since these substances can dissolve to some extent in the lipid layer of the membrane. It is thus possible for anions

and cations to pass through the membrane *via* the undissociated molecules that exist in equilibrium with them. This is probably true of a number of monocarboxylic acids. In the cases of dicarboxylic and tricarboxylic acids and phosphoric acid, on the other hand, the dissociation equilibria in neutral solution lie so far on the side of the anions that membranes are practically inpermeable to these substances[42].

In connection with the permeation properties of membranes it is interesting to note that the most important substrates of the mitochondria *i.e.* pyruvic acid and the fatty acids, are monocarboxylic acids. On the other hand, the intermediates of the mitochondrial substrate breakdown cycles (citric acid cycle and oxidation of fatty acids) are dicarboxylic or tricarboxylic acids or derivatives of coenzyme A (a compound containing phosphate), which cannot diffuse freely through the inner membrane. The same is true of the pyridine nucleotides, which take part in the substrate breakdown, and of the adenine and guanine nucleotides, which take part in the energy conservation.

5. Transport of Substrates

Both the pyruvic acid and the short-chain fatty acids can probably pass through the inner membrane without special carriers[42]. Recent findings concerning the occurrence of a special carrier for the pyruvate anion in the inner membrane[43] require further investigation.

Whereas the short-chain fatty acids are activated (*i.e.* bonded to coenzyme A) in the matrix space, the activation of the long-chain fatty acids, such as palmitic acid, occurs on the outer membrane or on the endoplasmic reticulum[36-39]. The mitochondria are thus faced with the problem of bringing the activated fatty acids into the matrix space through the inner membrane, which is impermeable to coenzyme A and its derivatives. This is achieved by a special transport mechanism, of which all the details have not yet been clarified. Three observations are important to discussions about a possible reaction course (Fig. 3): a) Carnitine [3-hydroxy-4-(trimethylammonio) butyrate] is required for the oxidation of palmitate[44]. b) Neither carnitine nor coenzyme A or its esters can pass through the inner membrane[45, 46]. c) Two different acylcoenzyme A—carnitine transferases have been discovered, one of which is bound in the inner membrane[47]. The acylcoenzyme A outside the inner membrane is assumed to be converted into acylcarnitine by the external transferase (I), with liberation of coenzyme A. The transferase in the inner membrane (II) is thought to be arranged vectorially[45], *i.e.* the bonding sites for carnitine and acylcarnitine are directed outward, and the bonding sites for coenzyme A and acylcoenzyme A toward the matrix. According to this scheme, acylcarnitine passes from outside to the inner membrane, and the acyl residue is "handed through" and reacts with the mitochondrial coenzyme A on the inside of the membrane. This would mean that a functional unit exists here between the chemical reaction and the directed transport through the membrane.

The inner membrane is impermeable to the intermediates of the citric acid cycle. This impermeability is overcome by specific carriers[48-53]. The dicarboxylic acid carrier transports malate and succinate in exchange with these dicarboxylic acids or with phosphate. The transport of citrate and isocitrate by the citrate carrier and the transport of α-ketoglutarate by the α-ketoglutarate carrier occurs in exchange with dicarboxylic acids. There is also evidence of a specific transport of glutamate.

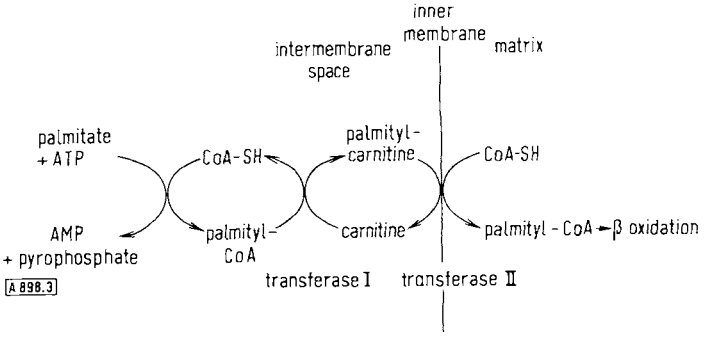


Fig. 3. Scheme of the activation of long-chain fatty acids and of the transport of activated fatty acids into the matrix space [45].

The transport of malate is important to gluconeogenesis. The initial step of this metabolic chain, *i.e.* the carboxylation of pyruvate, takes place in the matrix space[40]. The resulting oxalacetate can be transported out of the mitochondria as malate after reduction. The further synthesis steps of gluconeogenesis then take place outside the mitochondria.

The transport of citrate plays a part in lipogenesis[54]. The starting material for the synthetic chain of lipogenesis is acetyl-coenzyme A, which is formed in the mitochondria *e.g.* from pyruvate. Since the fat synthesis takes place outside the mitochondria, the acetyl-coenzyme A must be carried out of the mitochondria. Since the inner membrane is impermeable to coenzyme A and its thioesters, indirect transport occurs. Acetyl-coenzyme A condenses with oxalacetate in the mitochondria to form citrate, and this is transported into the extramitochondrial space by the citrate carrier, where it is converted back into acetyl-coenzyme A and oxalacetate.

6. Transport of Phosphate

The transport of phosphate by the phosphate carrier takes place in exchange with hydroxide ions or as a co-transport with protons[42, 49, 55]. These possibilities cannot be distinguished experimentally. The transport is inhibited by very low concentrations of compounds that block SH groups[56-58]. The phosphate carrier thus contains free SH groups. The phosphate required for the oxidative phosphorylation can pass into the matrix space through the phosphate transport. Since the transport of phosphate takes place without exchange with anions, apart from hydroxide ions, whereas the transport of dicarboxylic acids occurs in exchange with phosphate and the transport of tricarboxylic acids in exchange with dicarboxylic acids, the phosphate transport has a key function for the uptake of dicarboxylic and tricarboxylic acids into the mitochondria.

7. Transport of Adenine Nucleotides

A carrier transports the ADP into the mitochondria and the ATP formed out of the mitochondria (Fig. 4). This carrier is specific for ADP and ATP. AMP, guanine, and uracil, cytidine, and pyridine nucleotides are not transported[59]. The transport is an obligate exchange: for each molecule of adenine nucleotide transported in, another must be transported out. The carrier probably cannot pass through the membrane in the uncharged state[60]. In this way the total of mitochondrial adenine nucleotides remains constant. The affinity of the carrier is very high. Half of the maximum transport rate is reached at an ADP concentration outside the mitchondrion of only 12×10^{-6} M[42]. Atractyloside, a plant glycoside from the mastic thistle (Atractylis gummifera) and bongkrek acid, an antibiotic, are specific inhibitors of the adenine nucleotide transport[61-63]. Both substances are therefore very powerful poisons.

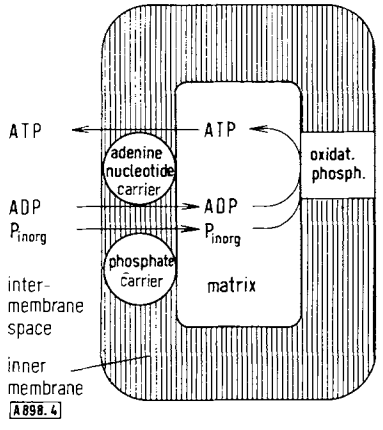


Fig. 4. Functional scheme of the adenine nucleotide transport.

The specificity of the adenine nucleotide carrier is different for the two transport directions. There are no measurable differences between ADP and ATP for the outward transport. For the inward transport, on the other hand, ADP is strongly favored over ATP. However, this is true only of intact mitochondria, in which a coupling exists between the transport of electrons by the respiratory chain and the ATP synthesis. If this coupling is eliminated by "uncouplers" (*e.g.* dinitrophenol), ADP is no longer favored for the inward transport; ATP is then transported as readily as ADP[59, 64]. It can be concluded from these findings that the preference for the transport of ADP requires the consumption of energy. This energy is supplied by the respiratory chain. It has not yet been established in detail how the transport is influenced by the energy. It is assumed that through the transport of electrons by the respiratory chain, a potential is built up across the inner membrane. Since ATP carries one negative charge more than ADP, a membrane potential could allow a discrimination against the transport of ATP through the inner membrane[42].

The asymmetry in the specificity of the transport of adenine nucleotides leads to an asymmetric distribution of ADP and ATP on the two sides of the membrane. The ATP/ADP ratio is greater outside the mitochondria than inside[65]. To check this, ADP was added to a suspension of aerobic mitochondria in the presence of substrate. After the ADP had been phosphorylated and the state of respiratory control had been reached, the mitochondria were centrifuged from the medium through a silicone layer into perchloric acid[66]. It was thus possible to measure the nucleotide concentrations in the matrix space and in the surrounding medium in the same experiment (Table 3).

Table 3. Phosphorylation potential $\Delta G'$ of ATP in mitochondria and in the medium in the state of respiratory control (20 °C) [65].
$\Delta G' = \Delta G'_0 - RT \times \ln([ATP]/[ADP] \times [Phosphate])$
$\Delta G'_0 = -8.8$ kcal/mol [70].

	$\frac{ATP}{ADP}$	Phosphate (mmol/Liter)	$\Delta G'$ (kcal/mol)
mitochondrial	3.9	3.5	−12.9
extramitochondrial	29	0.48	−15.2

The ATP/ADP ratio was found to be about 7 times as high in the medium as in the matrix space. With the aid of the measured phosphate concentrations it is possible to calculate the free energy of the hydrolysis of ATP, which is also known as the phosphorylation potential, for both spaces. The phosphorylation potential found for the ATP in the medium is 2.3 kcal/mol more negative than for the ATP in the matrix space.

Though the phosphorylation potential in the mitochondria certainly cannot be calculated exactly in this way, it can be seen that the energy consumption required for the release of the ATP from the mitochondria may be considerable. This has important consequences for the ratio of the ATP formed to the oxygen consumed (P/O ratio) in the cell. It is well known that a P/O ratio of 3 is found in mammalian mitochondria for substrates that enter the respiratory chain at the NADH stage, and a P/O ratio of 2 for substrates that attack at the flavoprotein, *e.g.* succinate. However these figures are obtained only if the ATP/ADP ratio outside the mitochondria is artificially kept low. This can be achieved by addition of glucose and hexokinase to the medium; the terminal phosphate residue of the extramitochondrial ATP is then transferred to glucose. Lower P/O values are observed without this "ATP trap", since part of the energy gained in the respiratory chain must be used up to release the ATP from the mitochondria[67].

The question arises whether the differences between the ATP/ADP ratios inside and outside the mitochondria in the test tube also occur in the living cell. To answer this question, the reactions occurring in a perfused liver were stopped by sudden cooling to −195 °C, and the frozen liver was freeze-dried and then homogenized in heptane. Mitochondria and nonmitochondrial cell material were separated by centrifugation of the homogenate in a heptane-carbon tetrachloride density gradient, and the adenine nucleotides were determined enzymatically in the resulting fractions. This experiment showed that the ATP/ADP ratio in the intact cell outside the mitochondria was more than 5 times as high as in the mitochondria[68]. Agreement with the results found for isolated mitochondria is therefore good.

8. The Importance of the Adenine Nucleotide Transport to the Energy Metabolism of the Cell

The living cell tends to maintain its ATP concentration at a constant value. A decrease in the ATP concentration on consumption of ATP can be offset for a short time by ATP reserves. Such reserves consist of the ADP that is in equilibrium with ATP and AMP in the presence of adenylate kinase, and creatine phosphate:

$$2\ \mathrm{ADP} \xrightleftharpoons{\text{adenylate-kinase}} \mathrm{ATP} + \mathrm{AMP}$$

$$\mathrm{ADP} + \text{Creatine phosphate} \xrightleftharpoons{\text{creatine-kinase}} \mathrm{ATP} + \text{Creatine}$$

These systems may be regarded as ATP buffers. The ATP consumption is ultimately compensated by ATP synthesis. In the aerobic metabolism of glucose, 95% of the ATP formed is synthesized in the mitochondria. Oxidative phosphorylation is thus the main source of the ATP in the cell.

The ADP-concentration in the matrix space controls respiration. The higher the concentration, the higher the respiration rate and hence also the rate of ATP synthesis. However, half of the maximum rate of oxidative phosphorylation is reached only when about half of the adenine nucleotide in the matrix space is in the form of ADP[69].

If the adenine nucleotide concentrations inside and outside the mitochondria were equal, a relatively large decrease in the cellular ATP concentration would be required to cause a fairly large increase in respiration. In this case the "ATP buffer" would be exhausted before increased ATP synthesis could occur. It has been observed for muscle, however, that after stimulation, a pronounced increase in respiration occurs before the creatine phosphate is exhausted[71]. The adenine nucleotides transport evidently plays an important part here. Because of the energy-dependent preference for the transport of ADP into the mitochondria, a small increase in the ADP concentration in the extramitochondrial space leads to a marked increase in the ADP concentration in the matrix space, with the result that the ATP synthesis in the mitochondria is stimulated. The energy consumption required for the adenine nucleotide transport could thus be regarded as a contribution to the maintenance of a constant cellular ATP concentration.

Received: May 21, 1971 [A 898 IE]
German version: Angew. Chem. *84*, 792 (1972)
Translated by Express Translation Service, London.

[1] *G. Schatz*, Angew. Chem. *79*, 1088 (1967); Angew. Chem. internat. Edit. *6*, 1035 (1967).
[2] *J. Henle:* Allgemeine Anatomie. Verlag F.C.W. Vogel, Leipzig 1841.
[3] *A. Kölliker*, Z. wiss. Zool. *8*, 311 (1857).
[4] *W. Fleming:* Zellsubstanz, Kern und Zelltheilung. Verlag F.C.W. Vogel, Leipzig 1882.
[5] *R. Altmann:* Die Elementarorganismen und ihre Beziehung zu den Zellen. Veit, Leipzig 1890, p. 145.
[6] *G. E. Pallade* in *O. H. Gaebler:* Enzymes, Units of Biological Structure and Function. Academic Press, New York 1956, p. 185.
[7] *F. Sjostrand*, Radiation Research, Suppl. 2, 375 (1960).
[8] *W. Stoeckenius* in *E. Racker:* Membranes of Mitochondria and Chloroplasts. Van Nostrand Reinhold, New York 1970, p. 53.
[9] *D. W. Fawzett:* Die Zelle. Ein Atlas der Ultrastruktur. Urban und Schwarzenberg, München 1969, p. 67.
[10] *H. Ferrandez-Moran, T. Oda, P. V. Blair*, and *D. E. Green*, J. Cell Biol. *22*, 63 (1964).
[11] *E. Racker* in *E. Racker:* Membranes of Mitochondria and Chloroplasts. Van Nostrand Reinhold, New York 1970, p. 127.
[12] *D. F. Parsons, G. R. Williams, D. Thompson, D. Wilson*, and *B. Change* in *E. Quagliariello, S. Papa, E. C. Slater*, and *J. M. Tager:* Mitochondrial Structures and Compartmentation. Adriatica Editrice, Bari 1967, p. 29.
[13] *D. F. Parsons* and *Y. Yano*, Biochim. Biophys. Acta *135*, 362 (1967).
[14] *W. Stoffel* and *H. G. Schiefer*, Hoppe-Seylers Z. Physiol. Chem. *349*, 1017 (1968).
[15] *G. F. Bahr* and *E. Zeitler*, J. Cell Biol. *15*, 489 (1962).
[16] *R. W. Brosemer, W. Vogell*, and *Th. Bücher*, Biochem. Z. *338*, 854 (1963).
[17] *D. J. Luck*, J. Cell Biol. *16*, 483 (1963).
[18] *M. M. K. Nass* and *S. Nass*, J. Cell Biol. *19*, 593 (1963).
[19] *G. Schatz* in *E. Racker:* Membranes of Mitochondria and Chloroplasts. Van Nostrand Reinhold, New York 1970, p. 251.
[20] *E. Wintersberger* in *J. M. Tager, S. Papa, E. Quagliariello*, and *E. C. Slater:* Regulation of Metabolic Processes in Mitochondria. Elsevier, Amsterdam 1966, p. 439.
[21] *P. Borst, E. F. J. Van Brüggen*, and *G. J. C. M. Rüttenberg* in *E. C. Slater, J. M. Tager, S. Papa*, and *E. Quagliariello:* Biochemical Aspects of the Biogenesis of Mitochondria. Adriatica Editrice, Bari 1968, p. 51.
[22] *W. Seebald, A. Schwab*, and *Th. Bücher* in *Th. Bücher* and *H. Sies:* 20th Mosbacher Colloquium. Springer-Verlag, Heidelberg 1969, p. 140.
[23] *E. Schnepf* in *P. Sitte:* Probleme der biologischen Reduplikation. Springer-Verlag, Heidelberg 1966, p. 372.
[24] *M. Klingenberg* and *E. Pfaff* in *J. M. Tager, S. Papa, E. Quagliariello*, and *E. C. Slater:* Regulation of Metabolic Processes in Mitochondria. Elsevier, Amsterdam 1966, p. 180.
[25] *E. Pfaff, M. Klingenberg, E. Ritt*, and *W. Vogell*, Eur. J. Biochem. *6*, 222 (1968).
[26] *C. A. Schnaitman* and *J. W. Greenawalt*, J. Cell Biol. *38*, 158 (1968).
[27] *C. Hoppel* and *C. Cooper*, Biochem. J. *107*, 367 (1968).
[28] *D. Brdiczka, D. Pette, G. Brunner*, and *F. Miller*, Eur. J. Biochem. *5*, 294 (1968).
[29] *M. Klingenberg*, Ergebnisse der Physiologie *55*, 131 (1964).
[30] *D. Pette* in *J. M. Tager, S. Papa, E. Quagliariello*, and *E. C. Slater:* Regulation of Metabolic Processes in Mitochondria. Elsevier, Amsterdam 1966, p. 28.
[31] *G. L. Sottocasa, L. Ernster, B. Kuylenstierna*, and *A. Bergstrand* in *E. Quagliariello, S. Papa, E. C. Slater*, and *J. M. Tager:* Mitochondrial Structure and Compartmentation. Adriatica Editrice, Bari 1967, p. 74.
[32] *H. W. Heldt* and *K. Schwalbach*, Eur. J. Biochem. *1*, 199 (1967).
[33] *H. Jacobs, H. W. Heldt*, and *M. Klingenberg*, Biochem. Biophys. Res. Commun. *16*, 516 (1964).
[34] *R. Charles, J. M. Tager*, and *E. C. Slater*, Biochim. Biophys. Acta *131*, 29 (1967).
[35] *L. Ernster* and *B. Kylenstierna* in *E. Racker:* Membranes of Mitochondria and Chloroplasts. Van Nostrand Reinhold, New York 1970, p. 172.
[36] *M. Aas*, Biochim. Biophys. Acta *231*, 32 (1971).
[37] *P. B. Garland* and *D. W. Yates*, Biochim. Biophys. Acta *231*, 385 (1971).
[38] *S. G. Van den Bergh*, Biochim. Biophys. Acta *231*, 400 (1971).
[39] *C. R. Rossi* and *N. Siliprandi*, Biochim. Biophys. Acta *231*, 411 (1971).
[40] *J. Böttger, O. Wieland, D. Brdiczka*, and *D. Pette*, Eur. J. Biochem. *8*, 113 (1969).
[41] *E. M. Wit-Peeters, H. R. Scholte, F. van den Akker*, and *J. de Nie*, Biochim. Biophys. Acta *231*, 23 (1971).
[42] *M. Klingenberg*, Essays in Biochemistry *6*, 119 (1970).
[43] *S. Papa, A. Francavilla, G. Paradies*, and *B. Meduri*, FEBS Lett. *12*, 285 (1971).
[44] *J. B. Fritz*, Amer. J. Physiol. *197*, 297 (1959).
[45] *B. A. Haddock, D. W. Yates*, and *P. B. Garland*, Biochem. J. *119*, 565 (1970).
[46] *J. T. Brosnan* and *J. B. Fritz*, Biochem. J. *125*, 94 p (1971).
[47] *D. W. West, J. F. A. Chase*, and *P. K. Tubbs*, Biochem. Biophys. Res. Commun. *42*, 912 (1971).
[48] *M. Klingenberg*, FEBS Lett. *6*, 145 (1970).
[49] *J. B. Chappel* in *Th. Bücher* and *H. Sies:* 20th Mosbacher Colloquium. Springer-Verlag, Heidelberg 1969, p. 335.
[50] *F. Palmieri, G. Prezioso, E. Quagliariello*, and *M. Klingenberg*, Eur. J. Biochem. *22*, 66 (1971).
[51] *F. Palmieri, J. Stipani, E. Quagliariello*, and *M. Klingenberg*, Eur. J. Biochem. *26*, 587 (1972).
[52] *S. Papa, N. E. Lofrumento, G. Paradies*, and *E. Quagliariello*, Eur. J. Biochem. *22*, 134 (1971).
[53] *J. D. McGivan* and *J. B. Chappel*, Biochem. J. *116*, 37 p (1969).
[54] *J. M. Lowenstein* in *T. W. Goodwin:* The Metabolic Roles of Citrate. Academic Press, New York 1968, p. 61.
[55] *S. Papa, N. E. Lofrumento, M. Loglisci*, and *E. Quagliariello*, Biochim. Biophys. Acta *189*, 311 (1969).

[56] *A. Fonyo*, Biochem. Biophys. Res. Commun. *32*, 624 (1968).
[57] *D. D. Tyler*, Biochem. J. *107*, 121 (1968).
[58] *B. Guerin, M. Guerin*, and *M. Klingenberg*, FEBS Lett. *10*, 265 (1970).
[59] *E. Pfaff* and *M. Klingenberg*, Eur. J. Biochem. *6*, 66 (1968).
[60] *M. Klingenberg* in: Symposium on Biochemistry and Biophysics of Mitochondrial Membranes. Academic Press, New York 1972, p. 465.
[61] *H. W. Heldt* in: 20th Mosbacher Colloquium. Springer-Verlag, Heidelberg 1969, p. 301.
[62] *P. J. F. Henderson* and *H. A. Lardy*, J. Biol. Chem. *245*, 1319 (1970).
[63] *M. Klingenberg, K. Grebe*, and *H. W. Heldt*, Biochem. Biophys. Res. Commun. *39*, 344 (1970).
[64] *E. Pfaff, H. W. Heldt*, and *M. Klingenberg*, Eur. J. Biochem. *10*, 484 (1970).
[65] *H. W. Heldt* and *M. Milovancev*, unpublished.
[66] *M. Klingenberg* and *E. Pfaff* in *R. W. Estabrook* and *M. E. Pullman:* Methods in Enzymology. Academic Press. New York 1967, Vol. 10, p. 680.
[67] *A. Kaltstein* and *M. Klingenberg* cited in *M. Klingenberg*, Essays in Biochemistry *6*, 150 (1970).
[68] *R. Elbers, H. W. Heldt, P. Schmucker*, and *H. Wiese*, Hoppe-Seylers Z. Physiol. Chem. *353*, 702 (1972).
[69] *H. W. Heldt* and *E. Pfaff*, Eur. J. Biochem. *10*, 494 (1969).
[70] *R. A. Alberti*, J. Biol. Chem. *243*, 1337 (1968).
[71] *P. E. Di Prampero* and *R. Margaria*, Pflügers Arch. Ges. Physiol. *304*, 11 (1968).

Self-Organization of Molecular Systems and Evolution of the Genetic Apparatus[**]

By Hans Kuhn[*]

The aim of the work described in this report is to find pathways leading to self-organization of molecular systems. The idea is not to trace the historical pathway of evolution but to describe a model whose experimental verification should help to clarify the important principles of evolution. The difficulty of accepting the origin of living organisms as a physico-chemical phenomenon and the deeply rooted notion that a system of such complexity as the genetic apparatus could never be the outcome of processes based solely on the known laws of physics have influenced philosophical thinking very strongly. This study is also intended as an attempt to overcome this psychological problem by systematic pursuit of a model pathway composed of many, readily comprehensible steps. A process thus becomes understandable which cannot be grasped as a whole, and is therefore alien to our conceptual habits.

1. Presentation of the Problem

A veil of uncertainty still surrounds the formation of the first biological systems from which the great variety of organisms developed during the further course of evolution[1-6]. Such systems must already have had the property of self-reproduction, and this can only have been possible if they were of considerable complexity. They must have had a mechanism employing very sophisticated strategies, comparable with those of the genetic apparatus of present-day organisms. How could this kind of system develop? Do the laws of physical chemistry suffice to explain this process or do we have to postulate principles that are still unknown? Let us suppose that the origin of life can be described as a physico-chemical process: does this process take place wherever appropriate conditions are to be found or is it a process of extremely low probability which nevertheless happened to take place on earth?

[*] Prof. Dr. H. Kuhn
Max-Planck-Institut für Biophysikalische Chemie
Karl-Friedrich-Bonhoeffer-Institut
34 Göttingen-Nikolausberg, Postfach 968 (Germany)

[**] Extended version of a lecture given at Marburg on January 29, 1971.

The basic hypothesis of the following is that the origin of life is a physico-chemical process which occurs by necessity under appropriate conditions. The following two problems then require solution: first of all, a basis has to be given for the hypothesis. If it is correct, the intuitive reluctance to accept it is a psychological difficulty, and consequently the second task is to overcome this difficulty.

Possibilities for the formation of self-organizing systems have been considered by the mathematicians *v. Neumann*[7], *Turing*[8], and more recently *Ulam*[9]. The search for general principles that are important for the evolution of self-organizing systems is the topic of studies by *Prigogine*[10] and *Katchalsky*[11] and particularly of *Eigen*'s comprehensive theory on the self-organization of matter and the evolution of macromolecules[12].

We proceed in a somewhat different manner: we try to find a model pathway offering a plausible route for the formation of a mechanism like the genetic apparatus. The model pathway consists of a number of small steps. Each step follows from the preceding one as an answer to the question of which type of behavior seems most likely. Possible ways are invented, the time requirement is estimated, and the fastest possibility is chosen as the next step (Fig. 1).

Thus, by applying legitimate variations one can search out reasonable model pathways and see where the procedure leads and whether the initial concept turns out to be a fruitful one.

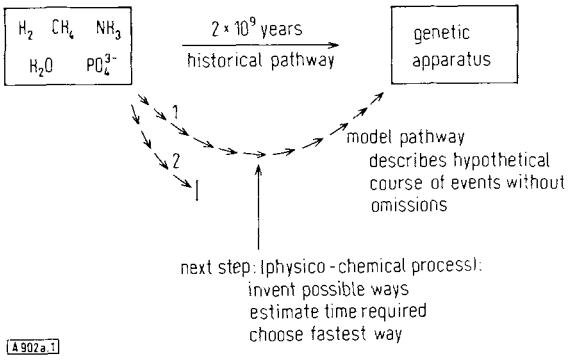


Fig. 1. Historical pathway of evolution and model pathways consisting of many individual physico-chemical steps. A model pathway must describe the hypothetical course of events as an uninterrupted chain of causative events. Otherwise it cannot be judged whether the pathway represents a meaningful approach. Model pathway 1 leads to a system with a genetic apparatus, pathway 2 leads to a dead end.

Each step is a customary physico-chemical process. We make no attempt to find generalizing concepts for self-organization and evolution. However, we do expect to be able to recognize the important aspects especially clearly in the special case of a model system. Using the procedure outlined we hope to arrive at self-organizing and self-reproducing systems so to speak blindly and automatically and to understand how the genetic apparatus, as we know it, could have developed during the available time span of about 2×10^9 years.

Our procedure is analogous to that employed in quantum chemistry where one tries to reach an understanding of the chemical bond by invention of appropriate test functions as approximations of wave functions. In quantum chemistry quite speculative test functions, like *Hückel*'s concept of the π-electron system, have proved to be extraordinarily fruitful. This encourages the discussion of speculative model pathways for a biological problem.

By systematically going through the many individual steps, we try to overcome the psychological difficulty of accepting the idea that an extremely well functioning mechanism like the genetic apparatus should follow solely from the known laws of physics: each individual step can be grasped easily, and the psychological difficulty arises from the fact that in the evolutionary process the chain of causative events can no longer be grasped as a whole because of the great number of steps and the great number of individuals involved. On considering the individual physico-chemical steps *Darwin*'s process of selection (survival of the fittest) seems self-evident. The frequently stated opinion that a system cannot organize itself because thermodynamics requires that a closed system should strive to attain the state of highest disorder is incorrect for a simple model far removed from equilibrium.

A model pathway must describe the hypothetical course of events completely. Many assumptions about individual steps which at first glance seem quite reasonable may lead to a dead end (Fig. 1), which can only be recognized and avoided by consistent pursuit of the causal chain of hypothetical steps.

It cannot be expected that a seemingly reasonable imaginative pathway actually represents the historical route, but even by tracing just one chain of causally linked steps leading to a system with a genetic apparatus it is demonstrated that the development of biological organisms can, in principle, be interpreted on a physico-chemical basis. We can hope that experimental checks of the steps involved in the model will provide some clues regarding the actual development.

A meaningful model pathway must lead to an understanding of the development of the genetic apparatus, an extraordinarily complex system exhibiting the following salient features[13]: The information for the structure and function of an organism is stored in the form of base sequences. The double helix replicates, thus the information is reproduced, and from one organism many others are

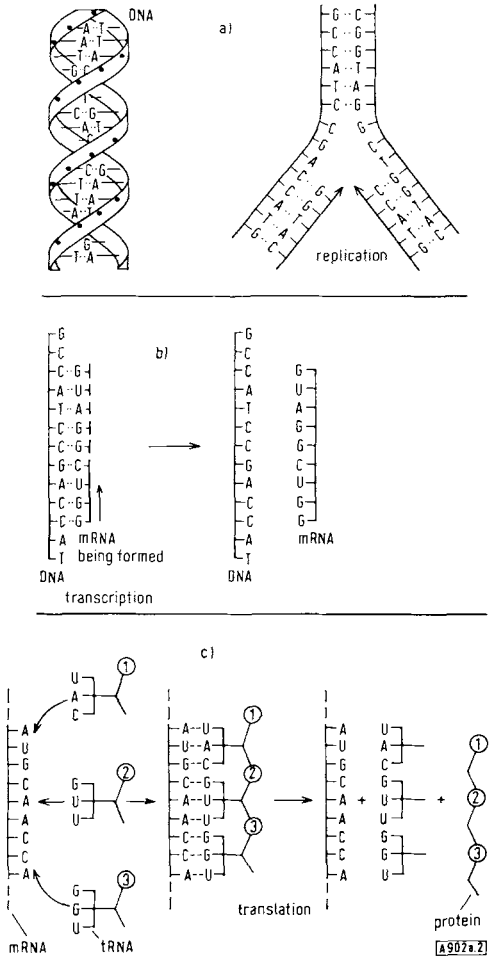


Fig. 2. Genetic apparatus.
a) DNA double strand (C = cytosine, G = guanine, T = thymine, A = adenine). Replication of a DNA strand by an enzyme system (replicase). T and A, and G and C are complementary bases. b) Formation of messenger-RNA (mRNA) on the template of a DNA strand by an enzyme system (transcriptase). In messenger-RNA the base thymine is replaced by uracil (U). c) Protein biosynthesis on the ribosome. Transfer-RNAs (tRNA) for amino acids 1, 2, 3, with anticodon triplet characteristic for the amino acid. Orientation of the triplets on the messenger-RNA, synthesis of the protein, release of tRNAs without amino acids and messenger-RNA.

formed (Fig. 2a). The information present in any one section of DNA is transcribed to messenger-RNA (Fig. 2b), on which the information is translated from a language written in four letters (the four bases A, U, G, C) into one containing 20 letters (the amino acids) (Fig 2c). The amino acid molecules are attached to their own characteristic transfer-RNA molecules which also carry the anticodon triplet, through which the information on the messenger-RNA is read off. On the ribosomes the amino acids thus combine to a protein, whose amino acid sequence is determined by the base sequence of the messenger-RNA. The proteins assume a specific tertiary structure, which is determined by their amino acid sequence and, as enzymes and structural elements, make up an organized functional network resulting in an organism.

2. Model Assumptions Pertaining to the Behavior of RNA

We shall assume that in the model environment an enzyme-free replication of RNA is possible (Fig. 3a) and that the replication error per base is $W = 1/100$, *i.e.* on the average one out of 100 bases is copied incorrectly. This means that in a newly synthesized strand about one out of 100 bases is not complementary to its partner on the template strand. An enzyme-free replication of RNA can be assumed on the grounds of experimental evidence[14], even though for the time being precise statements about the conditions for such a replication are not possible. A value of about $W = 1/100$ follows from the careful analysis by *Eigen*[12] and co-workers[15].

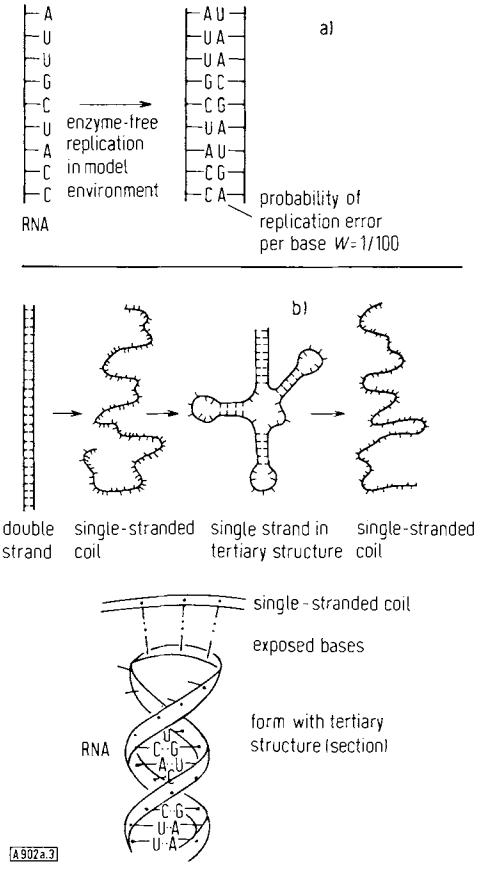


Fig. 3. Model assumptions concerning the behavior of RNA.
a) RNA is supposed to undergo enzyme-free replication under certain conditions: energy-rich mono- or oligonucleotides are supposed to associate with the open chain conformation in such a way that complementary bases form pairs and then proceed to condense. b) Transition of RNA from double strand to single stranded open chain conformation given appropriate changes of environment, from the latter to a conformation with tertiary structure given a suitable base sequence, and then back to the open chain conformation. c) During intervals, in which forms with tertiary structure appear, weak bonding should be possible between exposed bases of these species and the open chain single strands.

Furthermore we shall assume that strong fluctuations of quantities characterizing the environmental conditions take place with time. Such fluctuation may have been due to cycles which have always been present on the earth, for example day and night, the cycle of the seasons, and the rhythm of the tides. They should allow transitions of RNA from an open chain conformation to one with a tertiary structure. Suitable fluctuations may again transform the species exhibiting tertiary structure into an open chain conformation, which in turn may serve as a template for replication (Fig. 3b). Transitions of this type are known from experiments[16].

Finally we assume that under the model conditions loose association between open chain species and the exposed bases of species with tertiary structure may occur during the periods characterized by the appearance of molecules with tertiary structure. This is again in keeping with experimental results[17].

3. Starting Point: Spontaneous Polymerization of Energy-Rich Nucleotides during Phases of Formation; Hydrolysis of Polymers during Phases of Decay

In the early phase of evolution we cannot assume the presence of RNA molecules, but energy-rich nucleotides capable of polymerization may very well have occurred. This follows from the well-known experiments on the simulation of conditions that may once have prevailed on the earth[1-5].

Since we assume strong fluctuations of the environment, a solution of suitable substrates may alternately have been dissolved and evaporated to dryness, and warmed and cooled. This may lead to high concentrations of given substances in certain places or to a situation where energy-rich compounds formed by gas discharge or irradiation alternately appear and disappear. We may assume an alternation between phases during which polymers are formed from phosphonucleotides and those during which they gradually undergo hydrolytic decomposition (Fig. 4).

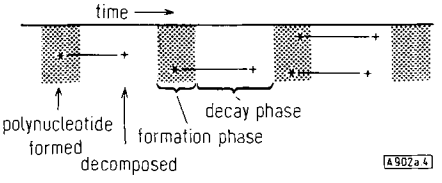


Fig. 4. Starting conditions: periodic fluctuations of the environment: alternation between formation phases (formation of polymers from energy-rich mono- or oligonucleotides) and phases of decay (hydrolysis of polymers).

Nucleic acids contain ribose. We have to assume that d- and l-ribose are present in equal concentrations and are incorporated into the polymer with the same probability.

4. Formation of Replicating Forms of RNA. Development of RNA Molecules of Uniform Chirality

One can imagine the chance formation of an RNA molecule with, say, 21 bases and containing exclusively d-ribose as sugar component (Fig. 5). The probability of the appear-

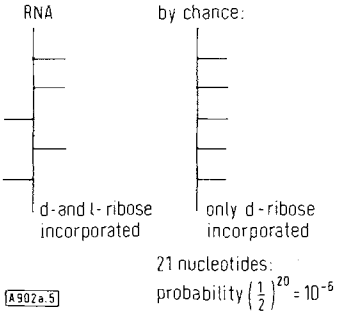


Fig. 5. Formation of RNA molecules having Uniform chirality. Random formation of a sufficiently large molecule containing just d-ribose. The molecule serves as template for the formation of a double helix. Those molecules containing both d- and l-ribose do not have this property because of lacking cooperativity. The double helix is stabilized by cooperative effects, and is thus able to multiply and has a longer life span.

ance of this type of molecule is $(1/2)^{20}$ if the same probabilities are assumed for the condensation of d- with d and d- with l-phosphonucleosides. Among $2^{20} \approx 10^6$ molecules having a degree of polymerization of 21, there is on the average one molecule that happens to contain only d- or only l-ribose. One can expect this type of molecule to have the following three properties lacking in the others (Fig. 6):

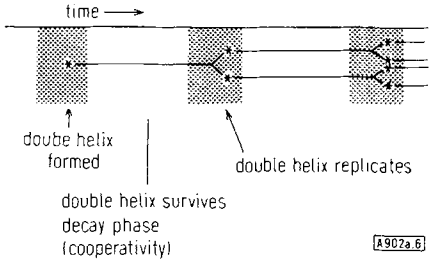


Fig. 6. Double helix molecules multiply and displace all the others. The originally divergent phase (formation of polymers with many different sequences of d- and l-ribose) has thus turned into a convergent phase during which d- or l-ribose is incorporated selectively.

1. During a phase of formation, the molecule may serve as template for the formation of a double helix because it may collect energy-rich mono- or oligonucleotides, which can then link up with one another. This is not possible with other polymeric molecules because of the lack of cooperativity. Incorporation of just one molecule having the wrong chirality destroys the tight packing present in the helix.

2. The cooperative effects holding all parts of the molecules tightly within the double helix make it especially resistant to hydrolysis and therefore able to survive the decay phase.

3. Upon entering a new formation phase one may expect replication of the double helix if the environment changes in a suitable way (entrance into a phase in which the double helix dissociates into single strands, followed by one in which the single strands serve as templates for the formation of new double helices). During following periods more and more double helices will be formed. The energy-rich phosphonucleosides will be used up and the formation of polymers having non-uniform chirality is suppressed.

The random formation of the first double helix initiates the first phase exhibiting a selection process: the initial, divergent phase (spontaneous formation of a large number of polymers having all possible sequences of d- and l-ribose) turns into a convergent phase characterized by selective formation of double helices and suppression of spontaneous polymerization as soon as one molecule with a sufficiently high degree of polymerization and containing only the d- or l-form of ribose is present.

The change from the divergent to the convergent phase is the result of pure chance. But even so, this event sooner or later takes place by necessity: Given a sufficient number of molecules and a sufficiently long time, the probability that *not* a single molecule will be formed containing exclusively d- or l-ribose is extremely small. Thus, the change is a necessity. This effect is typical for evolving systems: In any one case decisive events, although highly improbable, take place by constraint within a large population.

Only d-ribose is present in the nucleic acids we know today. According to our model it was merely by chance that a system capable of reproduction and happening to contain only d-ribose was able to assert itself; *i.e.* that species containing d-ribose happened to develop earlier and was therefore able to displace the species containing l-ribose.

It is conceivable that evolution of organisms with l-ribose could take place in one locality while organisms with d-ribose develop elsewhere. As soon as these two populations come into competition with each other, only that species will survive which happens to have attained the more advanced stage of evolution or which by chance is the first to find a way of inflicting sufficient damage on the other form. Competition may occur either very soon or after the system has already reached a high degree of differentiation, depending on which substrate necessary for development is lacking.

It seems reasonable to assume that the degree of polymerization of double helices capable of selection is about 20. Cooperative regions of this size are frequently encountered in soap- and dye micelles; according to *Debye*[18] this has energetic reasons.

5. Development of a Side-by-Side Existence of RNA Molecules with Differing Tertiary Structures

It is to be expected that identical double helices will from time to time undergo condensation according to Fig. 7a (with omission of the helical conformation of the strands)

thus affording species exhibiting intramolecular pairing of complementary bases. Further condensation yields species of clover-leaf structure—as found in tRNAs (example: tRNA for phenylalanine, Fig. 7b)[19].

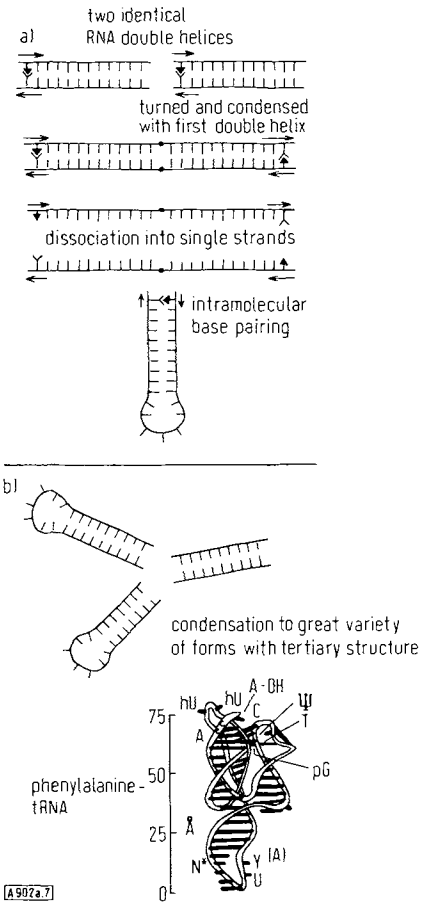


Fig. 7. Formation of RNA molecules by random condensation of double helices (drawn with omission of helical screwing of the strands).
a) Formation of hairpin molecules (from top to bottom): identical double strands: double strand on the right turned by 180° and condensed with the other one; strands separated from each other; bases form intramolecular pairs. b) Condensation of hairpin molecules, and possibly double helices (on the right), to give transfer-RNA-like molecules. Example of a transfer-RNA with a tertiary structure as proposed by *Cramer*.

It may be expected that this permits development of species with quite different tertiary structures. Thus, a divergent phase of evolution is reached again.

6. Selection of Individual Molecules on the Basis of Resistance to Hydrolysis Impossible Because of Too Many Reproduction Errors

RNA species with different tertiary structures will differ in their susceptibility to hydrolysis. More compact species will be more resistant than others and more likely to survive the decay phase. We therefore have to ask whether we can assume a selection of species which are more resistant to hydrolysis than others because of their tertiary structure.

In order to answer this question we shall make the simplifying assumption that only *one* species is initially present and that it replicates without error. During the formation phase replication takes place and, then the tertiary structure is formed; during the decay phase some of the molecules are hydrolyzed while those remaining replicate during the next formation phase (Fig. 8). The number of molecules will increase until saturation is reached and the same number Z of molecules is present at the end of each decay phase (Fig. 8).

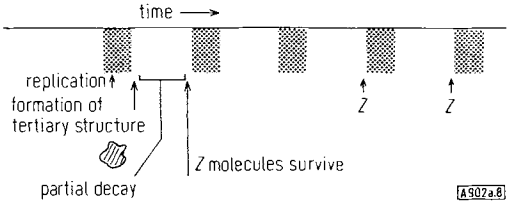


Fig. 8. Behavior of molecules as shown in Fig. 7b in the model environment. Formation phases: replication, transition to a tertiary structure. Decay phases: partial hydrolysis of the molecules. After arriving at a state of saturation at the end of each decay phase there are about Z molecules present.

Let us consider that a molecule with a different kind of tertiary structure is now formed as a result of a base copying error occurring randomly during replication (Fig. 9). This mutant shall be somewhat more resistant to hydrolysis than the preceding species (= normal form = most common species of the prevailing population). The multiplication factor r of the mutant is then somewhat larger than 1.

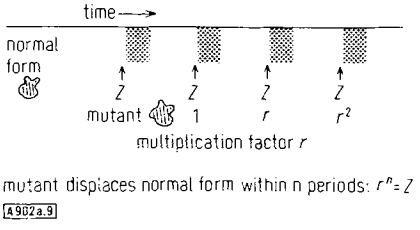


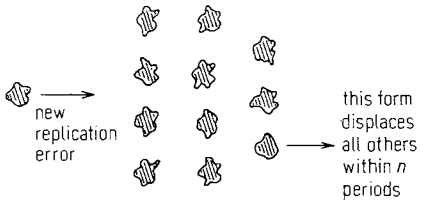
Fig. 9. Appearance of a mutant having the multiplication factor r. Number n of generations during which the mutant displaces the normal form.

(The multiplication factor r is defined as follows: if at the end of any phase of decay *one* individual of the mutant is present, then r is the average number of molecules of the mutant at the end of the next decay phase. At saturation the multiplication factor of the normal form is 1.) After an additional period an average of r^2 molecules will be present, *etc.* The mutant will have displaced the normal form after about n periods and will thus have become the new normal form. At that time about Z individuals of the mutant will be present, *i.e.* $r^n = Z$ (Fig. 9).

Example: if at the beginning we find $Z = 10^6$ molecules of the normal form (*i.e.*, if the advantageous mutant appears once among 10^6 molecules) and $r = 2$ (*i.e.*, if the mutant has twice the chance of surviving the next decay phase compared to the normal form), then $n = 20$. If $r = 1.01$, it follows that $n = 1400$.

After the selection of the mutant, another base copying error will be considered to occur in each individual (Fig. 10). In this way mutants of quite different shapes will be

formed. Most of them will be more susceptible to hydrolysis than the previously selected species. This is because it is highly improbable that a structure which has already proved resistant to hydrolysis, should further improve this property by another chance error. The globular mutant in Fig. 10 is assumed to be a favorable species and after about n periods will have displaced the others. However, this type of selection is only possible if the next error in reproduction does not take place too early. Otherwise, the probability that the favorable mutant will disappear instead of improving is too high. For a selection to occur it is therefore essential that the next error in reproduction should not occur earlier than after n periods, *i.e.* after the favorable mutant has asserted itself and is present in large numbers.



condition for selection: new replication error usually no earlier than after n periods

A902a.10

Fig. 10. Appearance of new mutants after the mutant of Fig. 9 has become prevalent: most of them have no advantage since it is highly improbable that a species which has already proved its value should be further improved by a random replication error. The most favorable mutant (most resistant to hydrolysis) displaces all other species within n periods.

Let P be the probability of a reproduction error occurring in an individual. In order for selection to take place, the number of errors after n successive reproductions may not be larger than 1, *i.e.* $P \times n \leq 1$ (Fig. 11). The reasoning behind this relation is given in Appendix 1. An illustration of the selection process by computer simulation may be found in a paper by *Försterling*, *Kuhn*, and *Tews*[20] appearing in this issue.

If we designate the number of bases in an RNA molecule N and the probability of a replication error per base W then $P = N \times W$ (if P is small compared to 1): the error may occur in the 1st or the 2nd *etc.* or in the n^{th} base. The condition for selection thus follows (Fig. 11):

$$N \times W \times n \leq 1 \quad \text{or} \quad W \leq 1/(N \times n)$$

P = probability of reproduction error of individual

n = number of periods

condition for selection: $P \cdot n \leqslant 1$

N = number of bases

W = replication error per base

$P = N \cdot W$

---

condition for selection

$N \cdot W \cdot n \leqslant 1$

$W \leqslant 1/(N \cdot n)$

Fig. 11. Selection conditions.

In the case considered we can expect about $N = 50$ and $n = 20$. Then W must be smaller than about 1/1000 in order for selection to take place. But as we saw before, $W \approx 1/100$. This means, that RNA molecules with a particularly favorable tertiary structure cannot be selected. Each favorable species is altered adversely by additional reproduction errors in a much shorter time than is necessary for selection. Therefore, a divergent evolution of RNA molecules with different tertiary structures is to be expected.

7. Formation of Aggregates from Molecules Fitting into Each Other

It is to be expected that, among a large number of different RNA molecules moving around in solution, once in a while one molecule will have a tertiary structure matching that of another very well (Fig. 12a). The resulting aggregates will come apart during phases of multiplication and the individual molecules will replicate. In the following phase each molecule reassumes its tertiary structure and the matching molecules will again form aggregates. The aggregates thus multiply (Fig. 12a).

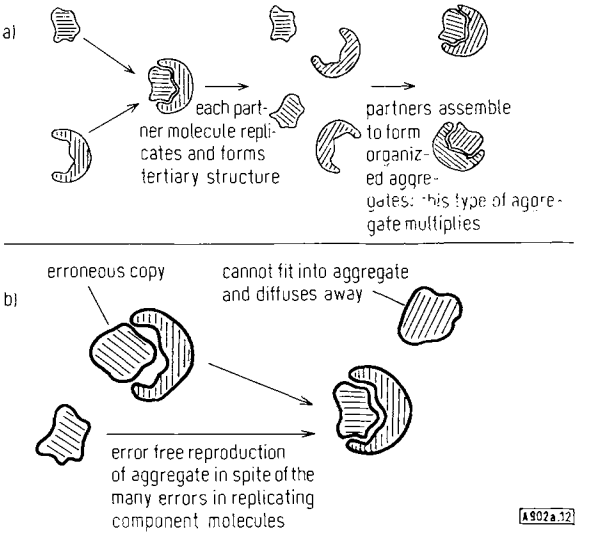


Fig. 12. a) Species of molecules which happen to match form aggregates. During formation phases the individual molecules separate and replicate. Afterwards they reassemble to form aggregates: this particular type of aggregate multiplies. b) Error copy does not fit and is replaced by one that has been reproduced correctly, thus ensuring error free reproduction of aggregate. Condition for selection (Fig. 11) can be fulfilled for aggregates.

During replication a reproduction error may occur. A faultily replicated molecule will assume an altered tertiary structure and no longer fit into the aggregate (Fig. 12b). It will diffuse off and be replaced by a molecule that has been replicated correctly. The result of this mechanism is that the aggregate is reproduced at a low error rate even

though the individual molecules are frequently reproduced erroneously. Since only correctly reproduced molecules may form aggregates, the condition for selection may be fulfilled for the aggregates (Fig. 11) even though it is not fulfilled for their precursors. It is clearly a prerequisite that the aggregates be formed in time and be sufficiently able to survive the decay phase. In other words: the condition for selection (Fig. 11, above) is only fulfilled if n is not too large, *i.e.* if according to Fig. 9 the multiplication factor r exceeds a critical value.

8. Necessity of Compartmentation to Ensure the Condition for Selection Is Fulfilled for the Aggregates

Within the aggregates the molecules protect each other from hydrolysis. We may therefore expect the aggregates to survive the decay phase more frequently than individual molecules. To provide for sufficiently fast aggregate formation, the molecules have to find each other within a time that is small compared to the duration of the decay phase.

This is only possible if we postulate the molecules to be enclosed within a compartment (Fig. 13). The compartment facilitates the agggregation process and may also provide another advantage for the selection of aggregates: by virtue of their size they cannot leave the compartment while the individual molecules unsuitable for incorporation into the aggregates can escape through the pores of the compartmental envelope during the decay phase.

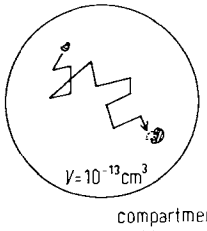


Fig. 13. Compartmentation: aggregates must be formed fast enough to attain the condition for selection: compartmentation prevents matching molecules from diffusing apart.

The maximum size of a compartment that still allows the molecules to find each other reasonably fast is about 10^{-13} cm^3 (for calculation see Appendix 2) provided the duration of the decay phases is of the order of one day. This value is roughly comparable with the volume of a bacterium. Cavities of this size are frequently met, *e.g.* between clay particles.

By the formation of aggregates of matching RNA molecules within these compartments, the transition to a strongly selective, convergent phase of evolution is once more initiated because the condition for selection is again satisfied.

Like the first change from a divergent to a convergent phase (onset of replication) this second change is again triggered off by pure chance (fortuitously matching tertiary structures are brought together by their random thermal motion). Here again an event that seems rather unlikely *per se* takes place sooner or later by constraint, thereby beginning a convergent phase. Looking at this simple case, we may recognize what time and again governs self-organization: the game of chance (the random motion of individual molecules and the chance formation of matching molecular shapes) leads to the formation of increasingly organized structural and functional units.

Because of the high frequency of errors during enzyme-free replication of RNA. *Eigen*[12] considered evolution to occur by cooperation between a system of nucleic acids and a second system consisting of a large number of different protein molecules engaged in mutual syntheses without a nucleic acid template in a reaction cycle which by itself is readily subject to perturbation.

In the model developed here, it is assumed that a system of nucleic acids capable of selection was first present. By forming aggregates the error rate during reproduction is reduced to such a degree that selection of pure RNA systems becomes possible. The assumption of strong periodic fluctuations of the environment is important for this model because they lead to the changes in molecular shapes that we just discussed. Such alterations in shape represent the decisive factor for selection. The other important concept that matching molecules may form self-organizing aggregates has an experimental basis: it has been shown with viruses and ribosomes that highly organized systems can be formed in solution simply upon mixing their constituents[21]. Ribosomes consist of more than 50 macromolecules.

9. Types of RNA Aggregates Capable of Selection: Aggregating Molecules Consist of About 50 Nucleotides

Let us now ask which types of aggregates will undergo selection. Aggregate a in Fig. 14 has no chance of asserting itself. Upon entering the multiplication phase all the molecules must disentangle and after replication and formation of tertiary structure they have to reassemble. This process is very time consuming. Only small isometric aggregates (b) and larger aggregates (c), in which the molecules are joined together in a chain, have any chance of being selected.

The degree of polymerization of those molecules which will displace the others can be estimated quite easily: each molecule capable of selection may consist of about 50 bases. Such a molecule is small enough to frequently replicate without error, since according to Fig. 3a an error in replication occurs in only one out of a hundred bases. On the other hand, molecules that associate to give stable aggregates must be sufficiently large to have a specific tertiary structure. This is the case for molecules of about 50 nucleotides, as we know from the transfer-RNAs (Fig. 7b). According to the concept of this model molecules having just about the same size as a transfer-RNA molecule will select.

Among the aggregates consisting of concatenated molecules, those made up of a nucleation molecule plus many identical line-up molecules must have selectional advan-

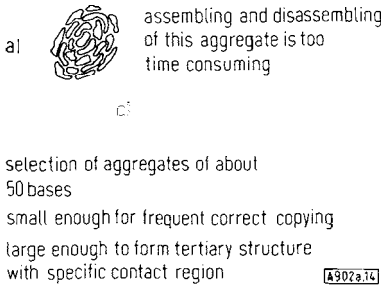


Fig. 14. Considerations on the nature of selecting RNA aggregate types.

tages, *i.e.* those which, like a crystal needle, are formed starting from a nucleation center (Fig. 15). Identical molecules form aggregates much faster than different molecules.

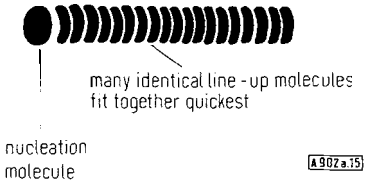


Fig. 15. Aggregates of two types of RNA with definite tertiary structure (nucleation molecule and many identical line-up molecules). This type of aggregate has selection advantages.

The latter need much more time to find each other during random diffusion. However, even with identical line-up molecules aggregate formation is still a relatively slow process (see Appendix 2).

10. Aggregates Consisting of Nucleation Molecule with Collector Strand and Line-Up Molecules

Let us consider a nucleation molecule which has a definite tertiary structure as described so far but in addition possesses a fairly long chain end of random sequence which keeps its open chain conformation (Fig. 16a). Line-up molecules may loosely associate with this chain, called the collector strand, and diffuse back and forth along its length; starting from the nucleation center they may proceed to form an organized associate (Fig. 16b). Thus the collector strand accelerates the collection of line-up molecules and the formation of an organized aggregate. Three-dimensional diffusion is now replaced by one-dimensional diffusion. Perturbations of the system by erroneous entanglement of the complicated forms of fitting elements are thus suppressed; the traffic problem of supplying line-up molecules is solved by the collector strand. The length of the collector strand determines the size of the aggregate. Since base replication errors do not abolish the action of this strand, its length is not dependent on the condition of containing about 50 bases which applies for molecules or parts of molecules having a tertiary structure (Fig. 14).

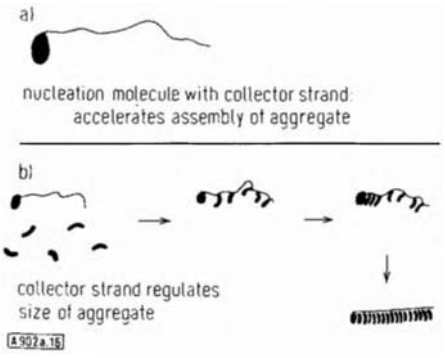


Fig. 16. Nucleation molecule (with tertiary structure) equipped with an open chain strand without tertiary structure (collector strand) represents a selection advantage for the aggregate: the collector strand facilitates construction of an organized aggregate. The collector strand reduces interference by incorrect entanglement of line-up molecules, and thus helps to solve traffic problems arising during formation of aggregates.

We now may expect that, apart from small, isometric aggregates, chain-like aggregates also undergo selection.

The tertiary structure of aggregate-forming molecules is fixed only in their matching regions. In other regions which are not important for the association, however, base reading errors do not influence aggregate replication. The exposed surfaces of the aggregates will thus constantly change during this evolutionary phase (Fig. 17a). Different

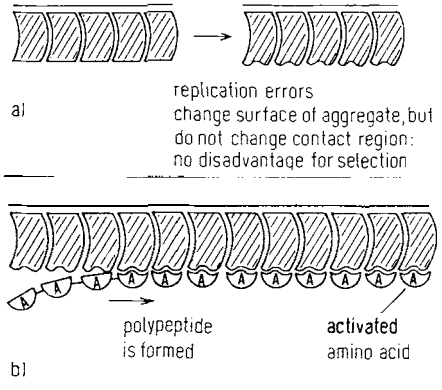


Fig. 17. Gradual alteration of the aggregate according to Fig. 16. Catalyzing properties facilitate, *e.g.*, polymerization of activated amino acids on the surface of the aggregate.

forms will coexist. Since random processes will form structures into which smaller molecules may be fitted, we can expect these structures to be capable of catalyzing reactions.

The catalytically active surfaces will partly disappear again when base reading errors occur and thus have no effect in further evolution. However, as soon as the fitting of foreign molecules becomes one of the crucial factors for the association of the aggregate, the catalytic system stabilizes itself for forthcoming generations. Here again we enter a divergent phase of evolution, in which many systems catalyzing different processes have about equal chances of survival.

12. Formation of Polypeptides on the Surface of an Aggregate Consisting of a Nucleation Molecule and Line-Up Molecules

One can imagine one of the numerous catalytic reactions occurring on surfaces of organized aggregates to be the formation of a polypeptide (Fig. 17b). We may take it for granted that under prebiotic conditions activated amino acids were present in sufficient concentrations. This follows from the experiments of *Miller* and others who obtained many different amino acids upon simulation of such conditions[1-5]. It is quite likely that polypeptides may be made this way: According to the work of *Katchalsky et al.*[22] certain kinds of montmorillonite also serve as catalysts for the formation of polypeptides. Activated amino acids react with one another on the surface of these minerals. Molecules of glycine cetyl ester, brought into contact with each other by forming a monolayer of the substance, react to form the polypeptide[22a], and we may expect a similar reaction in aggregates of corresponding line-up molecules.

Polypeptide-synthesizing systems would be of no importance if their presence did not create a very special situation: it is known that polypeptides obtained by heating dry amino acids form small globules in water. These globules represent polypeptide envelopes and have a diameter of several μm. These microspheres, which have been described by *Fox*[23], can act as semipermeable membranes.

13. Turning Point: Systems Produce Polypeptide Envelopes and Thus Become Independent of a Naturally Occurring Compartment

We now can assume that the polypeptide-synthesizing associates produce their own envelopes. This leads to a turning point: the systems are now independent of naturally occurring compartments; they are no longer confined to the spaces between clay particles and can reproduce whenever the necessary periodical fluctuations occur.

This development again leads into a convergent phase: any system able to complete synthesis of its envelope faster than another has selection advantages. A selection pressure now exists, favoring systems with a more sophisticated protein-synthesizing apparatus.

At this point the isometric aggregates (Fig. 14b) may come into the picture and contribute to peptide synthesis. Nucleation molecule and collector strand have thus become the primitive messenger-RNAs, the line-up molecules have become the primitive transfer-RNAs, and the isometric aggregates have turned into the primitive ribosomes.

The crucial event at the turning point is again highly improbable as an individual process, but in a large enough population it occurs cogently. The mutant is selected because it can now enter new areas. Without the formation of an envelope it would not have been possible to attain a higher degree of evolution. Here again the general direction of evolution seems to be logically predictable.

14. Accelerated Production of Envelope-Polypeptide by More Precise Fitting of Groups at the Site of Peptide Formation. Evolution of the Primitive Ribosome

Any change, even the smallest, leading to an improvement of the polypeptide-synthesizing device offers selectional advantages.

A multistep evolution of the primitive ribosome should now start. The isometric aggregate should gradually change in such a way as to ensure increasingly precise fitting of groups at the site of peptide linkage and to render the supply of amino-acid-carrying tRNA molecules progressively less sensitive to perturbation. To facilitate these improvements, the tRNA molecules must be held in position by a pincer-like device at the time of peptide linkage. This may be accomplished most easily by a primitive ribosome made up of two parts closing in on the reacting molecules. Polypeptide synthesis may be assumed to take place in the following way: to start with the two parts of the primitive ribosome form a complex of precisely fitting elements with the nucleation center and a primitive tRNA molecule. A second molecule of primitive tRNA then fits in at a precisely determined position so that a peptide bond can be formed. The second tRNA molecule can subsequently take the place of the first, the third take the place of the second, and polymerization can thus be sustained.

15. Pairing of Three Bases on the Primitive mRNA with a Base Triplet on the Primitive tRNA

Polypeptide synthesis will proceed with less interference and thus faster the better the amino acids fit together at the site of peptide bond formation. This will largely depend on how well the line-up molecules on the collector strand can be channeled into the primitive ribosome. The development

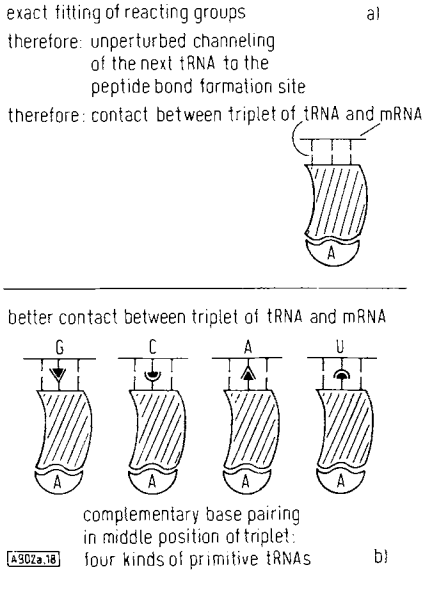


Fig. 18. Improvement of the device for polypeptide synthesis for the purpose of faster production of the envelopes.
a) Linkage between triplets of the tRNA and mRNA. b) Complementary base pairing between the middle position of the triplet and the respective place on the mRNA.

of a mechanism which fits the line-up molecules on the collector strand into the primitive ribosome, so that the next tRNA is transported smoothly to the site of peptide formation, seems to follow inevitably; and one can imagine that *inter alia* a mechanism develops where the bases on the primitive mRNA (collector strand) are paired three at a time with a base triplet on the primitive tRNA (line-up molecule) (Fig. 18a).

Let us assume that initially only the middle bases of the triplets have to fulfil the condition of complementarity (Fig. 18b). If a molecule of primitive tRNA with the wrong base in the middle position comes along, it is unable to form a stable complex with the collector strand inside the primitive ribosome and thus moves on. As soon as a molecule of the right kind comes along it is incorporated. If the RNA molecules are considered to be made up of four bases we have to differentiate between four kinds of primitive tRNAs. They have different bases in the middle position of the triplet but still lack amino acid specificity (Fig. 18b).

Precise and fast polypeptide synthesis provides the systems with such a tremendous selection advantage that the small disadvantage of complementary base pairing is unimportant. The time lost by the line-up molecule having to diffuse to its vacant site can be calculated and is found to be of little significance (Appendix 2).

16. Systems Produce Polypeptides with Specific Sequences. Sequence Cannot be Retained Owing to Excessive Replication Errors

The tertiary structures of the four kinds of primitive tRNAs we have just considered are gradually altered by replication errors. A change resulting in even a slight advantage is carried over to all molecules of the same strain after a few generations. The reasons for this are the same as those for the selection of aggregates with identical line-up molecules in earlier phases. The different tertiary structures lead to a certain specificity in the binding of amino acids, which may have kinetic or thermodynamic reasons. The system then produces a polypeptide with a sequence that is no longer random; however, the code cannot yet be fixed: the base sequence of the primitive mRNA is altered by replication errors before selection has taken place.

As shown in Appendix 3 an error probability during replication of about $W = 1/1000$ would be necessary for fixation of the code while the actual probability is assumed to be $W = 1/100$. Thus, even though a code exists for up to 4 amino acids it cannot be conserved.

We have now again reached a divergent phase of evolution: on the collector strand any number of replication errors may occur without disadvantage and therefore systems evolve that are able to produce polypeptides with different amino acid sequences. A species producing a polypeptide happening to be particularly useful cannot be selected: because of excessive replication errors all the progeny lose the ability to produce this polypeptide.

17. System Produces Polypeptide Reducing Probability of Replication Errors: Code for Four Amino Acids is Fixed

We can now assume that, among a large number of polypeptides in a population, one will evolve which, on account of its amino acid sequence, happens to exert an enzymatic effect on RNA replication and thus reduce the probability of error during replication from $W = 1/100$ to $W = 1/1000$. At the same time the system has to have a direct selection advantage and therefore a higher multiplication factor r. The first property conserves the information stored in the specific amino acid sequence, while the second property enables the individual to displace other individuals. Both properties may be coupled: the enzyme reducing the replication error frequency is simultaneously able to increase the replication rate itself. The code for four amino acids (or four groups of amino acids) thus gradually becomes fixed.

The divergent phase again turns into a convergent one: systems producing polypeptides with a predetermined amino acid sequence can now be selected. Again a selective pressure is present: systems happening to produce polypeptides with favorable sequences assert themselves.

The exact sequence of the following steps is unimportant. It is reasonable to assume the gradual formation of amino acyl synthetases for the four primitive tRNAs, which would increase the specificity for the binding of amino acids. However, the sequence of formation of the individual enzymes is of little importance because many different paths lead to the same result. As soon as the condition for selection is reached, *i.e.* once W falls below a critical value, further evolution of the genetic code occurs by constraint.

We have to bear in mind that no base replication error may occur in the middle of the anticodon triplet of the primitive tRNAs until selection has taken place. A mistake of this type would annul the coding. Once the species having an enzyme guaranteeing a low replication error rate has asserted itself, a replication error in the anticodon is no longer of any consequence: each erroneous individual produces a wrong polypeptide and is therefore eliminated. The code is thus fixed.

This consideration demonstrates a very important principle of evolution: the crucial change was brought about by a selection process which continuously refined an existing mechanism until a system resulted which began to serve an entirely new purpose. [The device for the synthesis of unspecific polypeptides was improved (complementary base pairing) so that the envelopes could be synthesized faster; this resulted in systems with predetermined amino acid sequence and thus in new varieties of chemical behavior.]

The change here again is triggered off by an event of low intrinsic probability (formation of an RNA-replicating enzyme) but which seems to occur by constraint in a favorable environment. It does not seem easy to think of a fundamentally different event likewise able to steer the systems from a divergent into a convergent phase and hence to a higher level of evolution.

Naturally the great demands made on the mutual fitting of groups at the site of peptide linkage can only be met by one chiral form of amino acids and not by the other at any one time. On the basis of this model, the fact that only l-amino acids are found in proteins now becomes intelligible.

After reaching the new level of evolution a vigorous development must set in: replication errors and selection effect improvements in the polypeptides and in their mutual adjustment. Their properties supplement each other increasingly well and the functioning of the system as a whole becomes more and more dependent on the presence of all polypeptides, which now form a functional network. The system of a number of protein synthesizing entities within a common envelope now becomes a primitive organism.

18. Code for Additional Amino Acids

Those systems which synthesize the best enzymes will survive, and good enzymes have a high molecular weight. Sooner or later a selective pressure towards larger proteins with a determined amino acid sequence will therefore occur. Those systems will survive which have the lowest probability of producing "nonsense" proteins, *i.e.* proteins made by skipping one base on the mRNA. This means that systems able to provide the best contact between anticodon and primitive mRNA will be selected. Thus those systems will gradually dominate where not only the middle but also the first base of the triplet bow to the condition of complementarity. The need for a polypeptide-synthesizing apparatus working with increasing precision must again lead to a turning point: the development of a code for additional amino acids. Again a selection process which effectively improves mechanisms already present necessarily leads to a sudden change of direction.

19. DNA Begins to Play a Role in the Genetic Apparatus

A difficulty preventing further evolution is soon bound to arise: aside from the RNA strands constituting the protein-synthesizing device (tRNAs, mRNAs, and ribosomal RNAs), the respective complementary strands are also made during the multiplication phase. They are of no use in protein synthesis and represent waste products giving rise to increasingly serious interference the more complex the systems become.

The formation of these complementary strands can be avoided by participation of DNA in the genetic process: One can imagine the development of two enzymes E_1 and E_2 (see Appendix 4), where E_1 makes the complementary DNA on the RNA template, and E_2 produces RNA on the template of the complementary DNA (Figure 19). One can further imagine that an RNA linking protein is subsequently formed, which permits the assembly of the entire information of the individual in a single strand of DNA. Sooner or later a protein enabling replication of DNA is bound to evolve by chance. Since this kind of system multiplies much faster, there will be a strong selective pressure towards the development of an increasingly

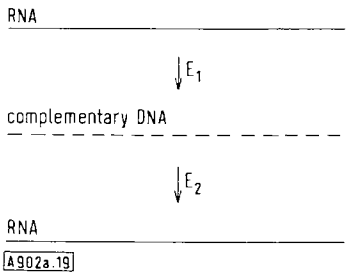


Fig. 19. DNA is beginning to play a role in the genetic apparatus.

precise DNA replicating device. DNA now becomes the carrier of genetic information, E_1 degenerates, and E_2 evolves to become transcriptase.

All the important elements of the genetic apparatus, as known from molecular biology, are now present. Further evolution becomes a necessary consequence: improvement of the ribosome to reduce its sensitivity to interference, the introduction of start- and stop signals; further evolution of the genetic code; and evolution of a replication and transcription device.

20. Time Required for Instruction of an Additional Protein in a System with a Fully Developed Genetic Apparatus

Let us now take a look at a species with a fully developed genetic apparatus. It produces many proteins with well determined functions, which as a group form a highly organized structural and functional network. The system furthermore will be assumed to produce a protein of random sequence which is not yet part of the functional network (Fig. 20a). Each replication error during reproduction, occurring in the instructed part, shall be lethal, *i.e.* the instructed proteins must fit together functionally like the parts of a watch, and practically any mistake stops the whole process.

It may then be assumed that, in a larger population of such systems, that part of the DNA which carries the information for the fully instructed proteins has the same sequence in all individuals. The section for the last protein, on the other hand, has a random distribution of sequences. The species in which this protein happens to have a function conferring the greatest advantage will assert itself. As shown by the estimate in Appendix 5, this takes about $n = 10^3$ generations. We can assume that the systems are optimized with regard to the probability of reproduction errors, *e.g.* according to Fig. 11 the error probability of replication has to be $W = 1/(n \times N)$, N (number of bases for instruction of a protein) being about 10^3. Thus $W \approx 10^{-6}$ (Fig. 20a). The number of generations needed for the instruction of a new protein can now easily be estimated to be about 10^8 (Appendix 5): This corresponds to about

10^5 years if we use an average of one day per generation[*]. For the instruction of the 10^3 proteins of a bacterium, the time requirement now turns out to be about 10^8 years. The entire time requirement for all the preceding steps of evolution of the genetic apparatus is small compared to this value of 10^8 years. This time estimate for the evolution of bacteria is within the limits set by geohistory (about 2×10^9 years). The result shows that the evolution of bacteria may be interpreted in terms of a physico-chemical phenomenon. This type of estimate is not meant to give precise figures on the time requirement for the evolution

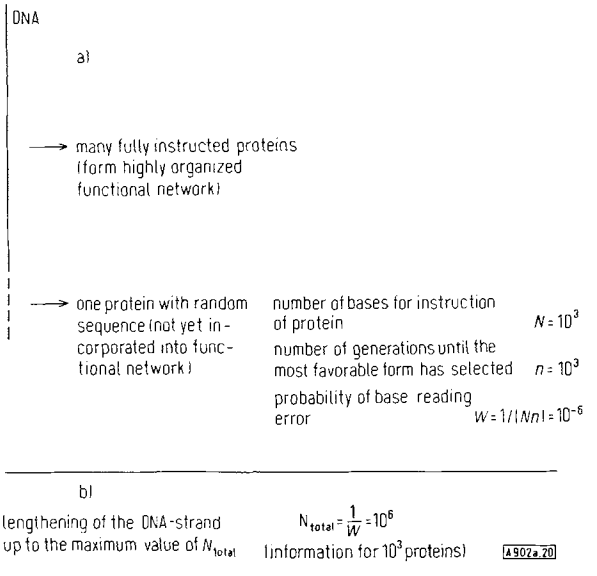


Fig. 20. a) System with fully developed genetic apparatus. Time requirement for the instruction of an additional protein not yet incorporated into the functional network. b) Upper limit of genetic information capacity of model systems. If this limit were exceeded, too many replication errors would occur per generation.

of bacteria, but rather to disprove the frequently voiced claim that the time historically available for development of such systems is much too short.

For the upper limit of the number of bases in the DNA strand, N_{total}, we find (using the value $W \approx 10^{-6}$): $N_{total} = 1/W \approx 10^6$. With higher values for N_{total} an error-free reproduction would rarely take place; a species of that type would soon disappear on account of lethal errors. $N_{total} \approx 10^6$ just about corresponds to the informational content of a bacterium[24] (information for about 10^3 proteins). At this point of the model we again reach a limit (Fig. 20b).

Replication errors occurring in the DNA will sometimes be not lethal but harmless or even useful. A divergent phase thus starts in which many species have comparable chances of survival. With systems having the information content of a bacterium, evolution seems to have come to an end.

However, the model indicates another turning point which may lead to the evolution of higher organisms containing a greater amount of genetic information. (For details see Appendix 6—8.)

21. Final Considerations

21.1. Basic Ideas and Discussion of Results

We started from the hypothesis that the laws of physical chemistry are sufficient to understand the evolution of selforganizing systems. The basic idea of this procedure was to acquire an insight into the principles of selforganization by discussion of a special model. A model pathway was considered as a causative chain of events. Each step results from the previous one by reflecting on how the system might behave under certain conditions. A crucial assumption in the model was strong periodic fluctuation of the environment of the evolving system. This procedure led to the essential mechanisms of the genetic apparatus and no steps of low probability had to be introduced. In an appropriate environment the evolution of selforganizing systems appears to be a normal physico-chemical process.

It may now be asked why this procedure, which is based on free inventions, leads to the genetic apparatus as we know it and not to entirely different systems. This may partly be due to the fact that inventions are based on what one already knows. On the other hand, each important evolutionary step is the solution of traffic- and organizational problems. With many of these steps, very different pathways will presumably lead to similar solutions, which simply represent the best solutions of particular problems.

The model has shown that changes between divergent and convergent phases of evolution repeatedly take place: during divergent phases many forms have similar survival probabilities and thus the population has a great diversity. A gradual improvement of mechanisms occurs. At a turning point, which may be logically predicted, a certain mechanism begins to serve an entirely new purpose. The process leading to this kind of turning point is highly improbable by itself; but even an improbable process sooner or later must take place by constraint in a population of sufficient size. The turning point initiates a convergent phase. It is strongly selective and the selection process has a definite direction: those random mutants survive which serve the new purpose best (Table 1).

For the turning points we endeavored to perform a careful analysis of how the condition for selection can be fulfilled, but we did not look for detailed models of evolution during the convergent phases. During these phases the system must develop in the direction prescribed by the selective pressure, and for the general points of view under discussion it is unimportant to know *exactly* in which way an impending problem of molecular traffic organization is solved.

Since the transitions from divergent to convergent phases may be grasped fairly well by quantitative approximations, it is possible to discern methods for an experimental appraisal of the model. Such an appraisal would be of great importance.

[*] The information on the construction plan of the individual, passed on from one generation to the next, increases by 1 bit in $10^5/(2 \times 10^3)$ years = 50 years (a base pair corresponds to 2 bits).

Table 1. Turning points from divergent to convergent phases of evolution.

Cause	Effect
Polynucleotide molecule uniformly contains d- (or l-)ribose	Molecule is capable of replication. Species multiplies
RNA molecules with tertiary structure fit together and form aggregates	Aggregate can be reproduced with low error rate because incorrect copies of individual molecules do not match. Aggregate species selects
Polypeptide synthesis on surfaces of aggregate	Polypeptide forms envelope, which impedes diffusion of precursors of aggregates. Species multiplies. It is independent of a given compartmentation and thus has new scope for propagation
Complementarity between bases of the triplets of the primitive tRNAs and the primitive mRNA	Protein with certain specificity of amino acid sequence reduces probability of a replication error to 10^{-3} per base. Genetic code. Proteins with specific functions evolve
DNA-RNA tandem	Useless complementary RNA strands are no longer made. Information for organisms merges in the DNA strand. DNA becomes carrier of genetic information. Development up to $N_{total} \approx 10^6$, $W \approx 10^{-6}$
Exchange of genetic material between individuals in addition to an improvement of the replication device, for example by triple storing of information	Evolution of pseudosexual mechanisms. Diminution of W and enlargement of N_{total} up to the limit given by thermal blows or radiation damage. Evolution of higher organisms
Language, writing, and information storage and retrieval technology	More information can be passed on to the next generation than by the genetic apparatus. Thus, evolution of functional networks needing a greater information capacity than given by the genetic apparatus

21.2. Further Possibilities for the Evolution of Selforganizing Systems. Scope of the Presented Conceptual Pattern

In this study the model asumptions were choosen to retain as many connections to known facts as possible in order to keep the hypothetical content as small as possible.

The method described here could also be used in a search for routes to selforganizing systems employing completely different tools than the organisms we know. It would be interesting, for example, to consider the selection possibilities for systems whose genetic information is stored, replicated, and read off in a planar fashion instead of linearly.

It has often been asked whether living systems could, under different conditions (on different celestial bodies), evolve from entirely different compounds. This question is reasonable, because elements like boron, nitrogen, phosphorus, *etc.* in non-aqueous media form a great variety of compounds with each other. Specialists in the field suspect an abundance of compounds comparable with that of carbon chemistry.

Here we also encounter a difficulty which would equally arise in carbon chemistry if we did not know anything about nucleic acids and proteins: a special model for the formation of selforganizing systems would remain speculative because it could not be substantiated at all stages by comparison with what we know.

In principle, after what has already been said, one could imagine the evolution of selforganizing systems according to a comparable sequence of divergent and convergent phases where the carriers of information and function belong to completely different classes of substance from nucleic acids and proteins. With this kind of system also, all the important model steps would be steps to solve problems of traffic regulation and organization on the molecular level, which must likewise occur with other types of substances and under different conditions.

It seems rewarding to apply the described method (conceiving systematically of a hypothetical pathway as a causative chain of events, checking individual steps by quantitative estimates) to later evolutionary steps of an apparently highly teleological nature, for example to the phylogenesis of the bombardier beetle.

Tracing the logical pattern of the evolutionary formation of important biological processes by model considerations should prove to be one of the main applications.

The situation in biology is comparable to that in chemistry: Basically chemical phenomena should be predictable from the Schrödinger equation, but the Schrödinger equation is applicable only if enormous simplifications are introduced. Quantum chemical model systems may serve as a frame, in detail however chemistry is largely based on experience. In biology, the complex structure of each individual and of the evolving populations introduces similar restraints for a strict treatment, and the search for simple models will be an important task.

21.3. Chance and Necessity

The process leading to a turning point from a divergent to a convergent phase of evolution for the individual in question is a random event of very low probability. But in a sufficiently large population even a highly improbable process takes place by necessity. This is similar to the event of throwing 10 sixes in a row which takes place by constraint if the dice is thrown often enough.

In the above discussion only *one* possibility leading to a turning point was found on each occasion. On the level

of the evolution of aggregates, for example, the step leading to the formation of an envelope seemed necessary to provide an escape from the divergent phase. The systems remain captives of their evolutional level until the occurrence of the decisive random event which raises them to the next level. Since this event sooner or later must take place by constraint, not its occurrence as such but the time of occurrence is pure chance. Means of overcoming difficulties impeding further development after a divergent phase has been reached are thus apparently intelligible, and the general lines of the evolutionary process, as determined by the turning points, are not unpredictable. Under appropriate conditions the origin of life and the evolution of increasingly highly organized systems, with respect to the decisive aspects, therefore seems to be a necessity.

The situation does not seem basically different from that in other areas of physics, where individual processes are described by random laws of chance while the overall behavior of large ensembles is deterministic in approximation.

In the model no step of low overall probability has to be introduced. Instead, the evolution of life can be considered to be a process which must occur under suitable circumstances. The triggering process would certainly not appear to be of such low probability that it is unique in the universe.

If the conditions as they have prevailed on earth could be simulated, forms of life would again develop. The inevitable steps leading to higher levels of evolution would occur again, and these steps appear to be replication, formation of aggregates, envelope formation, evolution of the genetic code, the coupling of the genetic material containing the construction plan of an individual, the exchange of genetic material between individuals as well as later steps, such as steps similar to the formation of an envelope enabling the system to find new living space. On the other hand it could be expected that all those steps representing solutions for molecular organization problems of minor importance, *i.e.* problems having different, equally reasonable solutions, would go in different directions if they were repeated. Therefore it can be assumed that the elements of the genetic apparatus (for example the ribosome) would have a different structure and would be part of a different functional network; and it also seems likely that the translation pattern of the genetic apparatus would be different. The development of other metabolic pathways, which happen to have been found earlier and form different functional networks, is conceivable. It may be expected that enzymes with corresponding functions would have a different structure.

The overall course of evolution would be expected to be the same, but in detail the evolving systems would find different functional networks and precursor elements, which would still serve the same general purposes. The random accidents are the triggering elements of evolution and determine the time of occurrence of decisive events and all the details concerning the structure of self-organizing systems, but they do not determine the general features of self organization.

22. Appendix 1: Can a Model Step be Realized? General Considerations for the Estimates

When we discussed Figure 9 we presumed that one individual of an advantageous mutant, formed spontaneously and at random, would be found in the given population. This prerequisite is practically always fulfilled for the following reason: in a large population there will be spontaneous production of many mutants with a slight advantage and a few with a greater advantage. In general, only one specimen of the mutant with the greatest advantage of all will occur at random. Since this mutant is usually the one that asserts itself it is the only one that has to be taken into consideration apart from the normal form.

From the molecular architecture of the system, we can estimate the probability of formation of an imaginary mutant by random reproduction errors. From this probability we are able to derive the size of the population, *i.e.* the number Z of individuals of the respective normal form displaced on selection of the mutant. (Z equals the reciprocal value of this probability.) Furthermore, on the basis of the advantages we assumed for the new mutant, we can estimate by how much its reproduction frequency or its chance of survival has increased compared to the normal form.

We thus obtain a value for r which we can use, according to Figure 9, to determine the number n of generations necessary for selection. Furthermore, we assumed that after having evolved through replication errors the mutant does not suffer another replication error during those n generations, because in a highly differentiated system practically any error would incur a disadvantage. In Figure 11 we then introduced the error probability P, *i.e.* the probability of a new error occurring during reproduction of an individual of this mutant. This means that after $1/P$ generations practically all the progeny of this mutant are afflicted with an error. Simplifying, we may imagine that no error occurs during the $1/P$ generations after the first appearance of the mutant, but after precisely this number of generations an error in reproduction occurs in each individual of the mutant. This simplification does not change the result very much but it makes the situation easier to grasp.

We now have to differentiate between two cases:

$$1/P < n \quad \text{and} \quad 1/P > n$$

n is the number of generations (counting from the first appearance of the mutant) in which the mutant displaces the normal form. If $1/P > n$, the mutant has not asserted itself before the next error occurs. The mutant thus only represents a minute fraction of the population. The probability of finding one individual in this small group which would profit from the error is exceedingly small. The mutant almost certainly dies off.

If $1/P \geq n$, the whole population is made up of the mutated species. The number of individuals suffering a new error is high. However, we can now assume that among the many individuals there is one which has profited from the new error: a new improved mutant develops which again asserts itself.

If $1/P \geq n$, the random error is no longer disadvantageous but is useful instead. The condition for selection as given in Figure 11 applies. As soon as this condition is obeyed, evolution takes place faster the faster the new random error occurs: The time before the occurrence of the next error inducing a new evolutionary step is much too long if the error probability is reduced. The condition for optimal probability of reproduction error is therefore:

$$1/P = n\,.$$

When looking for a meaningful model pathway one thus proceeds in the following manner: Z, r, and P are estimated for an imaginary mutant on the basis of molecular architecture. It is then established whether the condition $1/P > n$ for selection to take place is fulfilled for the step considered. Only those steps may be considered for which this condition holds (Fig. 21).

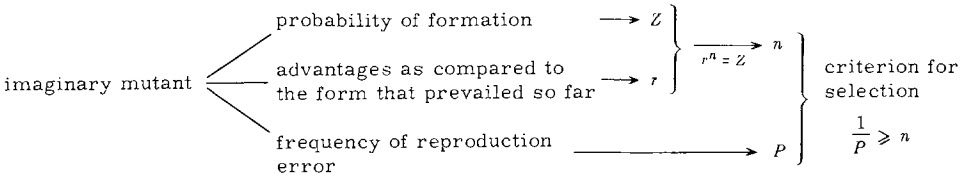


Fig. 21. Test to see if a model step may be realized.

The method will be illustrated for the selection conditions of individual molecules (Fig. 9 and 10). During the multiplication phase a replication error occurs with a probability of $P = N \times W$ (Fig. 11). This is true if the species replicates only once during the entire multiplication phase. Each molecule serves as template for the synthesis of the complementary molecule, and during the next multiplication phase the complementary molecule itself now functions as a template on which the original molecule is synthesized again. Both species have corresponding tertiary structures during the decay phase because intramolecular base pairing occurs at corresponding sites. It can be assumed that because of their complementary tertiary structures both species have a similar chance of survival. Our considerations in Figures 9 and 10 were based on molecules having $N = 50$ bases each, such as are met in tRNAs. Molecules of this size can assume specific tertiary structures and they will have particular selection advantages: larger molecules will be formed too slowly whereas smaller molecules will have poorer chances of survival and will display no significant differences with respect to their resistance to hydrolysis.

Among $Z = 10^6$ molecules with $N = 50$ *one* will be assumed to be twice as likely to survive the decay phase than the great majority of the others because of its tertiary structure. Species even more resistant to hydrolysis will be assumed not to occur. It thus follows that $r = 2$ and $n = 20$ (Fig. 9). Therefore $1/P > 20$ (Fig. 11) must apply in order for selection to take place. In the case considered (only one replication step in the multiplication phase, $P = N \times W$) $W < 1/(20 \times 50)$ is the condition for selection. If in the multiplication phase several (for example s) replications take place in a row, then $P = N \times W \times s$ if $P \ll 1$. With increasing s the portion of error-free individuals is reduced upon entering the phase of decay, and accordingly the value of r becomes smaller. Both effects (increase of P and decrease of r and thus increase of n) make the condition for selection stricter.

As mentioned in Section 6 the condition for selection of individual molecules is not fulfilled even in the most favorable case, *i.e.* $s = 1$, because $W = 1/100$. For aggregates, on the other hand, the condition for selection can be fulfilled, even though $P = N \times W = 50 \times (1/100) = 1/2$ holds for the precursor molecules (see Appendix 2). At the end of the multiplication phase, however, there must be a sufficient number of error-free molecules able to form an organized aggregate. Particular interest therefore attaches to the ratio of the number of error-free copies to the total number of molecules formed by replication in the multiplication phase as a function of s.

In the course of the multiplication phase, one molecule yields $V = 2^{(s-1)}$ molecules of the same type and $V' = 2^{(s-1)}$ of the complementary form. We can now easily calculate numbers v and v' of error free copies:

if $s = 1$	$v = 1$ $v' = 1 - P$
if $s = 2$	$v = 1 + (1-P)^2$ $v' = 2(1-P)$
if $s = 3$	$v = 1 + 3(1-P)^2$ $v' = 3(1-P) + (1-P)^3$
if $s = 4$	$v = 1 + 6(1-P)^2 + (1-P)^4$ $v' = 4(1-P) + 4(1-P)^3$ *etc.*
therefore	$v + v' = [1 + (1-P)]^s$
or	$(v + v')/(V + V') = (1 - P/2)^s$.

In the case $P = 1/2$ under consideration the ratio $(v+v')/(V+V')$ thus amounts to

0.75 (for $s = 1$)
0.56 (for $s = 2$)
0.42 (for $s = 3$)
0.31 (for $s = 4$).

The proportion of error free copies for $s = 4$ is therefore less than half that for $s = 1$.

The selection of aggregates is dependent upon the availability of compartments (Fig. 13). In this case, the selection criterion is somewhat different because selection first takes place within the compartment. Later on the especially

favorable individuals take over the other compartments. The condition for selection then is less stringent than without compartmentation, because the advantageous species has to displace a smaller number of individuals (the individuals within the compartment). The condition for selection here again is given by the equations of Fig. 9 and 11, Z now representing the number of individuals of the normal form in the compartment and n representing the number of generations during which the species becomes dominant in the compartment. The prerequisite here is $Z \gg 1$.

The number of generations needed for the fittest species to becomes dominant in the entire population depends on how quickly the fittest form enters the neighboring compartments. Let us consider the following case: n generations after the favorable species has dominated the compartment it takes over just one more compartment, and this event keeps on occurring after each n generations. After about $g \times n$ generations the fittest form will have displaced the entire population (G compartments). Then $2^g = G$.

23. Appendix 2: Estimate of Time Required for Formation of Organized Aggregates

In order for the macromolecule B to be able to associate with A (Fig. 22a), a and b have to approach each other closer than the critical distance d of about 1 Å. Furthermore, the molecules have to have the correct orientation. Let us assume that molecule A is fixed. We now want to estimate the average time that elapses until part b of molecule B approaches part a of molecule A to within distance d. To simplify the problem, let us further assume

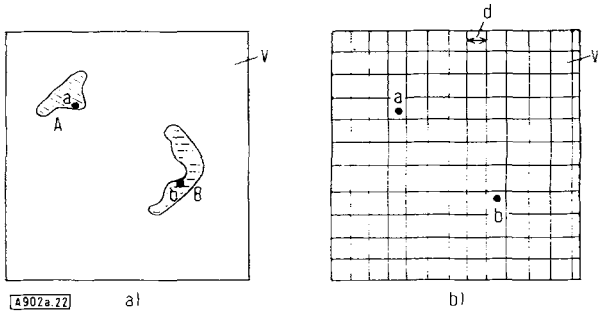


Fig. 22. Estimate of the time requirement for formation of an aggregate of matching molecules.

that part b is in the center of the molecule and therefore only takes part in translational but not in rotational diffusion of the molecule. Let us divide up the volume of the compartment V into cells with an edge length of d (Fig. 22b). According to *Einstein-Smoluchowski*, the average time τ needed by b to reach the next cell is $\tau = d^2/2D$, where D is the diffusion constant of the molecule B. The average time t required for b to reach the cell containing a, is τ times the number of cells of volume V, *i.e.*

$$t = \tau(V/d^3) = V/(2Dd)$$

In order to calculate the time needed for incorporation of molecule B into system A we still have to multiply t by a steric factor α, which makes allowance for the necessity of proper orientation of molecule B.

An RNA molecule of about 50 bases forming a compact tertiary structure has a mean radius of about $R = 40$ Å (Fig. 7b). The diffusion constant is $D = kT/6\pi\eta R$ [(k = Boltzmann's constant, T absolute temperature, η viscosity of the solvent (10^{-2} poise for water)], and thus about $D = 6 \times 10^{-7}$ cm^2/s. For $d = 1$ Å and $V = 10^{-13}$ cm^3, t amounts to 10 s. If we put $\alpha = 1/100$ the time of formation is found to be about 20 min. If there are several identical molecules B which can take each other's place in the aggregate then assembly occurs correspondingly faster. The formation of an aggregate from a nucleation molecule (Fig. 15) and, say, 20 line-up molecules, under the respective conditions takes $(1/20 + 1/19 + \ldots + 1/2 + 1) \times 20$ min $= 1$ hour.

In a system consisting of a nucleation molecule with collector strand and line-up molecules, not only the time for diffusion of line-up molecules to the collector strand (according to the above estimates about one minute), but also the time for arrangement of the molecules to form an organized aggregate becomes crucial. We can assume that the time required for incorporation of an additional molecule is 100 times that for one rotation around the axis of the molecule by diffusion. The latter amounts to $t = (2\pi)^2/2D_{rot}$ where $D_{rot} = kT/8\pi\eta R^3$, from which $t = 10^{-5}$s is derived. Within an aggregate of 20 molecules the matching would take $20 \times 100 \times t$, that is less than one tenth of a second.

In the model considerations the RNA concentrations can be taken to be one quarter of the concentration of transfer RNA in a bacterial cell. In a compartment of 10^{-13} cm^3 there are then about 10^4 RNA molecules, and, for example, 10^2 aggregates could be made, each containing 10^2 RNA molecules. If only one type of aggregate is present, the time required for association of the molecules becomes correspondingly shorter because each molecule can be fitted into any aggregate, provided that it carries no reproduction errors. The probability for this results from the concepts presented in Appendix 1.

24. Appendix 3: Probability Estimate for the Step Triggering the Evolution of the Genetic Code

According to Section 17 we can assume the synthesis of a polypeptide which supports RNA replication in such a way that its own synthesis takes place with sufficient sequence specificity. This results from the following estimate:

A specific contact region, which reduces W from 1/100 to one tenth or one twentieth of this value, can be attributed to the imaginable polypeptide, in order that it may display a sufficient degree of catalytic activity. It seems reasonable to assume that the amino acids must be predetermined in, say, $\nu = 10$ positions. This means that the base also has to be predetermined in 10 places of the collector strand. The probability of this type of polypeptide being

produced by an aggregate at random is then $(1/4)^{\nu} \approx 10^{-6}$, which means that $Z = 10^6$. If it is assumed that the presence of the catalyst increases the multiplication factor by 30% ($r = 1.3$), then according to the equation in Fig. 9: $n \approx 50$. Now from the condition for selection it follows that (Fig. 11) $P \leq 1/50$. In this case P is the probability that during reproduction an error occurs in the first or the second, *etc.*, of these ν positions on the collector strand (replication errors elsewhere in the collector strand have no effect, and if the molecules contain errors spoiling their tertiary structure they are not incorporated into the aggregate). P is dependent upon the frequency W of replication errors and on the numbers of consecutive replications in the multiplication phase (Appendix 1). $P = \nu s W$.

Here s must have a value of at least 2. During the multiplication phase each molecule then functions as template for synthesis of one complementary molecule and the complementary molecule subsequently serves as template for the synthesis of one individual of the original kind. At the end of the multiplication phase there are now two molecules of the original kind instead of one; if $s = 4$ there are four molecules, *etc.* We thus obtain $W = P/(s \times \nu) \leq (1/50)/(2 \times 10)$, which means that $W \leq 1/1000$ for $s = 2$, or $W < 1/2000$ for $s = 4$. W therefore must be 1/1000 to 1/2000 for selection to take place. Systems with the postulated polypeptide therefore must select.

In the preceding considerations we assumed that the contact regions on the four primitive tRNAs are sufficiently specific to guarantee formation of the postulated polypeptide in sufficiently high yield. In the following we shall consider the possibility that this specificity is lacking. The step considered would then require the presence of polypeptides effecting a specific linkage between the activated amino acids and the primitive tRNAs (amino acyl synthetases).

At this particular stage in the model there may be many polypeptide-synthesizing entities within a common envelope. It will be assumed that by chance five of these entities have just that base sequence on the mRNAs which would lead to the synthesis of the four amino acyl synthetases and of the replication enzyme if the four synthetases were present to serve as starters. The difficulty is that these synthetases are not present. It can be easily seen, though, that in this type of system they must gradually be formed in an autocatalytic process. Then the system can select.

The following argument demonstrates that such a system develops with sufficient probability:

A polypeptide acting as synthetase must have a specific recognition site for the amino acid and another one for the tRNA. If it is assumed that for each recognition site five digits have to be occupied in a specific way in order to attain sufficient specificity, then the probability of being produced by one entity is $(1/4)^{10} \approx 10^{-6}$.

According to Appendix 2 it may be assumed that there are, for example, 100 aggregates consisting of 100 RNA molecules in a compartment of 10^{-13} cm^3. The probability of finding one that acts as synthetase among these 100 aggregates is then $100 \times 10^{-6} = 10^{-4}$. The probability of also finding aggregates producing the above mentioned replicase and four different synthetases in one compartment, is then $(10^{-4})^5 = 10^{-20}$. It can thus be assumed that among 10^{20} systems of this kind there is one having this particular property and therefore selects. A population of this size does not seem unrealistic. The volume of 10^{20} compartments of 10^{-13} cm^3 is $10^{-13} \times 10^{20}$ cm^3 = 10 m^3. In a smaller population it would take proportionately longer for such a system to be formed at random.

25. Appendix 4: Interference by Complementary RNA Strands; DNA Evolves

In accordance with Appendix 2, RNA molecules and their complementary strands form tertiary structures, and the question arises whether disturbances are produced by faulty incorporation of complementary molecules into an aggregate. It can be assumed that the molecules in organized aggregates are mainly linked together by complementary base pairing, and that complementary strains are therefore not incorporated but instead form aggregates among themselves. If polypeptide synthesis takes place on an aggregate, the complementary aggregate cannot at the same time serve as template for the matching of the amino acids.

In Section 19 the possibility was considered that production of the enzymes E_1 and E_2 would avoid the formation of useless complementary strands. At that point the further model steps were only hinted at and will now be examined in more detail.

The enzyme for RNA replication becomes superfluous once E_1 and E_2 are formed. The respective section on the primitive mRNA strand degenerates because replication errors in this section are no longer damaging. As soon as this section randomly gives rise to a protein with favorable properties this strain selects, and the properties of the protein are improved by further selection steps: An RNA section that has become superfluous will therefore only degenerate for a short period of time and will invariably be revived again by modification. Modification of an RNA section that has already been instructed will take place much faster than completely fresh instruction of a section with random sequence.

We shall now assume the formation of a protein L which joins up the open-chain RNAs to give a single strand. The polymerization of DNA on this strand as template is catalyzed by enzyme E_1.

At the beginning of the multiplication phase L links all the RNAs together, and the DNA strand thus formed contains the information for the entire individual. Protein L will be linked more tightly to the newly formed DNA strand than to the tail ends of the RNA chains. It then serves as a block for further polymerization of RNA, and all the individual RNA molecules can be produced on the one DNA strand. The merging of the entire information of the individual within the DNA is a selection advantage. Perturbations occurring through the loss of one

or the other messenger RNA from the network of the organized systems are avoided, and traffic problems during construction are alleviated.

We can now assume the formation of a DNA-dependent DNA-polymerase. DNA replication now appears as additional factor in reproduction: the enhanced reproduction effect represents a selection advantage. After each replication the molecules of protein L occupy those sites on the DNA strand where synthesis of an RNA molecule is initiated. They are able to find these sites on account of their recognition region, which enables them to differentiate between complementary DNA strands.

The new reproduction principle replaces the preceding one: enzyme E_1 has become superfluous and degenerates. Apart from DNA, each daughter individual must now be provided by the parent with protein E_2 (for RNA formation on the DNA template) and protein L (for adequate stopping of further polymerization of RNA molecules on the DNA).

26. Appendix 5: Estimate of Time Required for Instruction of 10^3 Proteins (Information Content of a Bacterium)

Regarding Figure 20 it was assumed that each replication error occurring in the DNA section for fully instructed proteins is lethal. This assumption admittedly simplifies matters but has little effect on the results: many errors are disadvantageous but not deleterious. The erroneous copies thus do not disappear immediately but only after a few generations, which clearly has the same overall effect.

Many errors are ineffective because some of the amino acids of a protein are unimportant for its function (substitution of one amino acid by another makes practically no difference). Also, the degeneracy of the genetic code permits exchange of some bases for others without consequences. Errors of this type are taken into consideration by not counting the corresponding bases when determining N_{total} (the fraction of such bases in the total DNA will be considered in Appendix 6).

Errors in the instructed section are ineffective in further evolution as long as their number is small. This is the case, if the critical length of the DNA is not exceeded ($N_{total} < 1/W$), which will be assumed to hold at this point.

Replication errors at the end of the DNA strand, which carries the information for the last protein, are no disadvantage because this protein does not yet have a function. We may therefore assume that a population of individuals is formed whose base sequence at the end of the strand has a random distribution while the base sequence of the remaining strand is practically the same in all individuals.

Noticeable selection advantages will appear in the protein to be instructed as soon as at least v positions are occupied by certain amino acids (one can imagine, for example, that these amino acids may be important for an active site). Then 3v codon digits have to be placed correctly by chance (degeneracy of the code is neglected for simplicity although it could easily be considered; in the extreme case of complete degeneracy of the third digit in the triplet, 2v would have to be put in the place of 3v). The probability of finding a specific base in 3v digits is $(1/4)^{3v}$, because a choice between 4 bases is possible. Thus, among $Z = 4^{3v}$ individuals *one* mutant of this type appears.

For a multiplication factor r,

$$n = \log Z / \log r$$

follows from the equation in Fig. 9. It is assumed that a replication system with optimal error probability W has already been formed. Therefore $n = 1/P = 1/(W \times N)$, where N is the number of bases coding for the protein at the end of the strand; thus

$$W = 1/(N \times n) = (1/N)(\log r/\log Z).$$

It is difficult to estimate the value for r which has adapted the system to an optimal value of W. For $v = 5$, for example, one may assume $r = 1.01$, which, for a protein with five determined amino acids, means a 1% increase in the chance of survival.

In favorable instances higher r values may be obtained with five determined amino acids. The optimal value of W will adjust itself in such a way that even minor improvements of adaptation of the protein to its function will induce selection of this strain. In many positions of the protein, however, the nature of the amino acid will be of such little importance that, even upon the best choice of bases, an r value will result in the DNA which is below 1.01. A selective adjustment is then no longer possible; nor would it be worthwhile. In other words, these areas do not have to be considered in counting the digits of the DNA which are essential for coding.

The value $r = 1.01$ for $v = 5$ follows from the following estimate: it can be assumed that the selection advantages of an additional, fully instructed protein in a simple or complicated organism will become immediately apparent, *i.e.* each additional protein will represent a substantial improvement, increasing the chances of survival for example by 20% ($r = 1.2$). The value of r must increase considerably with the number v of digits occupied by advantageous amino acids. It therefore seems reasonable to assume that the value for r increases exponentially with v:

$$r = e^{v/a}$$

and for $v = 300$ (number of amino acids in a larger protein) comes to the value of $r = 1.2$. It follows that $a = 500$ and for $v = 5$ r amounts to a value of 1.01. With these values for r and v and with $N = 10^3$ (protein of about 300 amino acids), and using the relationship given, we arrive at: $Z = 4^{3\times5} \approx 10^9$; $n = 10^3$ and $W = 10^6$

The instruction of an entire protein is an optimization process, during which the new protein is incorporated increasingly well into the functional network of the others. One can assume that this process takes about

$$k = N/(3 \times v \times W)$$

generations. [This equation is derived by using the following simplification: in $N/3\nu$ consecutive steps, ν amino acids are instructed at a time, and after each step the statistical distribution of the uninstructed amino acids must be allowed to establish itself. (Statistical distribution is reached after $1/W$ generations, *i.e.* after as many generations as are necessary for an average of one replication error to occur at each codon.)]

On the whole the number of selection steps is smaller than $N/3$, because not all N bases are used for coding. $1/W$ is too high an estimate for the number of generations it takes for the next selection step to occur: for each selection step there are many ways of determining ν amino acids, and the first possibility realized at random must occur much earlier than after $1/W$ generations for statistical reasons. On the other hand, sufficient adaptation of the new protein to its functions is attained only after a fairly large number of optimizing steps. These two effects should approximately counterbalance each other.

Minor optimization processes of the instructed proteins will, of course, always be taking place. As already mentioned, almost all errors occurring in the DNA section for these proteins are either ineffective or deleterious. However, useful errors will occasionally occur which then lead to selection of a particular strain.

The DNA strand of the individual concerned is considered to grow by attachment of an additional small element of DNA material so that another protein is produced. If the strand grows too early (before the protein coded for at the end of the original strand is fully incorporated into the functional network) selection disadvantages result; *i.e.* the system cannot afford to have several proteins without specified function because, in general, each useful error in the DNA section of one protein becomes ineffective if disadvantageous errors occur in the section for another protein. On the other hand, a system whose DNA strand grows after the protein resulting from the end of the strand has just been incorporated into the functional network of the other proteins will select, even if the additional protein has only a minor advantage.

It may therefore be assumed that according to this mechanism the systems we considered will grow by $N = 1000$ bases after $k = N/(3\nu W) = 10^8$ generations. It may then be asked how many generations K are necessary for the instruction of $B = 10^3$ proteins (that is about the number of different proteins in a bacterium). The answer is $K = Bk = BN/(3\nu W) = 10^3 \times 10^8 = 10^{11}$

If we take a time requirement of 20 min per generation (doubling time of a bacterium under optimal conditions, which are not fulfilled in its natural surroundings), we arrive at 10^7 years for 10^{11} generations. If we use one day per generation (assuming that the generation time is determined by the day-night cycle during the decisive stages of evolution) the time required is 10^8 years. Thus, within 10^8 years the evolution of a system as complex as a bacterium could have taken place starting from a more simple system having a fully developed genetic apparatus.

The arbitrary value $r - 1 = 0.01$ is uncertain, but according to the estimates given above it cannot be wrong by orders of magnitude. The number K of generations is not very strongly dependent on r:

$$K = (BN^2/3\nu)(\log Z/\log r)$$

and since $Z = 4^{3\nu}$

$$K = BN^2(\log 4/\log r)$$

With $N = 10^3$ and $B = 10^3$ we obtain:

$$K = 10^{10} \quad \text{for} \quad r = 1.1$$
$$K = 10^{11} \quad \text{for} \quad r = 1.01$$
$$K = 10^{12} \quad \text{for} \quad r = 1.001 .$$

The larger the population, the more favorable the mutants occurring with sufficient probability, and the faster the evolution will advance. In a population of $Z = 10^{24}$ (a very large population) $\nu = 11$; if $Z = 10^5$ (a very small population) $\nu = 3$. Since $\log r$ is proportional to ν, K is inversely proportional to ν. If $Z = 10^{24}$ is reduced to $Z = 10^5$, K changes by a factor of only 3/11. An increase in population thus does not reduce the time requirement for evolution decisively.

These considerations were based on the assumption that instruction of all the proteins of an individual must occur one by one. We did not take into account the possibility that information may accumulate in different populations simultaneously, and that these systems evolving parallel to one another may interact and fuse to give an organism containing the information of both. This possibility could reduce the time required for the instruction of proteins considerably. It is highly probable, however, that this type of mechanism, which was certainly important during later phases of evolution (Appendix 6—8), did not play an important role in the instruction of the first 10^3 proteins. This phase saw the evolution of the main biochemical processes necessary for development of the genetic apparatus and the safe delivery of its building blocks. These processes make up such a closely-knit functional network that it seems safe to assume that evolution could only have occurred by stepwise incorporation of single functional elements.

27. Appendix 6: Maximum Information Capacity of Simple Organisms, and Error Frequency During Their Replication

a) Total Number of Base Pairs in DNA Double Strand and Proportion of Instructed Base Pairs

According to Appendix 5 the total number of base pairs of a DNA double helix is larger than the number of instructed base pairs (N_{total}). The proportion of non-instructed pairs depends on (i) what proportion of amino acids can be replaced by others without impeding protein function and (ii) how much of the DNA strand is used for protein biosynthesis. The number of amino acids that may be changed without affecting its function differs considerably from one protein to another. In hemoglobin, whose molecular function is known best[25, 26], 10% of the amino acids can be exchanged for others without producing any significant interference. In histones this proportion is smaller than 0.1%, in cytochrome 3%, in myoglobin 10%, but in fibrinopep-

tides it is almost 100%[27]. The fraction of DNA used for protein biosynthesis in bacteria is probably very large. Thus we may assume that N_{total} represents a considerable portion of the total amount of DNA, which in various bacteria lies between 3×10^6 and 6×10^6 bases[28]. The theoretical result of N_{total} being of the order of magnitude of 10^6 is therefore supported by experimental findings.

b) Frequency of Errors During Replication in Bacteria

According to the frequency of neutral mutations in *E. coli*, the probability of replication errors per base pair is found to be $W = 10^{-8}$[29]. This value is about two orders of magnitude smaller than that in the model of Appendix 5, even though according to Section 27a the value of N_{total} is in agreement with the model. This discrepancy is probably the result of the phenomenon of conjugation in *E. coli*: two bacteria happen to come into contact with each other and exchange genetic material[30]. Thus one individual receives advantageous genetic material from the other. After this conjugation, the bacteria undergo repeated cell division until conjugation again takes place at the next random contact. During the time between two conjugations the progeny of the partner carrying the more favorable genetic material will displace all other strains. This pseudosexual process of conjugation provides for recombination of genes and subsequently for faster accumulation of favorable genetic material by selection. The strain with the best combination of genes probably has a selection advantage which is so great that it only takes a few generations to select. If we assume that $Z = 10^6$ individuals interact with each other, and if the individual with the best gene combination is attributed a survival probability which on average is increased by 20% ($r = 1.2$), then according to Figure 9 the number of generations after which the strain is selected is $n = 10^2$. A maximum of *one* error is allowed in the DNA strand after 10^2 consecutive divisions if the condition for selection (Fig. 11) is to be satisfied, *i.e.*

$$N_{total} \times W \times n \leq 1$$

must hold. Thus, W may not exceed the value

$$W = 1/(10^6 \times 10^2) = 10^{-8}$$

and at about this value we expect the highest rate of evolution. Individuals with this value of W will select. The experimental value of $W \approx 10^{-8}$ may thus be easily understood.

According to the model, the instruction of further proteins has reached a limit at $N_{total} \approx 10^6$. Further evolution is restricted to a rearrangement of the informational DNA already present. At this point any mechanism leading to a faster selection of favorable strains will displace the others. The conjugation mechanism mentioned offers a new possibility for collection and combination of favorable mutants. It needs an improved replication device, because it is subject to the condition $N_{total} \times W \times n \leq 1$ (see Appendix 7, a). The *E. coli* organism thus represents a system that is very different from the systems in Figure 20, and may have developed from these by multiple step evolution.

28. Appendix 7: Considerations of the Limits of Genetic Information Capacity

a) How to Overcome the Limit Reached at $N_{total} \approx 10^6$ and $W \approx 10^{-6}$ by Exchange of Genetic Material

According to Figure 20b a limit of genetic information capacity is reached at $N_{total} \approx 10^6$. If W were smaller than 10^{-6}, N_{total} could become larger and more proteins could be instructed. However, reduction of W would not lead to immediate advantages, and only immediate advantages lead to selection. An individual whose replication device has been changed by random errors in such a way that W has only half the value of that of other individuals will be considered. Even though this strain could now instruct twice as many proteins, it has selection disadvantages because W is not optimized as it is in other strains. It therefore disappears long before it has the chance to instruct more proteins in order to gain selection advantages.

Reduction of W could be an immediate advantage under the following conditions: One can imagine that by chance a strain develops which has the ability of exchanging genetic material by fusion of individuals. According to Appendix 6 this process in itself would not yet provide selection advantages. A strain which, on account of this exchange mechanism, has accumulated particularly favorable genetic material, could not select because too many reproduction errors would occur. For selection to take place, the condition $N_{total} \times W \times n \leq 1$ would have to be fulfilled.

As soon as this type of strand by chance acquires a reduced W so that the above condition is fulfilled a turning point is reached and the direction for selection is now clearly defined. Those systems must evolve whose mechanism for exchange of genetic material becomes increasingly precise. Also the mechanism guaranteeing a reduced value of W must become less prone to interference. It therefore seems easy to understand how pseudosexual processes as discussed in Appendix 6 could arise.

Exchange of genetic material at this point seems to be the only way in which systems with $N_{total} = 10^6$ and $W = 10^{-6}$ can escape from a divergent phase. This turning point is again brought about by a process which is highly unlikely for an individual but becomes necessary in a large population.

It may be that this turning point permits further development of the genetic apparatus leading all the way up to higher organisms by gradual reduction of W and respective increase of n as well as N_{total}. According to Appendix 8 in the highest organisms we have to expect $n \approx 10^3$ and $N_{total} \approx 4 \times 10^7$. These values would give $W = 1/(n \times N_{total}) = 2 \times 10^{-11}$, which is close to the value found.

However, increasing improvement of the genetic apparatus must reach a limit owing to the loss of information by thermal collisions. We have to establish when this limit is reached and how it could be overcome.

b) Loss of Information by Thermal Collisions

In the preceding considerations it was assumed that the information is fully maintained during the time t between consecutive replications. The probability W' of a base on the DNA strand exchanging during this time t was considered to be small as compared to W. During further evolution W can only be reduced until $W = W'$, *i.e.* $W \geq W'$ must hold. Further reduction of W without simultaneous reduction of W' offers no further selection advantages.

Exchange of a base during the time between two consecutive replications can be due to radiation or chemical effects. Here we only consider the inevitable exchange by thermal knocks. As a crude approximation, W' will be given as the probability of dissociation of a bond. It follows that

$$W' = f \times t \times e^{-\Delta E/kT}$$

where ΔE is the activation energy and f the frequency of thermal vibrations of the atoms forming the bond.

From the values $f = 10^{12}\ s^{-1}$, $T = 300°K$, and $t = 2$ hours (estimated time between two divisions of *E. coli* under natural conditions) with $\Delta E = 33$ kcal/mol it follows that $W' = 10^{-8}$. In a system of the complexity of an *E. coli* bacterium ($W + W' \approx 10^{-8}$) the activation energy must be greater than 33 kcal/mol in order for the condition $W' \leq W$ to be fulfilled. In a higher organism [$W + W' \approx 10^{-11}$; $t = 5$ days (Appendix 8)] it becomes $\Delta E \geq 40$kcal/mol, *i.e.* the activation energy must have a value that is only reached when the information (as in natural systems) is fixed by formation of a chemical bond, and if the information carriers are also highly protected by incorporation into a strictly ordered matrix. In this case the simple expression $W' = f \times t \times e^{-\Delta E/kT}$ no longer applies and has to be replaced by one which takes into account that for breakage of a bond a sufficiently large area of the matrix has to be "melted" (relatively high activation energy), but also that the reaction can proceed *via* many different directions, *i.e. via* many different activated states (high activation entropy; f is replaced by a higher value). But this does not basically change the reasoning.

Bacteria have developed mechanisms for repairing damage in cases which do not completely erase an element of information. In this way W and W' are reduced considerably, but again a limit is reached at a certain value of W'. It seems possible that this limit has been reached in higher organisms. The fact that $W + W'$ probably has almost the same value in all higher organisms would point in that direction. However, it is also even possible that this limit has already been reached in bacteria, since the value $\Delta E \geq 40$ kcal/mol calculated for higher organisms seems rather large.

After this limit has been reached, further evolution depends on a basic change in the system of transfer of genetic information. Consideration of this possibility might be interesting for a discussion of imaginable forms of evolution, independent of where the limit is.

c) Development of a System of Information Transfer Based on Multiple Reading

Systems will be considered in which W or W' cannot be reduced. The ability to transfer large amounts of information from one generation to the next in spite of this, logically requires the development of a system based on multiple storing of information. The possibility will now be considered that a system is formed which has both triple storing of information and a mechanism, by which the three double strands of DNA are constantly being repaired so that they always have the same sequence (Fig. 23). In addition, an enzyme system is postulated which constantly

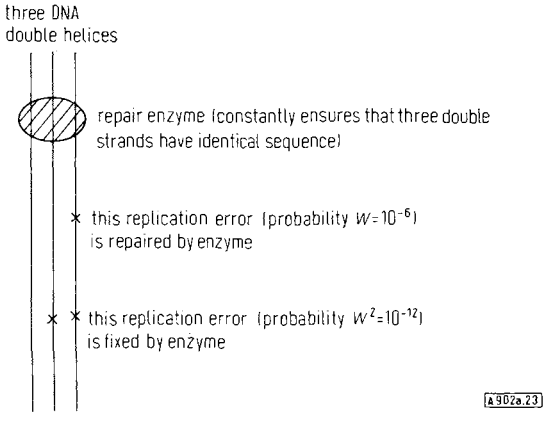


Fig. 23. The limit for genetic informational capacity set by thermal impacts or radiation damage is overcome. Triple coding and repair mechanism ensuring the same base sequence of the three double strands.

runs up and down the three double strands and checks whether the three respective base pairs agree. If they do not agree, the deviating base pair is replaced by the enzyme in such a way that the double strands always have completely identical sequences. For the enzyme to have an unequivocal function and with three different base pairs present, chance is supposed to decide which of the three base pairs remains and which are replaced in the other double strands. The enzyme corrects errors induced during replication by thermal knocks or radiation damage, and only retains them when the same error occurs on the same digit in two of the three double strands. The probability that the same error occurs on one digit in two of the three double strands during replication is $3 \times (W + W')^2$ (the factor 3 appears because the error can occur in strands 1 and 2, 1 and 3, or 2 and 3). Each base pair can be replaced by any of the others with the same probability. The probability that an error is retained under the conditions mentioned is thus $(7/9) \times 3 \times (W + W')^2 = (7/3) \times (W + W')^2$. If, according to Figure 20, the value 10^{-6} is assumed for $W + W'$, we then obtain $(7/3) \times (W + W')^2 \approx 10^{-12}$. The empirical value for the probability of replication errors in higher organisms is about 10^{-11} (see Appendix 8).

The circumstances necessary for this type of mechanism to evolve should be studied more closely. However useful a mechanism may seem, it will have no chance of being found by the selforganizing system if it does not offer an immediate advantage. The three-strand mechanism could

develop during a phase, in which exchange of genetic material takes place between systems with $W = 10^{-6}$ and $N_{total} = 10^6$, and therefore a considerable reduction of the probability of reproduction errors is necessary in order to reach the condition for selection. In a later stage this mechanism would hardly offer any selectional advantage. A lost opportunity will never return.

Biological evolution may possibly have missed this three-strand mechanism, but it does not seem out of place to imagine that bacteria were maneuvered into a dead end by reduction of W and W', and that the three-strand mechanism led to eukaryotes.

d) How to Overcome the Limits of Genetic Information Capacity

Apparently during evolution of eukaryotes the possibility of finding a mechanism working at a lower error rate than $W \approx 10^{-11}$ was missed. This is independent of the fact that one or the other possibility is realized in the genetic apparatus of these organisms. With $N_{total} \approx 10^7$, $n \approx 10^3$ a limit was reached which is determined by $nN_{total}\, W \leq 1$ (Appendix 6). Therefore a divergent phase (development of higher organisms) must have started.

Appearance of the human being meant that another turning point leading to a convergent phase had been reached: language writing, and information storage and retrieval technology represent an additional device for transfer of larger amounts of information from one generation to the next. Thus the evolution of functional networks demanding an information capacity exceeding that of the genetic apparatus became possible. Such a functional network may be seen in the technology of industrial products from which further functional networks, like space technology, evolve. From this viewpoint the evolution of the human is a fundamental biological event because the extent of the functional networks now feasible is no longer limited by the condition of Appendix 6.

Here again the initial missing of an opportunity (formation of a replication device working at an error rate below 10^{-11}) could have triggered the development of larger functional networks. It would be challenging to study the many imaginable courses of evolution more systematically.

One could ask, for example, what possibilities would exist for evolution if the prolonged action of ionizing radiation were to change the minimum value of $W + W'$ to 10^{-5}. In this case, the only way of keeping N_{total} above 10^5 would be multiple storage of information in connection with a repair mechanism. Organisms with $W + W' = 10^{-5}$ could hardly be sufficiently differentiated to be able to form such a mechanism, and evolution would come to an end at this level.

A similar limiting condition must exist for the turning point reached with man and computer: the existence of intelligent beings having a considerably lower degree of differentiation than given by $N_{total} = 4 \times 10^7$, $n = 10^3$ is hardly possible, *i.e.* the probability of replication errors per base pair in one cell generation may only be about 10^{-11} at the most. The intensity of radiation may thus not amount to much more than about 1 rad per cell generation, since 1 rad causes the exchange of 1 base pair in haploid cells with a probability of 10^{-11} [30a].

This also follows from the fact that in *Drosophila* one lethal mutation per gene locus is caused by a dose of 1 Krad with a probability of 10^{-5} [30b], meaning that the error probability per base pair per rad amounts to about $10^{-5} \times 10^{-3} \times 10^{-3} = 10^{-11}$. (It may be mentioned that 0.1 rad is considered to be the maximum radiation intensity permitted per week; that would be 0.1 rad per cell generation.)

29. Appendix 8: Frequency of Reproduction Errors and Genetic Information Capacity in Higher Organisms

a) Frequency of Replication Errors in Higher Organisms

From changes in the amino acid sequence of proteins within phylogenetic series, it was concluded for vertebrates that the probability of base exchange is only dependent on time. It is therefore independent of the time between successive generations of a biological species and amounts to 3×10^{-9} per year, irrespective of whether a quickly evolving organism (mammals) or a "living fossile" (carp) is studied[31]. In order to deduce the probability of replication errors we shall consider a chain of ancestors of cells in which each daughter cell emerges from the parent cell by division. The time between two consecutive cell divisions in this chain will be regarded as constant and of the order of five days. This assumption is realistic: the separation of a sperm from a spermatogonium occurs about once every five days[32]. Separation of an egg cell from its mother cell occurs at a much lower frequency. However, since the chain we are considering involves equal numbers of male and female organisms we can assume the average time per cell division after completion of embryonic development to be about 10 days. During embryonic development a cell division occurs about once every 10 hours[33], and an estimate shows, that the total number of consecutive cell divisions during embryonic development is similar to the number of cell divisions taking place from then on until puberty. Thus on the average a cell division occurs about once every five days (10^{-2} years). The probability of an error in a cell generation is therefore $3 \times 10^{-9} \times 10^{-2} = 3 \times 10^{-11}$. A similar probability is to be assumed in *Drosophila*, as we shall see below.

In *Drosophila* an average of 3×10^{-6} lethal mutations occurs per generation per locus[34]. The probability of base exchange is thus about $3 \times 10^{-6} \times 10^{-3} = 3 \times 10^{-9}$ because each locus corresponds to about 10^3 base pairs, whose alteration leads to lethal mutations. There are about 10^2 cell generations per generation[35], and thus the error probability of base exchange becomes $3 \times 10^{-9} \times 10^{-2} = 3 \times 10^{-11}$. The fact that this value is almost constant, suggests that the replication mechanism and the mechanisms for conservation of information have remained practically unchanged during the course of evolution of

higher organisms. The calculated error probability of replication is comparable with the probability resulting from the model in Figure 23 and Appendix 7.

b) Genetic Information Capacity of Higher Organisms and Chromosomal Structure

The total amount of DNA in a haploid cell of protozoa and algae contains at least 10^7 base pairs, but values 30 times higher than that have also been found (it is suspected that in such cases many copies of the same DNA strands are present)[36]. In mammals this number is about 4×10^9, in *Drosophila* it is 2×10^8. There is evidence that in higher organisms only a small fraction of the total DNA is used for instruction of the amino acid sequence of proteins and thus only this small portion contributes to N_{total}[34,37]. In *Drosophila* there are about 10000 gene loci[34] (therefore $N_{total}\approx10^4\times10^3=10^7$, *i.e.* about 5% of the total DNA). In humans *ca.* 40000 loci are assumed[34] ($N_{total}\approx4\times10^7$, *i.e.* about 1% of the total DNA). Although doubling of genes repeatedly took place during evolution[27,38], which increased the total content of DNA, N_{total} did not apparently increase correspondingly because most DNA sections were no longer used for protein biosynthesis. Such a small value of N_{total} is also required by theory (Appendix 6)[31] because no more than one error per generation (*i.e.* per cell generation) is allowed to occur in the fully instructed part of the DNA; with $W=3\times10^{-11}$ and $n=10^3$, N_{total} can be about $1/(n\times W)\approx3\times10^7$ at the most. On the other hand, if $N_{total}\approx3\times10^7$, n can be 10^3 at the most, or (taking 5 days per cell generation) the time requirement per generation is 10^4 days at the most (the value that has been reached in mammals).

After what we have said, the possibility of accumulation of genetic information to $N_{total}\approx10^7$ base pairs, which later never increased very much, does not seem unrealistic. X-ray and electron microscopic studies indicate that chromosomes contain several DNA double strands coiled around one another to form a strand of about 100 Å in diameter (superhelix)[39]. It might even be that there are three strands involved and the postulated "three-strand mechanism" thus cannot be excluded as a possibility.

I am grateful to Dr. Jutta Peters for translating the paper, discussions, and advice regarding the literature.

Received: July 8, 1972 [A 902a]
German version: Angew. Chem. *84*, 838 (1972)

[1] *M. Calvin:* Chemical Evolution. Clarendon Press, Oxford 1969.
[2] *M. G. Rutten:* The Origin of Life. Elsevier, Amsterdam, London, New York 1971.
[3] *C. Ponnamperuma:* Exobiology. North-Holland, Amsterdam, London 1972.
[4] *R. Buvet* and *C. Ponnamperuma:* Molecular Evolution 1, Chemical Evolution and the Origin of Life. North-Holland, Amsterdam, London 1971.
[5] *F. H. C. Crick*, J. Mol. Biol. *38*, 367 (1968); *L. J. Orgel, ibid. 38*, 381 (1968).
[6] *J. Monod:* Le hasard et la nécessité. Edition du Seuil. Paris 1970; Zufall und Notwendigkeit. Piper, München 1971.
[7] *J. v. Neumann:* Theory of self-reproducing automata. University of Illinois Press, Urbana 1966.
[8] *A. M. Turing*, Mind *59*, 433 (1950).
[9] *W. A. Beyer, M. L. Stein*, and *S. M. Ulan:* Los Alamos Report *1971*, 4822.
[10] *I. Prigogine* in: Proceedings of the Fifth Nobel Symposium. Almquist and Wiksell, Stockholm 1967.
[11] *G. Oster, A. Perelson*, and *A. Katchalsky*, Nature *234*, 393 (1971).
[12] *M. Eigen*, Naturwissenschaften *58*, 465 (1971).
[13] *J. D. Watson:* Molecular Biology of the Gene. 2nd Edit., Benjamin, New York 1970; *E. Harbers:* Nucleinsäuren. Thieme, Stuttgart 1969; *G. Schreiber*, Angew. Chem. *83*, 645 (1971); Angew. Chem. internat. Edit. *10*, 638 (1971).
[14] *R. Naylor* and *P. H. Gilham*, Biochemistry *8*, 2722 (1966).
[15] *M. Eigen* and *D. Pörschke*, J. Mol. Biol. *53*, 123 (1970); *D. Pörschke* and *M. Eigen, ibid. 62*, 361 (1971); *D. Pörschke*, Biopolymers *10*, 1989 (1971); *D. Pörschke* and *F. Eggers*, Eur. J. Biochem. *26*, 490 (1972).
[16] *R. L. Baldwin*, Accounts Chem. Res. *4*, 265 (1971); *I. E. Scheffle, E. L. Elson*, and *R. L. Baldwin*, J. Mol. Biol. *36*, 291 (1968).
[17] *O. C. Uhlenbeck, J. Baller*, and *P. Doty*, Nature *225*, 508 (1970); *J. B. Lewis* and *P. Doty, ibid. 225*, 510 (1970).
[18] *P. Debye*, J. Phys. Chem. *53*, 1 (1949); Ann. N. Y. Acad. Sci. *51*, 575 (1949).
[19] *F. Cramer*, Progr. Nucleic Acid Res. *11*, 391 (1971).
[20] *H. D. Försterling* and *H. Kuhn:* Physikalische Chemie in Experimenten. Verlag Chemie, Weinheim 1971; *H. D. Försterling, H. Kuhn*, and *K. H. Tews*, Angew. Chem. *84*, 862 (1972); Angew. Chem. internat. Edit. *11*, 821 (1972).
[21] *P. J. G. Butler* and *A. Klug*, Nature, New Biol. *229*, 47 (1971); *M. Nomura*, Scientific American, December 1969, and in *F. O. Schmitt:* The Neurosciences, 2nd Study Program, Rockefeller University Press, New York 1970, p. 913; *R. A. Garret* and *H. G. Wittmann* in *T. B. Anfinsen:* Aspects of Protein Biosynthesis. Academic Press, New York 1971.
[22] *M. Paecht-Horowitz, J. Berger*, and *A. Katchalsky*, Nature *228*, 636 (1970); *M. Paecht-Horowitz*, ref. [4], p. 245.
[22a] *K. Fukuda et al.*, 6 Int. Congr. on Surface Active Agents, Zürich, Sept. 1972.
[23] *S. W. Fox*, Science *132*, 200 (1960); Naturwissenschaften *56*, 1 (1969).
[24] *C. D. Laird*, Chromosoma *32*, 378 (1971).
[25] *M. F. Perutz*, Nature *219*, 902 (1968).
[26] *M. F. Perutz*, Nature *228*, 728 (1970).
[27] *M. O. Dayhoff*, [3], p. 266, especially table 2, p. 287.
[28] *E. Harbers*, [13], p. 171.
[29] *E. C. Cox* and *C. Yanofsky*, Proc. Nat. Acad. Sci. (U.S.) *58*, 1895 (1967).
[30] *E. L. Wollman, F. Jacobs*, and *W. Hayes*, Cold Spring Harbor Symp. Quant. Biol. *21*, 141 (1964).
[30a] *H. Dertinger* and *H. Jung:* Molekulare Strahlenbiologie. Springer, Berlin 1969 (see p. 238).
[30b] *C. Bresch:* Klassische und molekulare Genetik. Springer, Berlin, 2 Edit. 1970.
[31] *T. Ohta* and *M. Kumura*, Nature *233*, 118 (1971); *M. Kimura* and *T. Ohta*, J. Molec. Evolution *1*, 1 (1971); *M. Kimura*, Proc. Nat. Acad. Sci. U.S. *63*, 1181 (1969); *J. L. King* and *T. H. Jukes*, Science *164*, 788 (1969).
[32] *T. Lanz* and *G. Neuhäuser*, Z. Anatomie Entwicklungsgesch. *123*, 462 (1963).
[33] *J. Langman:* Medizinische Embryologie. Thieme, Stuttgart 1970.
[34] *J. L. King* and *T. H. Jukes*, Science *164*, 788 (1969), especially p. 794.
[35] *J. W. Fristom*, Ann. Rev. Genet. *4*, 325 (1970).
[36] *H. Ris* and *D. F. Kubai*, Ann. Rev. Genet. *4*, 263 (1970); *D. Werner* and *M. Petersen*, unpublished.
[37] *F. Crick*, Nature *234*, 25 (1971).
[38] *M. Nei*, Nature *221*, 40 (1969).
[39] *J. F. Pardon, M. H. F. Wilkins*, and *B. M. Richards*, Nature *215*, 508 (1967).

Computer Model of the Formation of Self-Organizing Systems

By Horst-Dieter Försterling, Hans Kuhn, and Karl-Heinz Tews[*]

A model of a simple self-organizing system is investigated. Mechanisms that are important to a molecular-biological understanding of evolution are studied with the aid of the model.

1. Introduction

The behavior of simple self-organizing systems[1] is simulated below by a computer model. A system possessing a genetic apparatus is considered, and it is assumed that the formation of proteins is possible on the nucleic acid template. The course of the further evolution of such a system is investigated.

A protein formed by the system can react on the system in three ways. It can affect the average time τ_R that elapses between two successive replications, the average time τ_L after which the system is destroyed, or the probability W of the occurrence of an error in the replication (Fig. 1). The protein may either directly favor the replication process or protein synthesis (decrease in τ_R and W) or protect the system against destruction (increase in τ_L). However, τ_R, W, and τ_L can also be influenced indirectly. For example, the proteins formed may encapsulate the system and so

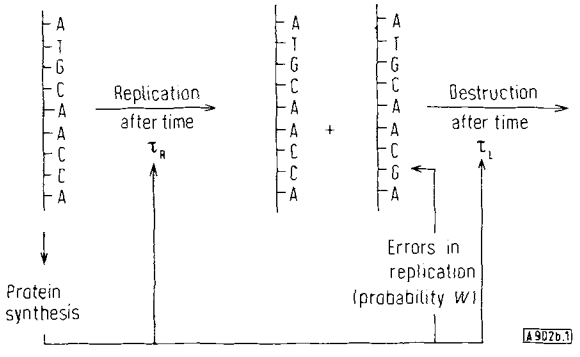


Fig. 1. Modification of τ_R, τ_L, and W by proteins. A = adenine, T = thymine, G = guanine, C = cytosine.

prevent important reactants from diffusing away, protect the system against external attacks, or facilitate the synthesis of a component that is important for the multiplication of the system. If such a facilitation is caused by a protein that has resulted over the generations from reading errors in the replication of the DNA, the system, once formed, has a selection advantage over systems with other base sequences. In the course of many generations, the accumulation of reading errors gradually leads to a change in the base sequences of the DNA strands and in the amino acid sequences of the corresponding proteins, and selection leads to forms with proteins whose amino acid sequence (real sequence) tends toward an optimum (ideal sequence).

If the probability W of an error occurring in the elementary step of the replication process is very low, it takes a very long time for a mutation to appear and for the system to approach the ideal sequence by selection of advantageous mutants. If W is relatively large, mutations occur very often, and the ideal sequence or a sequence very close to it may be very rapidly reached by chance; however, errors then occur so frequently in the course of further replication that the advantageous descendants cannot gain precedence over the numerous others in spite of their selection advantages. No convergence toward the ideal sequence therefore occurs. For the fastest possible selection, therefore, W must have an optimum value.

2. Computer Calculation

To make the mechanism of the selection of a protein easier to grasp, we first assume that W and τ_R are constant and only τ_L is influenced by the amino acid sequence. We shall consider a simple model with a DNA strand of only 9 bases, *i.e.* with the information for a protein consisting of three amino acids. Of the $4^9 = 6.3 \times 10^7$ possibilities of altering the four possible bases, one possibility, which we arbitrarily specify, will be assumed to lead to a protein that provides optimum protection of the system, *i.e.* that leads to the maximum τ_L (ideal sequence). The less the sequence actually present (real sequence) differs from the ideal sequence, the greater will τ_L be. We arbitrarily write:

$$\tau_L \sim r^{-F} \tag{1}$$

where F is the number of defects, *i.e.* of disagreements between the real sequence and the ideal sequence; r is the factor by which the chance of survival of an individual is increased by an advantageous mutation. We arbitrarily take $r = 1.5$. The greater F, the smaller is τ_L, and hence the earlier the individual must die.

We assume that the evolution begins with 50 identical DNA strands having a chance starting sequence; we allow the 50 individuals to replicate (error frequency $W = 1\%$, error positions randomly fixed) and then remove 50 individuals. Thus the total number of individuals remains constant. The removal is carried out randomly, but in such a way that relatively more individuals with a high τ_L survive than

[*] Dr. H. D. Försterling
Physikalisch-chemisches Institut der Universität
355 Marburg, Biegenstrasse 12 (Germany)
Prof. Dr. Kuhn and Dr. K. H. Tews
Max-Planck-Institut für Biophysikalische Chemie
34 Göttingen-Nikolausberg, Postfach 968 (Germany)

with a low τ_L. This is followed by renewed replication and removal, and so on. The chance introduction of defects in the replication step and the chance removal of individuals are carried out in the computer by control of the further course by a random number before each step.

The sequences of the initially formed DNA strands will still be very different from the ideal sequence, since it is improbable for the correct possibility out of 4^9 to occur by chance. If an error in replication leads to better agreement with the ideal sequence, the mutated form will live longer and therefore replicate more often and thus multiply preferentially; if the opposite is the case, the error will lead to the death of the species. In this way the number of individuals that differ only slightly or not at all from the ideal sequence will steadily increase.

The ideal sequence is arbitrarily fixed. The chance sequence of the starting molecules is fixed by throw of dice. To take into account an important aspect of evolution, several ideal sequences are given, *i.e.* there is not just one sequence that corresponds to a particularly advantageous protein, but very many. Depending on the initial chance sequence, the evolving forms tend toward one ideal sequence or another. This shows that the initial random incidents are decisive to the course of evolution.

The result of such a computer calculation[2] is shown in Table 1 for the ideal sequences (A = adenine, C = cytosine, G = guanine, T = thymine)

G C A T T C T A A
A T G C A G G G T
A G T T C C G A G
T G G G A C C A C

and the initial chance sequence

C G T A T C G T C

Table 1. Selective matching of a system of 50 DNA strands (initial sequence C G T A T C G T C) to a protein with the ideal sequence A G T T C C G A G; frequency of errors in the replication $W = 1\%$ (*i.e.* out of the 450 bases of the 50 individuals, 4 to 5 are wrongly copied in the replication step); at the beginning (generation 0) all the DNA strands agree with the ideal sequence in 4 places ($F = 5$).

Generation	Number of examples with 0 sites of error	1	2	3	4	5	6	7	8	9
0						50				
10					4	42	4			
20				14	23	12	1			
30			5	45						
40		3	34	13						
50		14	36							
60		23	26	1						
70	1	33	15	1						
80	14	31	5							
90	41	8	1							
100	46	4								
110	47	3								
120	41	9								
130	49	1								

The computer heads for the third ideal sequence, for which F has the smallest value ($F = 5$).

Table 2 shows the result for the same ideal sequences when the initial chance sequence is

G C T A T G A A C

In this case the tendency is toward the first ideal sequence ($F = 5$).

Table 2. Selective matching of a system of 50 DNA strands (initial sequence G C T A T G A A C) to a protein with the ideal sequence G C A T T C T A A. Error frequency $W = 1\%$ as in Table 1.

Generation	Number of examples with 0 sites of error	1	2	3	4	5	6	7	8	9
0						50				
10				7	8	35				
20				40	10					
30			2	48						
40			27	23						
50			43	7						
60		2	45	3						
70		3	42	5						
80	4	22	21	3						
90	17	27	6							
100	34	15	1							
110	38	10	2							
120	48	2								
130	46	4								

It can be seen from the two tables how the matching to the ideal sequence in question gradually occurs in the course of 100 to 120 generations.

If the calculation for the first case (Table 1) is repeated with different values of W ($W = 0.25\%$ or $W = 4\%$), the results shown in Tables 3 and 4 are obtained. Whereas

Table 3. Selective matching of a system of 50 DNA strands as in Table 1, but with $W = 0.25\%$.

Generation	Number of examples with 0 sites of error	1	2	3	4	5	6	7	8	9
0						50				
50					47	3				
100				49	1					
150			49	1						
200		2	48							
250			46	4						
300		43	7							
350		48	2							
400		50								
450	44	6								
500	49	1								
550	50									

according to Table 1, 92% of the 50 DNA strands have the ideal sequence after 100 generations ($W = 1\%$), the matching is very much poorer with $W = 4\%$ (only 66% of the individuals have the ideal sequence after 100 generations, though the evolution is initially much faster than with $W = 1\%$); with $W = 0.25\%$ the evolution is very slow (not one individual has the ideal sequence after 100 generations), but practically 100% are ideally matched after a sufficiently long time (500 generations).

Table 4. Selective matching of a system of 50 DNA strands as in Table 1, but with $W = 4\%$.

Generation	Number of examples with sites of error								
	0	1	2	3	4	5	6	7	8	9
0						50				
10				11	29	6	3	1		
20		1	12	33	4					
30		6	34	9	1					
40	4	10	23	13						
50	19	17	13	1						
60	18	19	12	1						
70	15	25	10							
80	29	17	3	1						
90	30	13	7							
100	33	15	1	1						
110	28	20	2							
120	30	16	3	1						
130	28	16	5	1						

3. Estimation of the Optimum Mutation Frequency

The optimum value of W is estimated below for the model considered in Section 2.

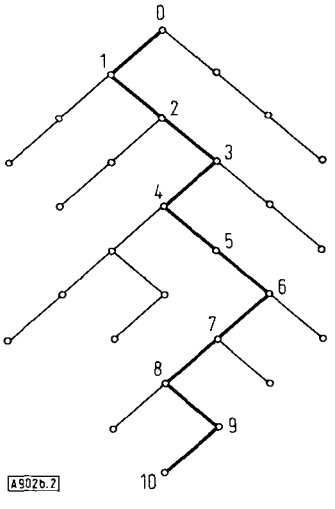


Fig. 2. Genealogical chain with $n = 10$ generations (continuous thick line). Replication occurs at each branching point (further branches have been omitted for clarity).

Let us consider genealogical chains of n generations (Fig. 2); let n be so large that there is an average of 1 replication error per chain. If N is the number of bases in the DNA ($N = 9$ in our model), then $N \times n \times W = 1$, *i.e.*

$$W = 1/(N \times n) \tag{2}$$

We shall first calculate n and start from the assumption that there are a individuals with identical base sequences at the start of the multiplication process ($a = 50$ in our model). The number of replication errors that occur in the course of n generations is therefore a; for F disagreements, the probability that one of these errors is advantageous is $F/(3N)$ [the replacement of one base by another leads to an advantageous mutation only if one of the bases that do not agree is changed (probability F/N) and if at the same time the correct base is inserted (probability 1/3)]. The number a' of advantageous errors is therefore

$$a' = aF/(3N) \tag{3}$$

In our model ($F = 5$, $N = 9$, $a = 50$), therefore

$$a' = 5 \times a/(3 \times 9) = 0.19a$$

i.e. only about 20% of all errors lead to advantageous mutants. We assume for simplicity that each of the a' errors that occur *on average* in the course of n generations occurs *precisely* after n generations. The a' advantageous mutants that are then suddenly present have an r-fold probability of survival over the other individuals ($r = 1.5$ in our model), so that they multiply more rapidly than any of the others. After n generations, therefore, there are a' individuals of the advantageous mutant that have been formed spontaneously, or out of

$$Z = a/a' = 3N/F \tag{4}$$

individuals in the population there is exactly one individual of the advantageous mutant. The ratio of the number of individuals of the advantageous mutant (m_v) to the number of other individuals (m) is therefore $m_v/m = a'/(a-a') = 1/(Z-1)$. After $n+1$ generations, the ratio m_v/m is greater by approximately the factor r (since each advantageous mutant has approximately an r-fold probability of survival over an unmutated individual), after $n+2$ generations it is greater by the factor r^2, and after $2n-1$ generations it is greater by the factor r^{n-1} (replication errors occur for the second time after exactly $2n$ generations). Thus the ratio m_v/m after $2n-1$ generations is

$$m_v/m = r^{n-1}/(Z-1)\,. \tag{5}$$

Before replication errors occur for the second time, the advantageous mutants must have practically entirely displaced all other individuals; we shall assume to have ten times as many individuals of the mutant than of the original form, *i.e.*

$$m_v/m = 10\,. \tag{6}$$

According to equations (5) and (6), $r^{n-1} = 10(Z-1)$ or

$$n = 1 + [1 + \log(Z-1)]/\log r\,. \tag{7}$$

According to equation (4), the selection becomes slower with decreasing F, and is slowest for $F = 1$. At this point, according to equation (4), $Z = 3N$; in the model investigated ($r = 1.5$, $N = 9$) this gives $n = 15$, and hence according to equation (2), $W = 0.8\%$.

In agreement with the computer result, the optimum value of W is about 1%; an advantageous mutant should have been formed after 15 generations, and should have been selected after 15 further generations. Since the initial chance sequence in the example considered differs in 5 places from the nearest ideal sequence, the selective matching should have occurred after approximately $5 \times 2 \times 15 = 150$ generations. This was in fact found (Tables 1 and 2).

For large values of Z and n, equation (7) changes into the simpler relation $n = \log Z/\log r$[11].

Note: In the above calculation the ratio m_v/m was assumed to increase in each generation by a factor r. This holds for $r-1 \ll 1$ and is only approximately true for larger values of r: In n generations we have a' individuals of the preferential mutant and $a-a'$ individuals of the normal form, and after replication $2a'$ and $2(a-a')$ individuals respectively. A total of a individuals must decay for the original number to be regained. Thus x and y being the

number of decays of individuals of the normal form and the mutant respectively, $x+y=a$. Since the probability of decay of an individual of the normal form is r times that for the mutant, $x/y=[(a-a')/a']\cdot r$. With these equations the relation

$$(m_v/m)_{n+1} = (m_v/m)_n \cdot f$$
$$f = [2a' + 2(a-a')r - a]/[2a' + 2(a-a')r - ar]$$

are obtained. In the case of $r-1 \ll 1$, we find $f=r$; in the case of the computer calculation ($r=1.5$; $a'=0.19a$) the value $f=1.38$ is obtained which is somewhat different from r.

The numerical calculations were carried out on the TR4 computer of the Zentrale Rechenanlage in Marburg. We are grateful to G. Lauer and T. Lichtenberg for their assistance.

Received: March 10, 1971 [A 902b IE]
*German version: Angew. Chem. 84, 862 (1972)
Translated by Express Translation Service, London

[1] *H. Kuhn*, Angew. Chem. *84*, 838 (1972); Angew. Chem. internat. Edit. *11*, 798 (1972).

[2] *H. D. Försterling* and *H. Kuhn*: Physikalische Chemie in Experimenten. Verlag Chemie, Weinheim 1971.

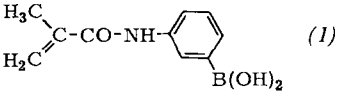
COMMUNICATIONS

New Dihydroxyboryl-Substituted Polymers for Column-Chromatographic Separation of Ribonucleoside-Deoxyribonucleoside Mixtures[**]

By *Herbert Schott*[*]

Complex formation by boric acid with *cis*-glycol groups has been used for separation of mixtures of ribo- and deoxyribonucleic acid components by paper chromatography or electrophoresis[1]. This principle was later applied also to column chromatographic separation of these mixtures on boric acid carriers on an analytical scale[2].

However, for preparative separations dihydroxyboryl-substituted polymers ("boric acid gels"), which have been synthesized from polymerizable boric acid derivatives, seem more suitable than boric acid carriers since, unlike boric acid carriers, boric acid gels can in principle be synthesized with exclusion limits as high as desired and with notably larger contents of boric ester groups.



(1)

The synthesis of boric acid gels[3] has hitherto been demanding and it was not clear whether these gels are suitable for separation of nucleic acid components. We have worked out a simple method of preparing boric acid gels and have studied their efficiency for separation of ribonucleoside-deoxyribonucleoside mixtures. *m*-Aminobenzeneboric acid is treated with methacryloyl chloride to give a polymerizable boric acid derivative *(1)*. This monomer unit undergoes radical polymerization with tetramethylene dimethacrylate to afford a cross-linked boric acid gel. By varying the concentrations of the monomer and cross-linking agent the exclusion of the boric acid gels and the introduction of boric acid groups and thus the separatory capacity can be widely varied.

A maximum of *ca.* 200 mg of boric acid gel is required for separation of *ca.* 1 mg of a ribonucleoside-deoxyribonucleoside mixture. The elution profile (Fig. 1) of this separation

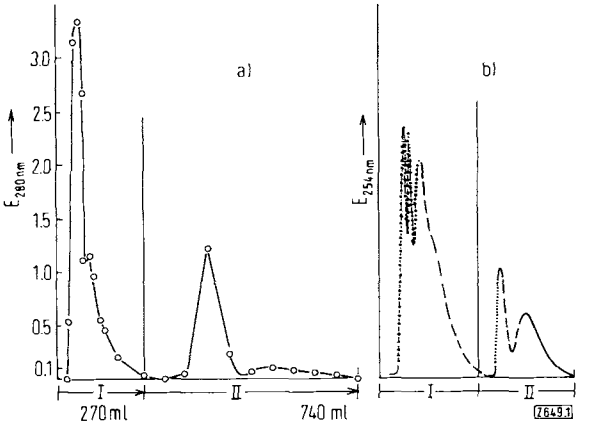


Fig. 1. Column chromatographic separation of a mixture of uridine, cytidine, guanosine, adenosine, and the analogous deoxyribonucleosides on a boric acid gel at 4 °C. Fraction I: 0.1% aqueous ammonia, pH 10.5; fraction II: H_2O, pH = 5.8. a) Elution profile measured at 280 nm; b) extinction of the fractions obtained, at 254 nm. (For details see text.)

shows not only that quantitative separation of ribonucleosides from deoxyribonucleosides occurs but also that both groups are presumably separated into purine and pyrimidine components.

Column chromatographic separations of ribonucleosides from deoxyribonucleosides has hitherto been carried out only in non-volatile salt buffers. With the boric acid gels described here separations are possible even in 0.1% aqueous ammonia; thus desalination of the nucleosides isolated becomes unnecessary, which makes preparative separation considerably easier.

[*] Dr. H. Schott
Institut für Biologie III
Universität Freiburg, Schänzlestrasse 9—11 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Experimental:

Synthesis of the boric acid derivative *(1)*: Commercial bis(*m*-dihydroxyborylanilinium) sulfate (*m*-aminobenzeneboric acid hemisulfate) (1.5 g) is dissolved in water (20 ml), then neutralized with NaOH, and the solution is evaporated to dryness in a vacuum. The residue is dissolved in dioxane (50 ml), and undissolved Na_2SO_4 is filtered off. The clear solution is evaporated to *ca.* 5 ml in a vacuum, treated with anhydrous dioxane (40 ml) and anhydrous triethylamine (5 ml), and warmed briefly at 50 °C until an almost clear solution is formed. Methacryloyl chloride (5 ml) is added in one batch to the warm solution, which is then cooled in ice. Triethylammonium chloride soon separates and after 12 hours' storage at room temperature is filtered off. The clear yellow solution is concentrated in a vacuum to 3—5 ml and the resulting syrup is dissolved in dioxane/ethanol (1:1; 15 ml).

Polymerization: Tetramethylene dimethacrylate (3 ml) and α,α'-azoisobutyronitrile (0.5 g) are added to the preceding solution, which is then gently warmed and sealed in a glass ampoule. After 24 h at 55 °C a solid yellow block has been formed; this is ground, sieved, and then freed from portions that escaped cross-linking by extraction in a Kutscher-Steudel apparatus with commercial ethanol. After drying, there is thus obtained a pale yellow, hard polymer powder (5 g, 10 ml). Before being filled into the column the whole of the polymer powder is allowed to swell in 5% aqueous acetone for *ca.* 5 h; this affords 30 ml of gel suspension.

Chromatography: The separatory efficiency of the column was first tested with U/T, A/dA, and C/dC mixtures and then with the following mixture of all four ribonucleosides and deoxyribonucleosides: (a) deoxyribonucleosides: thymidine 60 mg, deoxyadenosine 44 mg, deoxyguanosine 25 mg, and deoxycytidine 63 mg, dissolved in 15 ml of water: $E_{280}=282$. (b) Ribonucleosides: uridine 60 mg, adenosine 41 mg, guanosine 16 mg, and cytidine 52 mg, dissolved in 15 ml of H_2O; $E_{280}=248$. 0.5 ml of the deoxyribonucleoside solution and 1.5 ml of the ribonucleoside solution were placed on a column (10/2 cm) filled with boric acid gel and were eluted at a rate of 68 ml/h first with 270 ml of 0.1% aqueous ammonia (pH = 10.5) and then with 900 ml of water (pH = 5.8). The elution profile measured at 280 nm is reproduced in Fig. 1a. As control, Fig. 1b shows the extinction of the individual fractions of the same run recorded automatically at 254 nm. Aliquot parts of the united fractions (I and II) were characterized by paper chromatography in the borate system[1]; fraction I contained only deoxyribonucleosides (142 OD_{280}-units) while the ribonucleosides (341 OD_{280}-units) were contained in fraction II. Elution of the ribonucleosides was greatly accelerated by lowering of the pH (*e.g.* H_2O, pH 5.8), since at lower pH the boric acid complex becomes unstable.

Received: April 19, 1972 [Z 649 IE]
Publication delayed at author's request
German version: Angew. Chem. *84*, 819 (1972)

[1] *J. X. Khym*, Methods Enzymol. *12*, 93 (1967).

[2] *H. L. Weith, J. L. Wiebers*, and *P. T. Gilham*, Biochemistry *9*, 4396 (1970); *M. Rosenberg* and *P. T. Gilham*, Biochim. Biophys. Acta *246*, 337 (1971).

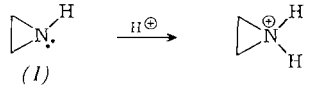
[3] *J. Solma* and *H. Deuel*, Chimia *11*, 311 (1957); *R. L. Letsinger* and *S. B. Hamilton*, J. Amer. Chem. Soc. *81*, 3009 (1959).

Effect of Protonation on Aziridine and Oxirane Bond Strengths[1]

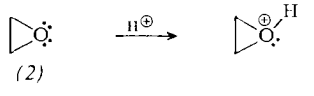
By *Wolf-Dieter Stohrer* and *Roald Hoffmann*[*]

Cyclopropane bond strengths, indeed the very equilibrium structure of cyclopropanes, should be responsive to π-electron donor and acceptor substituents[2, 3]. We have now found that the C—C bonds in oxiranes and aziridines are strengthened upon protonation or other coordination of the heteroatom lone pair.

Thus in aziridine *(1)* the overlap population of the C—C bond increases on protonation from 0.648 to 0.666 in an extended Hückel calculation[4], and from 0.262 to 0.291 in an *ab initio* computation[5]. In oxirane *(2)* an effect of similar magnitude is found. The effect can be rationalized in terms of perturbation theory[6].



(1)



(2)

The *structural* evidence for the protonation effect is ambiguous. Several crystal structures of aziridinium salts[7] show no consistent shortening of the C—C bond. Compared with aziridine[8] itself, an aziridine-borane[9] and a trimer of dimethylaluminum aziridide[10] show barely significant C—C bond shortening.

The *thermodynamic* and *kinetic* evidence for a protonation effect is fragmentary, but, we believe, in accord with our calculation.

1. In the equilibrium *(3a)*⇌*(4a)* the bicyclic form is favored in more polar solvents[11-13].



(3) *(4)*

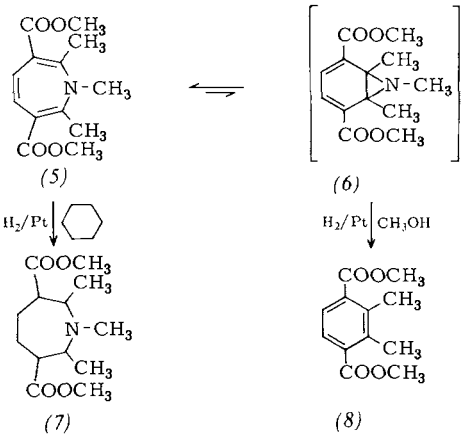
(a), X = O
(b), X = NR

The significance of this equilibrium in the first stages of the enzymatic formation of phenols[14], as well as in the general acid-catalyzed aromatization of oxepins[11, 13, 15a] should be noted.

2. Only some indirect observations have been made concerning the effect of protonation or coordination on the equilibrium *(3b)*⇌*(4b)*[16]. The substituted azepine *(5)* can be hydrogenated with H_2 over platinum in solution[17]. The resulting product depends on the nature of the solvent: *(7)* is formed in nonpolar cyclohexane while *(8)* is obtained in polar methanol, which is able to hydrogen-bond with the nitrogen. The different products may be explained by the assumption of *(6)* as an intermediate[13, 17], whose existence would be favored in the polar solvent. In the same way, one can understand the rapid aromatization of azepines to anilines under the influence of acids[13, 15, 18-20].

[*] Dr. W.-D. Stohrer [**] and Prof. Dr. Roald Hoffmann
Cornell University, Department of Chemistry
Ithaca, N. Y. 14850 (USA)

[**] Present address: Institut für Organische Chemie I der Universität 6 Frankfurt/Main, Robert-Mayer-Strasse 7—9 (Germany)



In this process, the formation of the bicyclic azanorcaradiene *(4b)* is proposed[13, 15, 18a, 19], whose existence in the equilibrium *(3b)*⇌*(4b)* would be favored by protonation[21].

Received: May 18, 1972 [Z 670 IE]
German version: Angew. Chem. *84*, 820 (1972)

[1] We are grateful to the Deutsche Forschungsgemeinschaft for a stipendium to W.-D. S., and to the National Science Foundation for support of our research.

[2] *R. Hoffmann*, Tetrahedron Lett. *1970*, 2907; *R. Hoffmann* and *W.-D. Stohrer*, J. Amer. Chem. Soc. *93*, 6941 (1971); *R. Hoffmann* in: Special Lectures at XXIIIrd International Congress of Pure and Applied Chemistry, Butterworth, London 1971, Vol. 2, p. 233.

[3] See also *H. Günther*, Tetrahedron Letters *1970*, 5173.

[4] *R. Hoffmann*, J. Chem. Phys. *39*, 1397 (1963); *R. Hoffmann* and *W. N. Lipscomb*, *ibid. 36*, 2179 (1962); *37*, 2872 (1962). The aziridine ring geometry was maintained on protonation.

[5] *R. Bonaccorsi*, *E. Scrocco*, and *J. Tomasi*, J. Chem. Phys. *52*, 5270 (1970). We are grateful to Dr. *Scrocco* for communicating these results to us.

[6] The argument involves a second order effect: *R. Hoffmann*, *L. Libit*, *W.-D. Stohrer*, and *J. Swenson*, unpublished results.

[7] a) *L. M. Trefonas*, *R. Towns*, and *R. Majeste*, J. Heterocyclic Chem. *4*, 511 (1967); *L. M. Trefonas* and *R. Towns*, *ibid. 1*, 19 (1964); b) For some related aziridine structures see *L. M. Trefonas* and *R. Majeste*, J. Heterocyclic Chem. *2*, 80 (1965); *L. M. Trefonas* and *T. Sato*, *ibid. 3*, 404 (1966); *H. M. Zacharis* and *L. M. Trefonas*, *ibid. 5*, 343 (1968); *7*, 755, 1301 (1970); *J. N. Brown*, *R. L. R. Towns*, and *L. M. Trefonas*, *ibid. 7*, 1321 (1970).

[8] *T. E. Turner*, *V. C. Fiora*, and *W. M. J. Kendrick*, J. Chem. Phys. *23*, 1966 (1955).

[9] *H. Ringertz*, Acta Chem. Scand *23*, 137 (1969).

[10] *J. L. Atwood* and *G. D. Stucky*, J. Amer. Chem. Soc. *92*, 285 (1970).

[11] a) *E. Vogel*, *W. A. Böll*, and *H. Günther*, Tetrahedron Letters *1965*, 609; b) *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967).

[12] *H. Prinzbach* and *P. Vogel*, Helv. Chim. Acta *52*, 396 (1969); *H. Prinzbach*, *P. Vogel*, and *W. Auge*, Chimia *21*, 469 (1967).

[13] *G. Maier*, Angew. Chem. *79*, 446 (1967); Angew. Chem. internat. Edit. *6*, 402 (1967).

[14] a) *D. M. Jerina*, *J. W. Daly*, *B. Witkop*, *P. Zaltzman-Nirenberg*, and *S. Udenfriend*, J. Amer. Chem. Soc. *90*, 6525 (1968); Biochemistry *9*, 147 (1970); b) *D. M. Jerina*, *J. W. Daly*, and *B. Witkop*, J. Amer. Chem. Soc. *90*, 6523 (1968); c) *G. J. Kasperek* and *T. C. Bruice*, J. Amer. Chem. Soc. *94*, 198 (1972); d) *D. M. Jerina*, *N. Kaubisch*, and *J. W. Daly*, Proc. Natl. Acad. Sci. (USA) *68*, 2545 (1971); e) *N. Kaubisch*, *J. W. Daly*, and *D. Jerina*, Biochemistry, in press; f) *G. J. Kasperek*, *T. C. Bruice*, *H. Yagi*, *N. Kaubisch*, and *D. M. Jerina*, J. Amer. Chem. Soc., in press. We are grateful to Dr. Bruice for bringing this work to our attention.

[15] *L. A. Paquette* in: Nonbenzenoid Aromatics. Academic Press, New York 1969. Vol. 1, p. 249; b) *L. A. Paquette*, *D. E. Kuhla*, and *J. H. Barrett*, J. Org. Chem. *34*, 2879 (1969).

[16] For evidence for the equilibrium *(3b)*⇌*(4b)* see *H. Prinzbach*, *D. Stusche*, and *R. Kitzing*, Angew. Chem. *82*, 393 (1970); Angew. Chem. internat. Edit. *9*, 377 (1970).

[17] *R. F. Childs* and *A. W. Johnson*, Chem. Commun. *1965*, 95; J. Chem. Soc. *C 1966*, 1950.

[18] a) *K. Hafner*, Angew. Chem. *75*, 1041 (1963); b) *K. Hafner*, *D. Zinser*, and *K.-L. Moritz*, Tetrahedron Lett. *1964*, 1733.

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

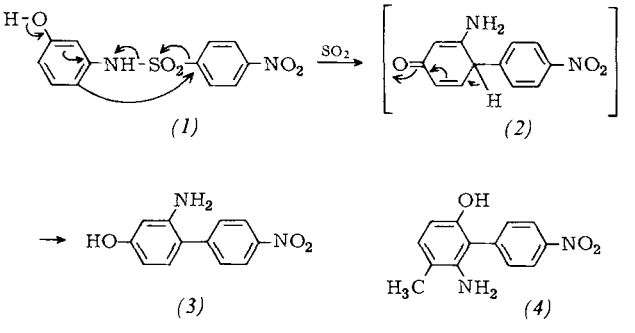
[20] *L. E. Chapman* and *R. F. Robbins*, Chem. Ind. (London) *1966*, 1266.

[21] In the case of the alkoxycarbonylazepines, it is not decisive for our arguments whether protonation occurs directly at nitrogen or—as suggested [18a, 15]—at the alkoxycarbonyl group; the electron pair on nitrogen will become involved in bonding in both cases: in the first case by the formation of a $^{+}N-H$ bond; in the second case by the formation of a $^{+}N=C$ bond.

Biaryls, Stilbenes, Benzo[*c*]cinnolines, and Dibenz[*c*,*mn*]acridines from Sulfonamides

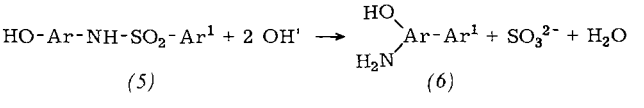
By *Eckart Waldau* and *Rolf Pütter*[*]

3'-Hydroxy-4-nitrobenzenesulfonanilide *(1)* reacts with alkali in water with formation of 3-amino-4-(4-nitrophenyl)phenol *(3)*.



If the *para*-position to the hydroxyl group of compound *(1)* is substituted by a methyl group, the nitrophenyl group enters between the hydroxyl and the amino group to form *(4)*. In each reaction no more than one biaryl compound was isolated. The specificity strongly suggests an intramolecular reaction course.

This reaction has a field of general application:



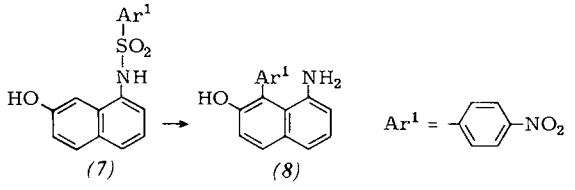
In order that it may take place the starting compound *(5)* must fulfil the following conditions:

1. In the aromatic group denoted Ar one *ortho*- or *peri*-position to the sulfonamide group, *i.e.* the position concerned in linkage to the other aromatic group Ar^1, must be unsubstituted *(7)*.

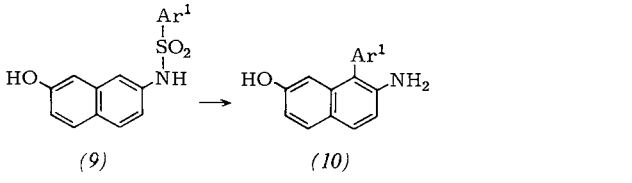
2. The hydroxyl group on Ar must enable electrophilic entry of Ar^1 to occur by virtue of its negativating effect.

[*] Dr. E. Waldau and Dr. R. Pütter
Bayer AG
509 Leverkusen (Germany)

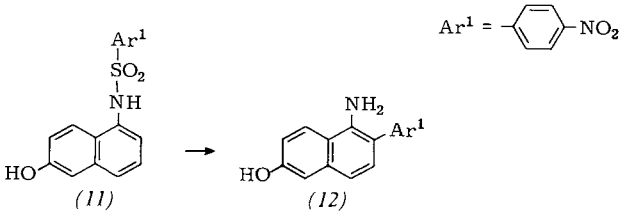
Thus its position decides the position at which linkage occurs, which can be *ortho* or *para* to this hydroxyl group. If Ar denotes a naphthalene derivative, then other positions must also be considered *(9)*, *(11)*.



(7) *(8)*

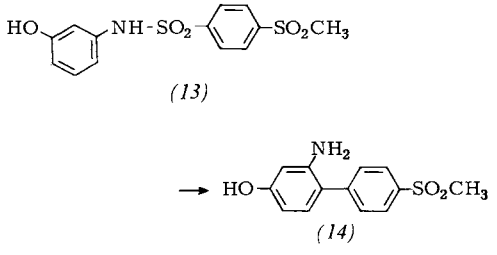


(9) *(10)*

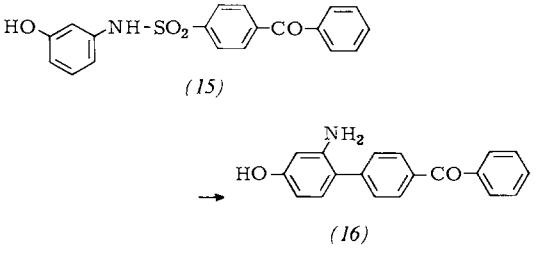


(11) *(12)*

3. During the reaction Ar^1 becomes bonded to Ar by the carbon atom carrying the sulfonamide group. This carbon atom must be rendered positive by Ar^1. The positivation can be effected by electron-withdrawing groups such as nitro, sulfonyl, or carbonyl in the *ortho*- or *para*-position *(13)*, *(15)*.

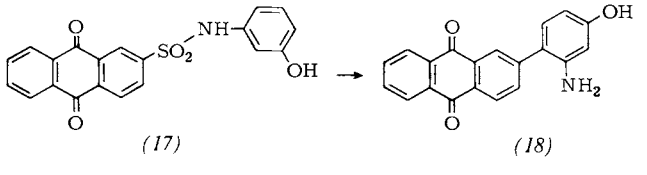


(13) *(14)*



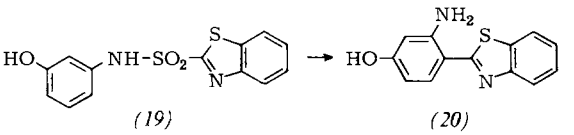
(15) *(16)*

The carbonyl group that positivates the aromatic group Ar^1 may also be contained in a cyclic system *(17)*.



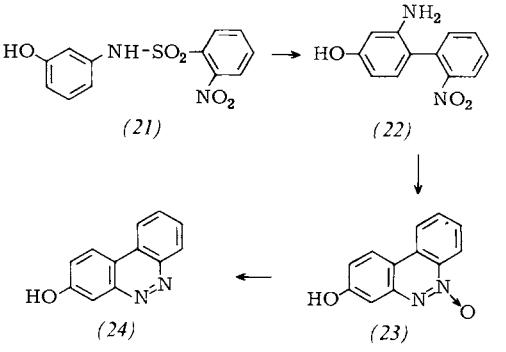
(17) *(18)*

Positivation also occurs if this carbon atom is a component of an aromatic heterocyclic ring *(19)*.



(19) *(20)*

In special cases further reaction may take place after formation of the biaryl. 3'-Hydroxy-2-nitrobenzenesulfonanilide *(21)* reacts with alkali in water at 250 °C to yield 3-hydroxybenzo[*c*]cinnoline *(24)*, *(22)* and *(23)* having been proved to be intermediates.

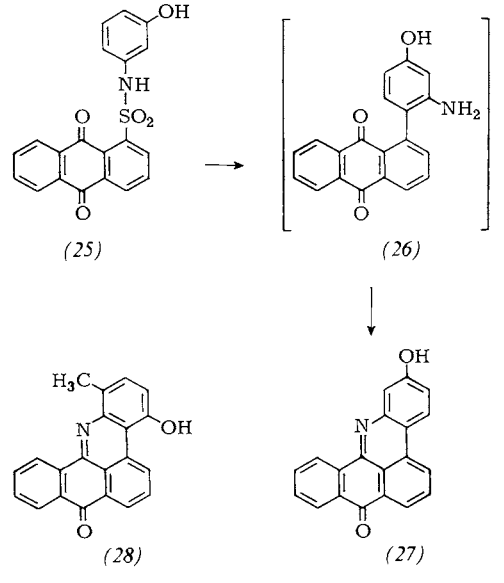


(21) *(22)* *(24)* *(23)*

Under the conditions chosen, reaction in dimethyl sulfoxide stops at the stage of 3-hydroxybenzo[*c*]cinnoline 6-*N*-oxide *(23)*, whereas in water *(23)* is reduced to *(24)* by the sulfite produced in the reaction. Because of its good yields (approximately 70%) this procedure provides a useful synthetic route to substituted benzo[*c*]cinnolines.

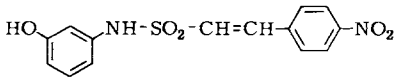
A subsequent reaction also occurs on treatment of 3'-hydroxyanthraquinone-1-sulfonanilide *(25)*; 2-hydroxy-8-*H*-dibenz[*c*,*mn*]acridin-8-one *(27)* is formed and the primary product *(26)* cannot be isolated.

If the *para*-position to the hydroxyl group of compound *(25)* is substituted by a methyl group, then 4-hydroxy-1-methyldibenz[*c*,*mn*]acridin-8-one *(28)* is obtained in a yield of 45%.

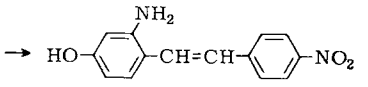


(25) *(26)* *(28)* *(27)*

Nitrostyrenesulfonamides *(29)*, as vinylogs of nitrobenzenesulfonamides, are also amenable to this reaction. Instead of biaryls one obtains stilbenes *(30)* with the *trans*-configuration.



(29)



(30)

General experimental procedure:

A sulfonamide of type *(5)* (0.1 mol) and potassium hydroxide (0.3 mol) are allowed to react in 2—3 liters of water or an organic solvent such as dimethyl sulfoxide or hexamethylphosphorotriamide under the conditions listed in Table 1. The crude product is precipitated by dilute mineral acid and filtered off. The pure products are obtained by recrystallization from alcohol or alcohol/water mixtures, if necessary with chromatography on alumina.

Table 1 gives a survey of the biaryls, benzocinnolines, dibenzacridines, and stilbenes synthesized. The yields were not optimized; they increase with decreasing concentration of the sulfonamide if the electron-withdrawing substituent can be reduced by the sulfite. Melting points are uncorrected. The structures of the products accord with elemental analyses and IR, NMR, and mass spectra.

Received: June 28, 1972 [Z 672 IE]
German version: Angew. Chem. *84*, 822 (1972)

Table 1. Compounds prepared.

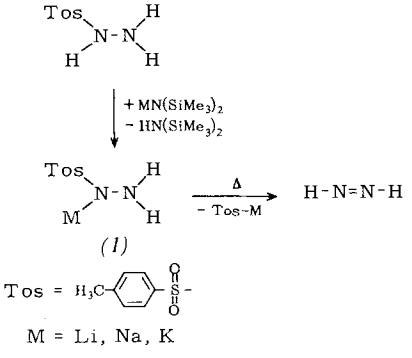
Starting material	Product	Conditions	Yield (%)	M.p. (°C)
3'-Hydroxy-4-nitrobenzenesulfonanilide	3-Amino-4-(4-nitrophenyl)-phenol	H_2O 14 h, 100 °C	80	180
3'-Hydroxy-4-(methylsulfonyl)-benzenesulfonanilide	3-Amino-4-(4-methylsulfonylphenyl)phenol	H_2O 1 h, 250 °C	58.6	203
5'-Hydroxy-2'-methyl-4-nitrobenzenesulfonanilide	3-Amino-4-methyl-2-(4-nitrophenyl)phenol	DMSO 30 min, 120 °C	10	221
1-Hydroxy-3-(4-nitrobenzenesulfonylamino)-5-naphthalenesulfonic acid	3-Amino-1-hydroxy-4-(4-nitrophenyl)-5-naphthalenesulfonic acid	H_2O 14 h, 100 °C	50	>360
5-(4-Nitrobenzenesulfonylamino)-1-naphthol	5-Amino-4-(4-nitrophenyl)-1-naphthol	DMSO 8 h, 120 °C	11	203
1-(4-Nitrobenzenesulfonylamino)-7-naphthol	8-Amino-1-(4-nitrophenyl)-2-naphthol	H_2O 12 h, 100 °C	23	203
7-(4-Nitrobenzenesulfonylamino)-2-naphthol	2-Amino-1-(4-nitrophenyl)-7-naphthol	DMSO 30 min, 120 °C	38	240
1-(4-Nitrobenzenesulfonylamino)-6-naphthol	1-Amino-2-(4-nitrophenyl)-6-naphthol	DMSO 45 min, 120 °C	55	230
3''-Hydroxybenzophenone-4-sulfonanilide	3-Amino-4-(4-benzoxylphenyl)-phenol	H_2O 1 h, 250 °C	45	190
3'-Hydroxyanthraquinone-2-sulfonanilide	3-Amino-4-(2-anthraquinonyl)-phenol	DMSO 45 min, 60 °C	18	238
3'-Hydroxybenzothiazole-2-sulfonanilide	3-Amino-4-(2-benzothiazolyl)-phenol	H_2O 10 h, 100 °C	44	191
3'-Hydroxyanthraquinone-1-sulfonanilide	2-Hydroxy-8 *H*-dibenz[*c*,*mn*]-acridin-8-one	DMSO 10 min, 120 °C	73	348
5'-Hydroxy-2'-methylanthraquinone-1-sulfonanilide	4-Hydroxy-1-methyl-8 *H*-dibenz-[*c*, *mn*]acridin-8-one	DMSO 2.5 h, 120 °C	45	295
3'-Hydroxy-2-nitrobenzenesulfonanilide	3-Hydroxybenzo[*c*]cinnoline	H_2O 1 h, 250 °C	67	283
3'-Hydroxy-2-nitrobenzenesulfonanilide	3-Hydroxybenzo[*c*]cinnoline-6-*N*-oxide	DMSO 15 min, 120 °C	67	272
4'-Chloro-3'-hydroxy-2-nitrobenzenesulfonanilide	2-Chloro-3-hydroxybenzo[*c*]-cinnoline	H_2O 5 min, 250 °C	49	287
3'-Hydroxy-4-nitrostyrene-β-sulfonanilide	2-Amino-4-hydroxy-4'-nitrostilbene	DMSO 30 min, 120 °C	58	199
3'-Hydroxy-2-nitrostyrene-β-sulfonanilide	2-Amino-4-hydroxy-2'-nitrostilbene	DMSO 30 min, 120 °C	62	157
5'-Hydroxy-2'-methyl-4-nitrostyrene-β-sulfonanilide	2-Amino-6-hydroxy-3-methyl-4'-nitrostilbene	DMSO 30 min, 120 °C	35	201

Isolation of Pure Diimine[1]

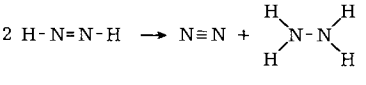
By *Nils Wiberg, Heinz Bachhuber,* and *Gerd Fischer*[*]

Unlike the organic azo compounds, which have considerable thermal (meta-)stability, their parent diimine, H—N=N—H[2], is extremely thermolabile[3]. Thus at room temperature it exists only as a reactive intermediate whose existence, founded in theory[4], can be recognized in the gas phase by mass spectroscopy[5–7] and in solution by reaction with double-bond systems[3]. It was concluded further from IR spectroscopic investigations that diimine must exist in the yellow or blue mixtures of compounds obtained on low-temperature photolysis of hydrogen azide in a foreign molecule matrix[8,9] or by quenching of the decomposition products of hydrazine[5,10,11] or hydrazoic acid[5,12] formed in an electric discharge at reduced pressure. Because of the heterogeneity of the product mixtures the infrared spectroscopic detection of diimine is inconclusive, being self-contradictory in detail in the various studies; the diimine was described as a yellow compound unstable above −150 °C.

In the thermolysis of alkali-metal tosylhydrazides *(1)*, which are readily accessible from tosylhydrazine and alkali-metal bis(trimethylsilyl)amides in benzene, we have found a process yielding diimine in isolable quantities.



The thermolysis of *(1)* must be carried out in a high vacuum ($<10^{-4}$ torr) in order largely to exclude subsequent disproportionation of the diimine by a reaction of higher order[3].



(As was proved by mass spectroscopy, diimine can be passed without loss at pressures of $<10^{-4}$ torr and room temperature through meter-long glass tubes.) Of especial preparative advantage is the fact that both *(1)* and the product Tos-M are involatile in the high vacuum.

As was found by mass spectroscopy, thermal decomposition of *(1)* gives nitrogen and hydrazine along with the diimine[13]. Apparently, when diimine is liberated from *(1)*, there are pressure conditions on the surface or in the interior of the crystals that lead to partial disproportionation of the diimine. The proportion of interfering "side reaction" in the total conversion decreases with decrease in the temperature of thermolysis and in the series *(1)*-Li > *(1)*-K > *(1)*-Na (Table 1).

Table 1. Formation of diimine on thermolysis of *(1)*.

	Optimal [a] thermolysis temp. (°C)	Proportion of diimine in the thermolysis gas (%) [b]
(1)-Li	80	40
(1)-Na	60	80
(1)-K	45	60

[a] Formation of about 1/10 mmol of diimine per h (cf. Experimental).
[b] Determined by mass spectroscopy.

After being passed through a tube cooled by dry ice, the gas mixture produced by thermolysis of *(1)* consists almost wholly of diimine and nitrogen[13]. If it is passed over a finger cooled to −196 °C (liquid nitrogen), the diimine is deposited as a brilliant yellow film. Diimine can thus be obtained in any desired amount, and its properties can be examined[14]. It can be sublimed off the cold finger at about −165 °C with partial decomposition *(ca.* $^1/_3$*)* (vapor pressure at −165 °C: *ca.* 10^{-6} torr)[15].

The mass spectrum (70 eV) of gaseous diimine contains, besides the molecular ions $N_2H_2^+$ (measured ionization potential 9.9 ± 0.3 eV; lit., 9.85 ± 0.1 eV[5]) and $N_2H_2^{2+}$, mainly ions with an intact nitrogen chain (HN_2^+, N_2^+), while ions with a cleaved nitrogen chain (H_2N^+, HN^+, N^+) appear with only low intensity.

Solid diimine decomposes very readily. Even brief irradiation by a flash at −196 °C or removal of the cooling medium suffices to introduce decoloration within a few seconds, release of nitrogen, and blistering of the deposit on the cold-finger. Nitrogen and hydrazine are the main compounds thus produced. As well as this *disproportionation* (around 90%) there is also *dimerization* of diimine to produce ammonium azide (cf.[16]) and—to a much smaller extent—*decomposition* of diimine to nitrogen and hydrogen or *cleavage* of diimine to nitrogen and ammonia.

Experimental:

For preparation of *(1)*, an alkali-metal bis(trimethylsilyl)-amide (alkali metal = lithium, sodium, or potassium)[17] (20 mmol) in anhydrous benzene (40 ml) is added dropwise over 2 h to a well stirred suspension of tosylhydrazine (20 mmol) in anhydrous benzene (250 ml) at room temperature. After reaction for 10 h, the finely crystalline *(1)* is filtered off and washed several times with anhydrous benzene (all operations with exclusion of water). The product is then dried in a high vacuum to a vapor pressure of $<10^{-6}$ torr.

The products formed on thermolysis of *(1)* are drawn by an efficient high-vacuum pump, first through a 1.6-m tube cooled to −78 °C and then through a double-walled vessel shielded from light and provided with a finger cooled to −196 °C. If *(1)* is heated just strongly enough for the pressure beyond the cold finger not to exceed 10^{-4} torr, then $^1/_{10}$ mmol of pure diimine is deposited on the cold finger per hour.

Received: July 3, 1972 [Z 673 IE]
German version: Angew. Chem. *84*, 889 (1972)

[*] Prof. Dr. N. Wiberg, Dr. H. Bachhuber, and Dipl.-Chem. G. Fischer
Institut für Anorganische Chemie der Universität
8 München 2, Meiserstrasse 1 (Germany)

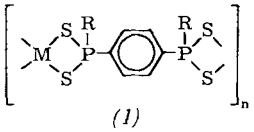
[1] Part 12 of Diimine and its Derivatives. This work was supported by the Deutsche Forschungsgemeinschaft. – Part 11: *N. Wiberg* and *W. Uhlenbrock*, Chem. Ber. *105*, 63 (1972).

[2] The name diimine for "neutral" N_2H_2 is preferable to the name diimide that is customary in the Anglo-Saxon literature. The name diazene would be welcome.
[3] Reviews: *S. Hünig, H. R. Müller*, and *W. Thier*, Angew. Chem. *77*, 368 (1965); Angew. Chem. internat. Edit. *4*, 271 (1965); *Ch. E. Miller*, J. Chem. Educ. *42*, 254 (1965); *A. Veefkind*, Chem. Tech. (Amsterdam), *23*, 69 (1968).
[4] *D. P. Wong, W. H. Fink*, and *L. C. Allen*, J. Chem. Phys. *52*, 6291 (1970), and further literature cited.
[5] *S. N. Foner* and *R. L. Hudson*, J. Chem. Phys. *28*, 719 (1958).
[6] *E. J. Corey* and *W. L. Mock*, J. Amer. Chem. Soc. *84*, 685 (1961).
[7] *K. H. Homann, D. E. MacLean*, and *H. G. Wagner*, Naturwissenschaften *52*, 12 (1965).
[8] *D. E. Milligan* and *M. E. Jacox*, J. Chem. Phys. *41*, 2838 (1964).
[9] *K. Rosengren* and *G. C. Pimentel*, J. Chem. Phys. *43*, 506 (1965).
[10] *E. J. Blau* and *B. F. Hochheimer*, J. Chem. Phys. *41*, 1174 (1964).
[11] *A. Trombetti*, J. Chem. Soc. *A 1971*, 1086.
[12] *D. A. Dows, G. C. Pimentel*, and *E. Whittle*, J. Chem. Phys. *23*, 1606 (1955).
[13] Apparently there is also a small amount of decomposition of *(1)* to give NH_3 and H_2.
[14] The physical and chemical properties of diimine will be reported in subsequent publications.
[15] At −183 °C (liquid oxygen) diimine is metastable and involatile.
[16] *N. Wiberg* and *W. Uhlenbrock*, Angew. Chem. *82*, 47 (1970); Angew. Chem. internat. Edit. *9*, 70 (1970); Chem. Ber. *105*, 63 (1972).
[17] *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).

Coordination-Polymeric Metal Complexes as Stationary Phases in Gas Chromatography

By *Jürgen Delventhal, Helmut Keck*, and *Wilhelm Kuchen*[*]

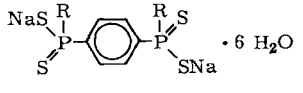
We recently reported the preparation and selective adsorption properties of coordination-polymeric metal complexes[1] of type *(1)* derived from bifunctional dithiophosphinic acids, and also their use for separations by column chromatography. The results induced us to study the use of *(1)* as stationary phases in gas chromatography.



(1)

R = CH_3-O-C$_6$H$_4$- *(a)*, M = $Ni^{(II)}$ *(b)*, M = $Co^{(II)}$

For this purpose we applied the complexes *(1a)* and *(1b)* to Chromosorb (WAWDMCS 80—100 mesh) by the



(2), R = CH_3-O-C$_6$H$_4$-

following method: The Chromosorb was suspended in an aqueous solution of disodium *p*-phenylenebis(*p*-methoxyphenyldithiophosphinate) *(2)*, and the suspension was slowly evaporated to dryness in a rotary evaporator at *ca.* 40 °C and water-pump vacuum. The residue was treated with an aqueous-methanolic (1 : 1) solution of $NiCl_2 \cdot 6H_2O$ or $CoSO_4 \cdot 7H_2O$ and the mixture was again evaporated as described above. The proportions of the components are chosen so that a Chromosorb loaded with 4 wt.-% of metal complex results, assuming quantitative complex formation. This product is washed thoroughly with water and dried for 12 h at 100 °C. The pale green powder is filled into glass columns which are then heated for a further 12 h at 100 °C in a stream of helium. The relative retention volumes for the various Lewis bases shown in Table 1 were determined with these columns.

Table 1. Relative retention volumes of some Lewis bases in gas chromatography on Chromosorb containing *(1a)* or *(1b)*. Gas chromatograph: 5750 D Hewlett-Packard. Column length 1500 mm, internal diameter 1.5 mm. Carrier gas: 42 ml He/min, temp. 100 °C isothermal. Detector WLD (320 °C). Injection block: 250 °C. Paper movement: 2.5 cm/min. Bridge current: 150 mA. Standard: [a] diethylamine, [b] *N,N*-dimethylbenzylamine.

Lewis base	Chromosorb with 4 wt.-% of *(1a)*	*(1b)*
Pyridine	1.57 [a]	1.36 [a]
Tributylamine	3.02 [a]	2.66 [a]
N,N-Dimethylbenzylamine	2.77 [a]	1.94 [a]
N,N-Dimethyl-2-ethylhexylamine	2.07 [a]	1.69 [a]
2-(Dimethylamino)ethanol	1.62 [a]	1.41 [a]
Dimethylaniline	4.85 [a]	2.11 [a]
Dimethylcyclohexylamine	1.84 [a]	1.72 [a]
Triethylamine	0.54 [b]	0.46 [b]
Thiophene	0.49 [b]	0.54 [b]

We believe that the main advantage of the column packings described above is their thermal and chemical stability, for the retention volumes of the Lewis bases as well as the throughput of gas remained constant even after many hours of use.

Received: June 28, 1972 [Z 674 IE]
German version: Angew. Chem. *84*, 832 (1972)

[1] *W. Kuchen, J. Delventhal*, and *H. Keck*, Angew. Chem. *84*, 485 (1972); Angew. Chem. internat. Edit. *11*, 435 (1972).

[*] Dipl.-Chem. J. Delventhal, Dipl.-Chem. H. Keck, and Prof. W. Kuchen
Institut für Anorganische Chemie der Universität
4 Düsseldorf, Ulenbergstrasse 127/129 (Germany)

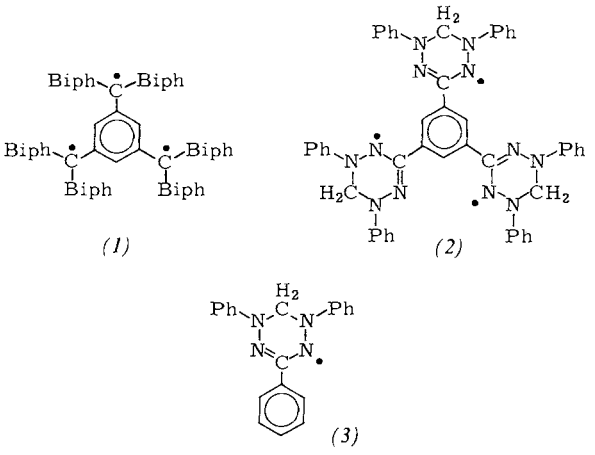
1,3,5-Benzenetriyltris(1,5-diphenyl-3-verdazyl): A Radical Having a Nearly Degenerate Doublet-Quartet Ground State

By *Gerd Kothe, Franz A. Neugebauer*, and *Herbert Zimmermann*[*]

Organic radicals with three unpaired electrons (three-spin systems) have been known for only a few years. As was shown recently, the three-spin system *(1)*[1] has a quartet ground state with parallel spins of the radical electrons[2].

[*] Dr. Gerd Kothe and Prof. Dr. Herbert Zimmermann
Institut für Physikalische Chemie der Universität
78 Freiburg, Albertstrasse 21 (Germany)
Doz. Dr. Franz A. Neugebauer
Max-Planck-Institut für medizinische Forschung
69 Heidelberg, Jahn-Strasse 29 (Germany)

The ESR spectrum of *(1)* can be interpreted quantitatively on the assumption that there is strong magnetic dipole coupling[2-4]. Similar magnetic properties are expected for the three-spin system *(2)* which was described recently by *Kuhn, Neugebauer,* and *Trischmann*[5,6].



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

However, previous measurements of the solid substance on the magnetic balance showed a paramagnetic susceptibility indicating three decoupled radical electrons[5,6]. Accordingly, *(2)* would be a true triradical and is to be considered as a three-fold monoradical without interaction between the radical electrons. The same paramagnetic susceptibility would, however, be obtained by finite interaction between the radical electrons if *(2)* consisted of a mixture of radicals in the doublet and the quartet state, in which the two radical species differed only slightly energetically and had the same occupancy of the corresponding electronic states. Unlike the situation for a quartet where the electron spins are parallel (↑ ↑ ↑), in the doublet the spins of two of the radical electrons compensate each other (↑ ↓ ↑) and the system then has the paramagnetic susceptibility χ_D of a monoradical. The limiting cases just discussed can be distinguished by ESR spectroscopy. We report here such investigations for *(2)*.

We have investigated the temperature- and concentration-dependence of the molar paramagnetic susceptibility χ of the radical *(2)* in dimethylformamide by quantitative ESR spectroscopy. The measuring set-up has been described previously[7]. The range of concentration was 6.7×10^{-5} to 2.7×10^{-4} mol/liter, and was limited by the solubility of the radical and the sensitivity of the apparatus. The temperature-dependence of χ was determined from $T = 230$ to $T = 340$ K[8].

The molar paramagnetic susceptibility χ/χ_D, referred to the susceptibility χ_D of a free monoradical as standard, was independent of the concentration or temperature within experimental error; it amounted to $\chi/\chi_D = 3$. This value accords with previous measurements of the solid substance on the magnetic balance and indicates either a triradical with decoupled radical electrons or a mixture of molecules with doublet and quartet ground states respectively. For a three-spin system with the quartet-doublet separation $J = E_{quartet} - E_{doublet}$ we have:

$$\chi/\chi_D = (1 + 5e^{-J/RT})/(1 + e^{-J/RT}) .$$

The expression accounts for the four doublet and four quartet spin functions in this system[9]. If the quartet-doublet separation in the temperature range studied is $|J| \ll RT$, then $\chi/\chi_D = 3$ and the quartet and doublet are nearly degenerate and equally occupied.

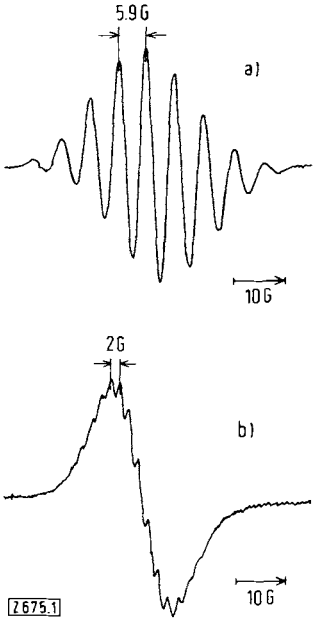


Fig. 1. ESR spectra in DMF at room temperature. a) 1,3,5-Triphenylverdazyl *(3)*. b) 1,3,5-Benzenetriyltris(1,5-diphenyl-3-verdazyl) *(2)*.

For a triradical without interaction an ESR spectrum would be expected that shows approximately the same hyperfine structure as the spectrum of the corresponding monoradical. As Figure 1 shows, the spectra of *(2)* and the monoradical *(3)* are completely different. Apparently *(2)* is not a triradical but is a doublet-quartet mixture in the sense discussed above. To demonstrate the quartet state we have studied the ESR spectrum of a solid glassy solution of the radical in DMF at 93 K (Figure 2); signals

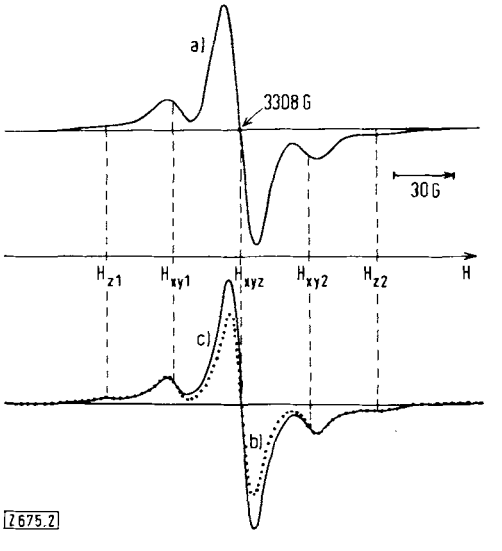


Fig. 2. ESR spectra of *(2)*. a) Experimental spectrum in DMF glass at 93 K. b) Calculated spectrum of the radical in the quartet state, zero field parameter $D' = 28.5$ G, half width of the Lorentz curve $B = 15$ G. c) Superposed spectra of the radical in the quartet and the doublet states, in the proportions 1 : 1, $D' = 28.5$ G, $B = 15$ G.

can be recognized in the $\Delta m = 1$ region which are characteristic of randomly oriented quartet radicals with threefold and higher-fold symmetry axes. They can be described by the spin Hamiltonian:

$$\mathcal{H} = g\beta\vec{H}\vec{S} + D(S_z^2 - \tfrac{1}{3}\vec{S}^2)$$

where g = the isotropic g tensor, β = the Bohr magneton, $\vec{H}$ = the external magnetic field, $\vec{S}$ = the total spin operator with the Cartesian component S_z in the direction of the main axis of rotation of the radical, and D = the zero field parameter.

The operator splits the degenerate quartet states. A first-order perturbation treatment yields the axial resonance field strengths at which the $\Delta m = 1$ transitions appear, as follows:

$$\left.\begin{aligned} H_{xy1} &= H_0 - D' \\ H_{xy2} &= H_0 + D' \end{aligned}\right\} \quad \vec{H} \perp \vec{z}$$

$$\left.\begin{aligned} H_{z1} &= H_0 - 2D' \\ H_{z2} &= H_0 + 2D' \end{aligned}\right\} \quad \vec{H} \parallel \vec{z}$$

$$H_{xyz} = H_0 \qquad \vec{H} \text{ at any orientation to } \vec{z}$$

where $H_0 = h\nu/(g\beta)$, $D' = D/(g\beta)$, ν = the frequency of the microwave field $\vec{H}_1 \perp \vec{H}$.

If the molecular axes $\vec{z}$ are oriented randomly to the direction of the external field $\vec{H}$, the ESR transitions are not limited to the axial resonance field strengths. The resulting ESR spectrum is then the sum of the spectra of the randomly distributed radicals.

If the line width is large or the zero field parameter small, the axial resonance field strengths can no longer be determined directly from the spectrum. In such cases the zero field parameter can be determined by spectral simulation and comparison with the experimental data. The ESR spectrum of *(2)* was calculated by a computer program[4]. For computing reasons a Lorentz curve was chosen as line form. The best agreement between the experimental and the calculated ESR spectrum was obtained with the zero field parameter $D' = 28.5$ G and a half width $B = 15$ G. The calculated spectrum and the corresponding axial resonance field strengths are reproduced in Figure 2. Comparison of Figures 2a and 2b shows the greater intensity of the central peak in the experimental spectrum. The difference is ascribed to the additional ESR absorption of the radical molecules in the doublet state. Superposing on the quartet spectrum a doublet spectrum with the same line form and half width yields the ESR spectrum shown in Figure 2c; in doing this, it was taken into account that the quartet and doublet states are nearly equally occupied and should occur in the ratio 1:1. The experimental and the calculated spectra now agree well. Thus it is shown that *(2)* is a radical with magnetic dipole coupling between the radical electrons, whose ground state is characterized by energetically very similar doublet and quartet states.

Received: July 6, 1972 [Z 675 IE]
German version: Angew. Chem. *84*, 890 (1972)

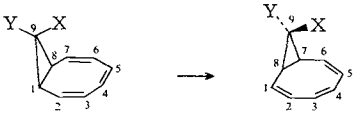
[1] *G. Schmauss, H. Baumgärtel,* and *H. Zimmermann,* Angew. Chem. *77*, 619 (1965); Angew. Chem. internat. Edit. *4*, 596 (1965).
[2] *G. Kothe, E. Ohmes, J. Brickmann,* and *H. Zimmermann,* Angew. Chem. *83*, 1015 (1971); Angew. Chem. internat. Edit. *10*, 938 (1971).
[3] *J. Brickmann* and *G. Kothe,* J. Chem. Phys., in press.
[4] *K. Reibisch, G. Kothe,* and *J. Brickmann,* personal communication.
[5] *R. Kuhn, F. A. Neugebauer,* and *H. Trischmann,* Angew. Chem. *77*, 43 (1965); Angew. Chem. internat. Edit. *4*, 72 (1965).
[6] *R. Kuhn, F. A. Neugebauer,* and *H. Trischmann,* Monatsh. Chem. *97*, 525 (1966).
[7] *E. Ohmes, G. Kothe, A. Naujok,* and *H. Zimmermann,* Ber. Bunsenges. Phys. Chem. *75*, 895 (1971).
[8] We thank Miss *Annemarie Naujok* for help with measurements.
[9] *A. Hudson* and *G. R. Luckhurst,* Mol. Phys. 13, 409 (1967).

A Degenerate Rearrangement of *cis*-Bicyclo[6.1.0]nona-2,4,6-triene[1]

By *Frank Gerrit Klärner*[*]

The thermal behavior of the *cis*-bicyclo[6.1.0]nonatriene system has been very intensively studied. Thus far three types of rearrangement have been reported: the formation of dihydroindenes[2], of *cis*-bicyclo[5.2.0]nona-2,5,8-trienes[3-5], and of bicyclo[4.2.1]nona-2,4,7-trienes[6-9].

We have now discovered a novel type of rearrangement, which in the case studied precedes the competing processes and consists of a degenerate rearrangement of the system.



(1) *(1')*

For experimental detection of this rearrangement *(1)*→*(1')* it was necessary to label the eight-membered ring as well as to provide a substituent on carbon atom 9.

The 4,9-dimethyl-*cis*-bicyclo[6.1.0]nonatriene-9-carbonitriles *(2a)* and *(2b)* were synthesized as model compounds. Bromination of the separated diastereomers *(1a)* and *(1b)*[9], followed by dehydrohalogenation with 1,5-diazabicyclo[4.3.0]non-5-ene[10] and methylation with $Li[Cu(CH_3)_2]$[11] gave only *(2a)* (m.p. 43 °C) and *(2b)* (m.p. 60 °C), respectively[12].

The stereochemistry at C-9 of the epimers *(2a)* and *(2b)* is fixed by that of the starting materials *(1a)* and *(1b)*. That the vinylic methyl group is at position 4 follows from the ^{1}H-NMR spectra in the presence of the paramagnetic europium complex $Eu(DPM)_3$[13]. Under the influence of the europium complex the vinyl protons of *(2a)* and *(2b)* show the same splitting as the corresponding protons of the starting materials *(1a)* and *(1b)*. The intensities of the signals ascribed to the protons H-2, H-3, H-6, H-7 and to H-4 and H-5 in the spectra of *(1a)* and *(1b)* occur for *(2a)* and *(2b)* in the ratio of only 4:1, as expected.

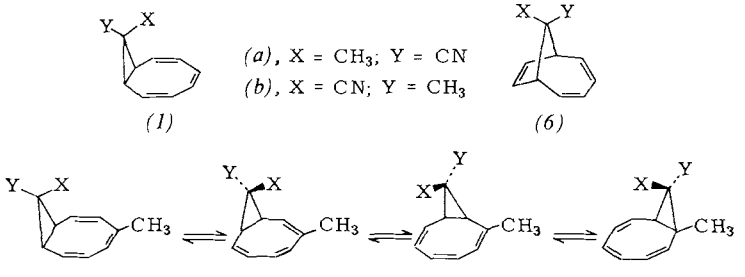
Thermolysis of either *(2a)* or *(2b)* leads, even at 102.5 °C in benzene solution, to complete equilibration of the isomers *(2)* to *(5)* (identified by their ^{1}H-NMR spectra) in the proportions stated (determined by ^{1}H-NMR measurements).

The rate constants[11] $k_{2a\,3a}$ and $k_{2b\,3b} = 1.3 \times 10^{-4}$ and $1.0 \times 10^{-4}\,s^{-1}$, respectively, and hence the free energies of

[*] Dr. F.-G. Klärner
Abteilung für Chemie der Universität
4630 Bochum-Querenburg, Buscheystrasse (Germany)

activation $\Delta F^{+} = 28.8$ and 29.0 kcal/mol, respectively, were determined by following the course of the isomerization *(2)*→*(3)* (up to 10% conversion at 102.5 °C).

Migration of carbon atom 9 around the periphery of the eight-membered ring occurs with high stereospecificity. No *exo-endo*-isomerization of compounds *(2)* to *(5)* was observed under the conditions of the thermolysis, even after reaction for several days. The stereochemical integrity of



	(2)	(3)	(4)	(5)
(a):	35%	33%	21%	11%
(b):	34%	38%	24%	4%

C-9 remains preserved up to a temperature of 180 °C, where *(1)* rearranges to *(6)* (at 180.2 °C: $k_{1a\,6a} = 0.5 \times 10^{-5}\ s^{-1}$; $k_{1a\,6b} = 3.0 \times 10^{-5}\ s^{-1}$; $k_{1b\,6a} = 4.8 \times 10^{-5}\ s^{-1}$; $k_{1b\,6b} = 2.0 \times 10^{-5}\ s^{-1}$)[14]. From the rate constants for the rearrangements *(1)*→*(6)* and *(2)*→*(3)* one can extrapolate that the stereochemistry at C-9 is retained, even after 10^4 reaction steps.

The observed stereochemistry corresponds to inversion at carbon atom C-9 and fulfils the stereochemical requirements for an orbital symmetry controlled process[15]. For the concerted process of the degenerate rearrangement *(1)*→*(1')* all eight orbitals involved in the isomerization must overlap in the transition state. The transition state thus requires that at least seven carbon atoms (C-1 to C-7) become largely coplanar and should show greater conformational strain than the ground state. This geometry has conformation requirements similar to those of the homotropylium cation[16], so that resonance stabilization of the transition state may involve participation of a polar homotropylium structure.

Apart from the stereochemical results, the concerted nature of the rearrangement *(1)*→*(1')* is made plausible by the activation parameters. The difference in free energies of activation for cleavage of the cyclopropane bond (C-1)–(C-9) in the reactions *(1)*→*(1')* and *(1)*→*(6)* amounts to *ca.* 7 kcal/mol and thus suggests an aromatic transition state[17].

Received: July 6, 1972 [Z 678 IE]
German version: Angew. Chem. *84*, 892 (1972)

[1] This work was supported by the Deutsche Forschungsgemeinschaft. The author is grateful to Professor *W. R. Roth* for stimulating discussions.

[2] For a review see: *J. C. Barborak, T.-M. Su, P. von R. Schleyer, G. Boche*, and *G. Schneider*, J. Amer. Chem. Soc. *93*, 279 (1971).
[3] *P. Radlick, W. Fenical*, and *G. Alford*, Tetrahedron Lett. *1970*, 2707.
[4] *A. G. Anastassiou* and *R. C. Griffith*, J. Amer. Chem. Soc. *93*, 3083 (1971).
[5] *L. A. Paquette* and *M. J. Epstein*, J. Amer. Chem. Soc. *93*, 5936 (1971).
[6] *T. J. Katz, C. R. Nicholson*, and *C. A. Reilly*, J. Amer. Chem. Soc. *88*, 3832 (1966).
[7] *E. Ciganeck*, J. Amer. Chem. Soc. *88*, 1979 (1966); *A. G. Anastassiou, R. P. Cellura*, and *E. Ciganeck*, Tetrahedron Lett. *1970*, 5267.
[8] *D. Schönleber*, Chem. Ber. *102*, 1789 (1969).
[9] *F.-G. Klärner*, Tetrahedron Lett. *1971*, 3611.
[10] *H. Oediger, K.-J. Kabbe, F. Möller*, and *K. Eiter*, Chem. Ber. *99*, 2012 (1966).
[11] *E. J. Corey* and *G. H. Posner*, J. Amer. Chem. Soc. *89*, 3911 (1967); *90*, 5615 (1968); *G. M. Whitesides, W. F. Fischer, Jr, J. San Filippo, Jr., R. W. Bashe*, and *H. O. House, ibid. 91*, 4871 (1969); *G. H. Posner* and *C. E. Whitten*, Tetrahedron Lett. *1970*, 4647; *C. P. Casey* and *R. A. Boggs, ibid. 1971*, 2455; *G. H. Posner* and *D. J. Brunelle, ibid. 1972*, 293.
[12] ^{1}H-NMR, IR, UV, and mass spectra have been determined for all the compounds described here and accord with the structures discussed.
[13] *J. K. M. Sanders* and *D. H. Williams*, J. Amer. Chem. Soc. *93*, 641 (1971).
[14] All the rate constants given were determined by NMR spectroscopy with an accuracy of ± 10%.
[15] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).
[16] *J. L. von Rosenberg, Jr., J. E. Mahler*, and *R. Pettit*, J. Amer. Chem. Soc. *84*, 2842 (1962); *S. Winstein, C. G. Kreiter*, and *J. I. Brauman, ibid. 88*, 2047 (1966).
[17] *M. J. S. Dewar*, Tetrahedron Suppl. *8*, 75 (1966); Angew. Chem. *83*, 859 (1971); Angew. Chem. internat. Edit. *10*, 761 (1971).

The Synthesis of Aromatic Bridged Didehydroaza[17]annulenes Bearing Alkyl Substituents Within the Cavity of the π-Electron Cloud[1][**]

By *Philip J. Beeby* and *Franz Sondheimer*[*]

We have recently reported the synthesis of the bridged pyridine *(1)*, and its conversion to aromatic methylene-bridged didehydroaza[17]annulenes [*e.g., (3a)*][1]. The pyridine *(1)* appeared to be a suitable precursor of aromatic didehydroaza[17]annulenes bearing substituents within the cavity of the π-electron cloud. We now report the achievement of this objective, the compounds synthesized [*(3b)—(3e)*] possessing alkyl groups as the substituents. Extensive work on related compounds bearing alkyl groups within the cavity of the π-electron cloud of aromatic bridged [14]annulene (15,16-dihydropyrene) derivatives has already been carried out by *Boekelheide et al.*[2]. The presently described synthesis has the advantage that the substituents are introduced essentially as the last step, making it simple to prepare the various substituted compounds.

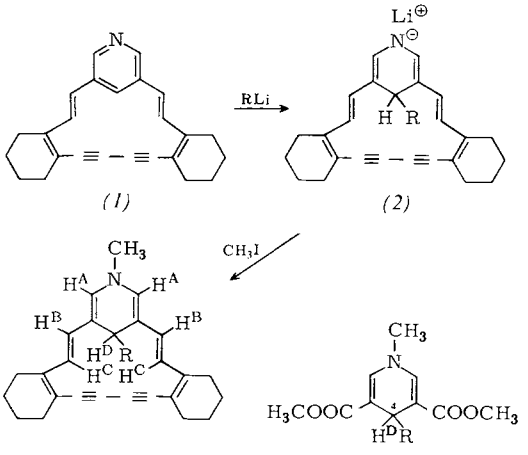
Treatment of *(1)* in dimethoxyethane and tetrahydrofuran (1:1 v/v) with an excess of CH_3Li in ether at 0 °C under N_2 for 15 minutes led to the 1,4-addition product *(2)*, R = Me. Direct methylation with CH_3I (15 min at 0 °C, 15 min at 20 °C), isolation with ether, and rapid chromatography on Al_2O_3 afforded the methyl compound *(3b)*[3] as stable red crystals in 65% yield, m.p. *ca.* 230 °C (decomp.)[4]; λ_{max} ($CHCl_3$) *ca.* 341 sh (ε 43000), 353 (49500), *ca.* 374 sh (28000), 426 (8600), *ca.* 460 sh (7000), *ca.* 500 sh (3500), and *ca.* 536 sh nm (1200).

Similarly, using the appropriate alkyllithium compound, *(1)* was converted to the ethyl derivative *(3c)* [75%, m.p. *ca.* 230 °C (decomp.)], the *n*-propyl compound *(3d)* [85%, m.p. *ca.* 200 °C (decomp.)], and the *n*-butyl compound *(3e)* [70%, m.p. *ca.* 220 °C (decomp.)].

[*] Dr. P. J. Beeby and Prof. Dr. F. Sondheimer
Chemistry Department, University College
Gordon Street, London WC1H OAJ (England)

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

The NMR spectra of the aza[17]annulenes *(3b)—(3e)* (100 MHz, $CDCl_3$) were almost identical, except for the bridge substituents, and exhibited bands at $\tau = 2.87$ (s, H^A), 2.47 (d, $J = 16.0$ Hz, H^B), 6.55 (d, $J = 16.0$ Hz, H^C), and

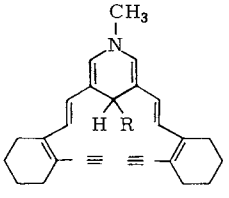


(3a), R = H
(3b), R = CH_3
(3c), R = C_2H_5
(3d), R = n-C_3H_7
(3e), R = n-C_4H_9

(4a), R = H
(4b), R = CH_3
(4c), R = C_2H_5
(4d), R = n-C_3H_7
(4e), R = n-C_4H_9

6.39 (s, N—CH_3). These spectra show the compounds to be diatropic (see Ref. [1]), although the diamagnetic ring current is appreciably less than in *(3a)* [$\tau = 2.79$(s, H^A), 2.34 [d, $J = 16.0$ Hz, H^B), 7.29 (d, $J = 16.0$ Hz, H^C), and 6.30 (s, N—CH_3)]. The decreased ring current in *(3b)—(3e)* is presumably due to the greater deviation from planarity caused by the alkyl groups.

In order to have available models for comparison of the NMR resonances of the bridge substituents in *(3b)—(3e)*, the 4-alkyl diesters *(4b)—(4e)* were prepared. They were synthesized by treatment of dimethyl pyridine-3,5-dicarboxylate[1] with the appropriate Grignard reagent, followed by reaction of the resulting 1,4-dihydropyridine[5] with NaH in dimethoxyethane and finally with CH_3I [*(4b)*, m.p. 61—62 °C; *(4c)*, m.p. 134—135 °C; *(4d)*, m.p. 107—108 °C; *(4e)*, m.p. 59—60 °C]. The diesters *(4b)—(4e)* appear to be suitable models, since in the NMR spectrum of the unsubstituted diester *(4a)* (m.p. 132—134 °C, prepared by *N*-methylation of dimethyl pyridine-3,5-dicarboxylate[1], and subsequent reduction with sodium dithionite[5]) the 4-H protons ($\tau = 6.80$) resonate at essentially the same position as in *(5a)*[1] ($\tau = 6.85$)[6].



(5a), R = H
(5b), R = Alkyl

The chemical shifts of the bridge substituent protons in the NMR spectra of *(3b)—(3e)*, as well as those of the corresponding protons in *(4b)—(4e)* are given in Table 1. The differences in chemical shift on passing from the model to the corresponding aza[17]annulene are given in parentheses. As expected, this difference is most extreme in the case of H^D (*ca.* +3.25 ppm); it decreases as the proton is further removed from the mean plane, although it is still appreciable for the δ protons (*ca.* +0.3 ppm).

Received: June 26, 1972 [Z 684a IE]
German version: Angew. Chem. *84*, 896 (1972)

[1] Unsaturated Macrocyclic Compounds. Part 91.–Part 90: *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972).
[2] *V. Boekelheide et al.*, J. Amer. Chem. Soc. *85*, 1545 (1963); *89*, 1695, 1704, 1709 (1967); *91*, 4931 (1969); *92*, 3669, 3675 (1970).
[3] The *N*-methyl compounds were studied, since they are more aromatic and more stable than the corresponding N–H compounds [1].
[4] Satisfactory elemental analyses and mass spectral data were obtained for all new compounds.
[5] *P. J. Brignell, U. Eisner*, and *P. G. Farrell*, J. Chem. Soc. *B 1966*, 1083.
[6] Attempts to prepare the models *(5b)* from the corresponding pyridine [1] by methods analogous to those used for the synthesis of *(3b)–(3e)* were unsuccessful.

The Synthesis of Stereoisomeric Bisdehydrothia-[17]annulenes and Their Dioxides[1][**]

By *Richard H. McGirk* and *Franz Sondheimer*[*]

Heteroannulenes of the pyrrole type may be diatropic ("aromatic") if they are $(4n+1)$-membered, and paratropic ("anti-aromatic") if they are $(4n+3)$-membered, provided the heteroatom can contribute two π-electrons to the delocalized system[2]. The only known macrocyclic heteroannulenes of this type to show significant ring current effects contain bridging groups[1, 3], and it was of interest to prepare unbridged members[4] to discover whether similar effects could be observed.

[*] Dr. R. H. McGirk and Prof. Dr. F. Sondheimer
Chemistry Department, University College
Gordon Street, London WC1H OAJ (England)

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

Table 1. ^{1}H-NMR chemical shift data (τ values, 100 MHz, $CDCl_3$) of compounds *(3b)–(3e)* and *(4b)–(4e)*.

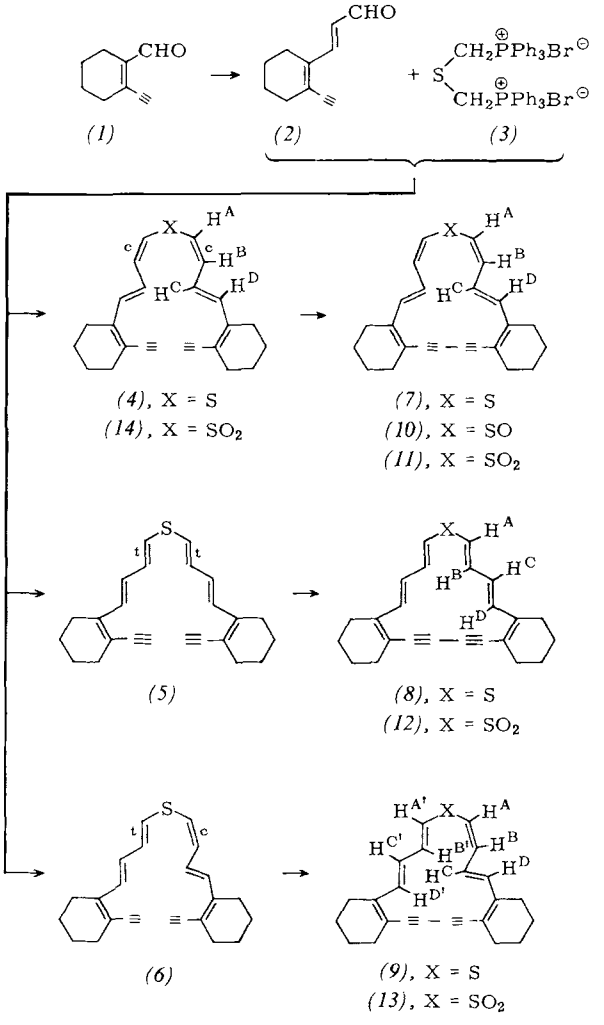
Compound	H^D	H^α	H^β	H^γ	H^δ
(3b)	9.49 (+3.24)	10.52 (+1.55)	—	—	—
(3c)	9.41 (+3.26)	10.14 (+1.56)	10.14 (+0.90)	—	—
(3d)	9.40 (+3.24)	10.09 (+1.45)	9.75 (+0.95)	9.75 (+0.56)	—
(3e)	*ca.* 9.4 (*ca.* +3.2)	10.11 (+1.46)	9.81 (*ca.* +1.0)	*ca.* 9.4 (*ca.* +0.6)	*ca.* 9.5 (*ca.* +0.3)
(4b)	6.25	8.97	—	—	—
(4c)	6.15	8.58	9.24	—	—
(4d)	6.16	8.64	8.80	9.19	—
(4e)	6.17	8.65	*ca.* 8.8	*ca.* 8.8	9.19

Homologation of *(1)*[5] by conversion to the diethyl acetal, condensation with ethyl vinyl ether and hydrolysis[6] gave *(2)* (45%, m.p. 58—59 °C[7], isolated by chromatography on SiO_2). Wittig reaction of *(3)*[8] and 2 molar equivalents of *(2)* in dimethylformamide with ethanolic lithium ethoxide at 70 °C, followed by chromatography on SiO_2 and crystallization, led to *(4)* (15%, pale yellow; stereochemistry established by analysis of the NMR spectrum in C_6D_6). The mother liquors consisted of *(5)* and *(6)* (64%), which could not be separated. Oxidative coupling of *(4)* with cupric acetate in pyridine (2 h at 55 °C) yielded the didehydrothia[17]annulene *(7)* [13%, light orange, m.p. 157—159 °C (decomp.)]. Similar coupling of the mixture of *(5)* and *(6)* led to *(8)* (10%, light orange) and *(9)* [3.5%, yellow, m.p. 121—124 °C (decomp.)].

Table 1. Some ^{1}H-NMR parameters of compounds *(4)* and *(7)*—*(14)* in $CDCl_3$ at 100 MHz (τ; *J* values in Hz).

Compound	Olefinic H atoms	Allylic H atoms
(4)	H^A, H^B, H^C, 3.32—4.01 (m) H^D, 3.02 (d, J = 15)	7.55—7.85 (m)
(7)	3.1—4.25 (m)	7.35—7.65 (m)
(8) [a]	H^A, 4.18 (d, J = 15), H^B, 4.73 (dd, J = 9,15) H^C, 3.19 (dd, J = 9, 15.5), H^D, 4.99 (d, J = 15.5)	7.30—7.60 (m)
(9)	3.2—4.2 (m)	7.45—7.95 (m)
(10) [a]	H^A, 3.99 (d, J = 11), H^B, 3.62 (dd, J = 11) H^C, 0.80 (dd, J = 11,16), H^D, 4.12 (d, J = 16)	7.75—8.05 (m)
(11) [a]	H^A, 4.32 (d, J = 11), H^B, 3.65 (dd, J = 11), H^C, —0.06 (dd, J = 11,16), H^D, 4.24 (d, J = 16)	7.75—8.10 (m)
(12) [a]	H^A, 4.35 (d, J = 15), H^B, 2.78 (dd, J = 5,15), H^C, H^D, 3.57 (m)	7.45—7.75 (m)
(13) [a]	H^A, 3.77 (d, J = 11), H^B, 3.50 (dd, J = 11), H^C, 2.20 (dd, J = 11,15), H^D, 3.72 (d, J = 15), $H^{A'}$, 2.46 (d, J = 15), $H^{B'}$, 3.06 (dd, J = 6,15), $H^{C'}$, 3.87 (dd, J = 6,15.5), $H^{D'}$, 1.69 (d, J = 15.5)	7.65—8.10 (m)
(14) [a]	H^A, 3.93 (d, J = 10.5), H^B, 3.28 (dd, J = 10.5), H^C, H^D, 2.73 (m)	7.55—7.85 (m)

[a] The assignments and conformations are based on decoupling experiments, nuclear Overhauser experiments, solvent shifts and/or NMR measurements in presence of Eu(fod)$_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III)].



Oxidation of *(7)* with *m*-chloroperbenzoic acid in CH_2Cl_2 at −20 °C for 2 hours yielded the sulfoxide *(10)* (90%, orange-red), while oxidation at 20 °C for 4 hours gave the sulfone *(11)* (60%, red). Similar oxidation of *(8)* and *(9)* at 20 °C for 4 hours led to *(12)* (85%, pale yellow) and *(13)* (60%, light orange), respectively. The stereochemical assignments of the sulfones *(11)*, *(12)* and *(13)* were based on the NMR spectra (Table 1). For comparison, *(4)* was similarly oxidized to the sulfone *(14)* (50%, yellow).

The didehydrothia[17]annulenes *(7)*, *(8)* and *(9)* are potentially diatropic (18π-electrons), and the sulfones *(11)*, *(12)* and *(13)* paratropic (16π-electrons), provided they are reasonably coplanar. Examination of the NMR spectra of these compounds (Table 1) shows that two possess small ring currents: The sulfide *(8)* appears to be diatropic, since the inner H^B and H^D protons resonate at significantly higher field than in *(4)*, the closest available model [H^D, +1.97 ppm; H^B (in C_6D_6), +0.86 ppm]; there is a corresponding downfield shift of the allylic protons (−0.25 ppm) and of H^C (exact shift unknown), but not of H^A[9]. The sulfone *(11)* appears to be paratropic, since the inner H^C protons resonate at lower field (−2.79 ppm) than in the model *(14)*, while the outer protons resonate at higher field (H^A, +0.39; H^B, +0.37; H^D, +1.51; allyl protons, *ca.* +0.25 ppm). Comparison of the NMR spectra of *(10)* and *(11)* shows that the sulfoxide *(10)* is also paratropic.

Received: June 26, 1972 [Z 684b IE]
German version: Angew. Chem. *84*, 897 (1972)

[1] Unsaturated Macrocyclic Compounds. Part 92.–Part 91: *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *84*, 896 (1972); Angew. Chem. internat. Edit. *11*, 833 (1972).

[2] *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972).

[3] *H. Ogawa, M. Kubo*, and *H. Saikachi*, Tetrahedron Lett. *1971*, 4859; *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972).
[4] *G. Schröder, G. Plinke*, and *J. F. M. Oth*, Angew. Chem. *84*, 472 (1972); Angew. Chem. internat. Edit. *11*, 424 (1972); *G. Schröder, G. Heil, H. Röttele*, and *J. F. M. Oth*, Angew. Chem. *84*, 474 (1972); Angew. Chem. internat. Edit. *11*, 426 (1972).
[5] *P. Schiess* and *H. L. Chia*, Helv. Chim. Acta *53*, 485 (1970); *G. M. Pilling* and *F. Sondheimer*, J. Amer. Chem. Soc. *93*, 1970 (1971).
[6] *O. Isler, H. Lindlar, M. Montavon, H. Rüegg*, and *P. Zeller*, Helv Chim. Acta *39*, 249 (1956); *H. Rüegg, M. Montavon, G. Ryser, G. Saucy, U. Schwieter*, and *O. Isler, ibid. 42*, 854 (1959).
[7] UV, IR and mass spectra compatible with the assigned structures were obtained for all compounds. All substances, unless indicated otherwise, were isolated by chromatography on Al_2O_3 (activity II), and consisted of crystals which decomposed on attempted melting point determination.
[8] *K. Dimroth, H. Follmann*, and *G. Pohl*, Chem. Ber. *99*, 642 (1966).
[9] In fact, H^A in the NMR spectrum of *(8)* resonates at higher field than that in *(4)*. There is no obvious explanation for this observation, and similar effects of α-protons in cyclic unsaturated sulfides have been observed [*E. Vogel, R. Feldmann, H. Düwel, H. D. Cremer*, and *H. Günther*, Angew. Chem. *84*, 207 (1972); Angew. Chem. internat. Edit. *11*, 217 (1972)].

Conjugation in Aromatic Amines and Phosphanes[1]

By *Werner Schäfer* and *Armin Schweig*[*]

The differing conjugative interaction between the lone pair on a nitrogen(III) and that on a phosphorus(III) atom with an aromatic system has recently become the object of intensive research[2]. With the aid of the photoelectron (PE) spectra[3] of *N,N*-dimethylaniline[4] *(1)* and dimethylphenylphosphane *(2)* we have now been able to provide clear proof of the differing interactions in these compounds and to depict them directly in a manner that cannot be realized by any other technique.

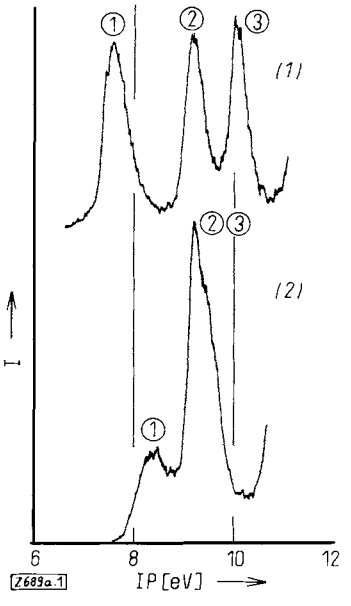


Fig. 1. Photoelectron spectra of *N,N*-dimethylaniline *(1)* and dimethylphenylphosphane *(2)*.

The PE spectra reproduced in Figure 1 show three almost equally intense resolved bands for *(1)* in the region of low ionization potentials at 7.6, 9.2, and 10.0 eV, and two bands of differing intensity for *(2)* at 8.4_5 and 9.2 eV. The ionization potentials (*IP*) of the lone pairs in trimethylamine *(3)* and trimethylphosphane *(4)* are 8.5[5] and 8.6 eV[6], respectively; the degenerate π orbital of benzene lies at 9.24 eV[4]. These data suggest that the band ① corresponding to the HOMO in the compounds *(1)* and *(2)* should be assigned to the lone pair. Depending upon the extent of conjugation, the antibonding interaction with the system should raise this orbital while the corresponding bonding linear combination should be stabilized by about the same amount (see Fig. 2).

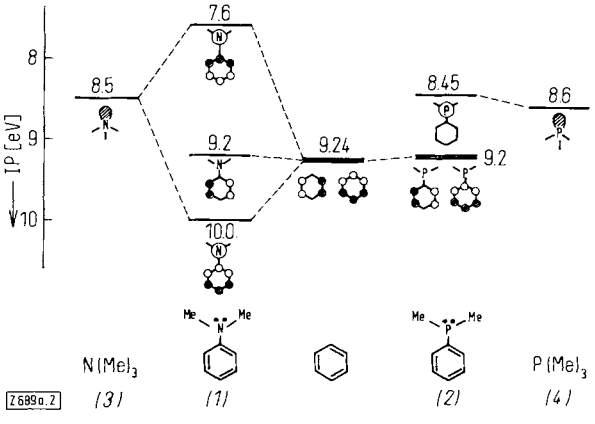


Fig. 2. Correlation diagram of the relevant highest occupied MOs of trimethylamine *(3)*, *N,N*-dimethylaniline *(1)*, benzene, dimethylphenylphosphane *(2)*, and trimethylphosphane *(4)*. The hatched (unhatched) circles in the six-membered ring indicate negative (positive) sings of the p_π-AOs on the respective atoms. The larger circles on the heteroatoms symbolize the lone pairs which are not oriented parallel to the p_π-AOs.

In the case of *(1)* the HOMO is destabilized by 0.9 eV by this antibonding interaction; the corresponding π orbital having a non-zero coefficient at the point of linkage is lowered by 0.76 eV as bonding combination (band ③). The π-MO having a node at the point of linkage stays at a constant *IP* of 9.2 eV (band ②). In the phosphane *(2)*, however, the HOMO is raised only slightly by 0.15 eV and the bands ② and ③ corresponding to the degenerate benzene π-MOs show no splitting.

The above results indicate, directly and unequivocally, that there are two practically uncoupled partial systems (the benzene system and the lone pair in the trialkylphosphane system) in dimethylphenylphosphane *(2)* in contrast to the situation in *N,N*-dimethylaniline *(1)*.

Received: May 29, 1972 [Z 689a IE]
German version: Angew. Chem. *84*, 898 (1972)

[*] Dipl.-Chem. W. Schäfer and Prof. Dr. A. Schweig
Fachbereich Physikalische Chemie der Universität
355 Marburg, Biegenstrasse 12 (Germany)

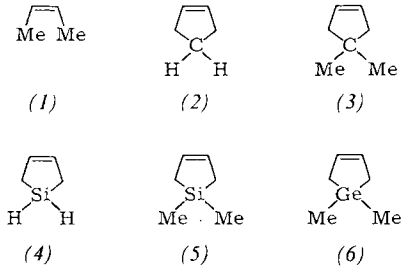
[1] Theory and Application of Photoelectron Spectroscopy, Part 13. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie. – Part 12: *W. Thiel* and *A. Schweig*, Chem. Phys. Lett., in press.

[2] *E. N. Tsvetkov* and *M. I. Kabachnik*, Russ. Chem. Rev. *40*, 97 (1971); *R. F. Hudson*: Structure and Mechanism in Organophosphorus Chemistry. Academic Press, London 1965.
[3] The He-I (584 Å) photoelectron spectra were recorded on a PS 16 spectrometer produced by Perkin-Elmer Ltd., Beaconsfield (England).
[4] *A. D. Baker, D. P. May*, and *D. W. Turner*, J. Chem. Soc. *B 1968*, 22; and *D. W. Turner, C. Baker*, and *C. R. Brundle*: Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970; *J. Daintith, J. P. Maier, D. A. Sweigart*, and *D. W. Turner*: Electron Spectroscopy. North Holland, Amsterdam 1972, p. 289.
[5] *A. B. Cornford, D. C. Frost, F. G. Herring*, and *C. A. McDowell*, Can. J. Chem. *49*, 1135 (1971).
[6] *I. Hillier*, and *V. R. Saunders*, Trans. Farad. Soc. *76*, 2401 (1970).

Photoelectron Spectroscopy and Transannular Interactions—The Question of Transannular d-π Interactions in 1-Sila- and 1-Germa-3-cyclopentenes[1]

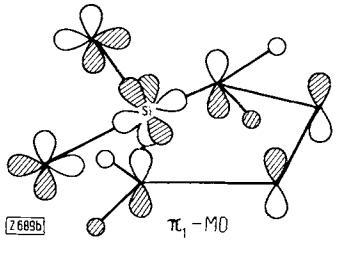
By *Armin Schweig, Ulrich Weidner,* and *Georges Manuel*[*]

Unlike cyclopentene *(2)*, 1-sila-3-cyclopentene *(4)* and 1,1-dimethyl-1-germa-3-cyclopentene *(6)* have been shown by vibrational spectroscopy[2, 3] and theory[4] to have a planar ring. A transannular interaction[5] between the d-AOs on the Si atom and the π-MO of the ethylene system (d-π interaction) has been postulated to account for the planarity of *(4)*[3]. In the present communication we present evidence from photoelectron spectroscopy and quantum chemistry that definitely rules out any such interaction.



(1) *(2)* *(3)* *(4)* *(5)* *(6)*

In accord with model calculations[6] the two highest occupied π-MOs in *(5)*[7] can be regarded approximately as an antibonding (π_1: nodes over both Si—C ring bonds) and a bonding combination (π_2: no nodes over the Si—C ring bonds) of the H-C hyperconjugative antibonding π-MOs of *cis*-2-butene *(1)* on the one hand and the combination of the two extraannular Si—C MOs that is antisymmetric with regard to the molecular plane on the other hand. Alongside these two π-MOs we predict an antibonding (δ_1) and a bonding combination (δ_2) of the two ring Si—C MOs as further high-energy MOs.



PE measurements show the π_1-MO in *(1)* to lie at 9.33 eV and that in *(2)* at 9.18 eV[8]. Si—C ionization in tetramethylsilane Me_4Si occurs at 10.5 eV[9], and ionization of the σ- and π-Si—C combinations of correct symmetry for *(5)* is found to take place at 10.0, 10.6, and 11.0 eV in dimethyldivinylsilane $Me_2Si(CH{=}CH_2)_2$[10]. The comparison values form the basis for the MO assignment of the PE bands of *(5)* as shown in Figure 1[11]. The same assignments are also valid for the analogous germanium compound. The observed shift of the bands (0.3—0.5 eV)[12] of the second PE peak, which is essentially ascribable to Ge—C MOs, is in accord with such an assignment.

The above analysis shows the HOMOs of the systems *(2)* to *(6)* to contain the HOMO of *(1)* as one partial system

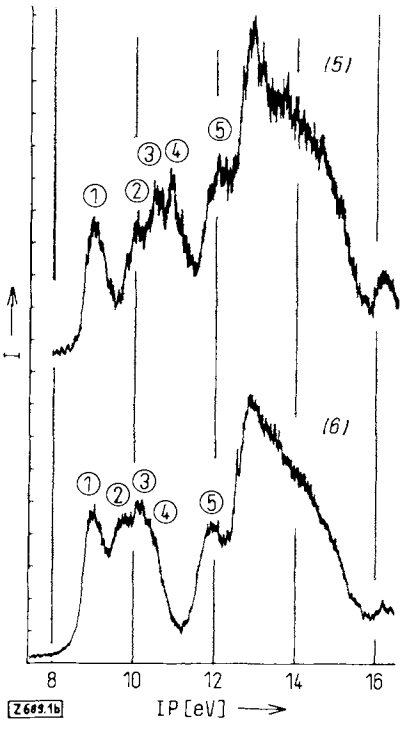


Fig. 1. Photoelectron spectra [15] of 1,1-dimethyl-1-sila-3-cyclopentene *(5)* and 1,1-dimethyl-1-germa-3-cyclopentene *(6)*. The vertical ionization potentials (in eV), relative corrected [16] intensities, and assignments of the bands 1 to 5 are: for *(5)*: ① 9.0/1/π_1; (②, ③, ④) (10.0/0.9, 10.5 1.0, 10.9/1.3)/(σ_1, π_2, σ_2) [11] ⑤ 12.0/?; – for *(6)*: ① 9.0/1/π_1; (②, ③, ④)/(9.7/1.0, 10.15/0.9, 10.4/0.9)/(σ_1, π_2, σ_2) [11]: ⑤ 12.0/?.

and a π-type MO of the groups $-CH_2-$, $-CMe_2-$, $-SiH_2-$, $-SiMe_2-$, or $-GeMe_2-$ as the other partial system. Hyperconjugative antibonding coupling of the two partial systems effects the following observed (PE) or calculated (MINDO/2) HOMO shifts relative to *(1)*: 0.15 eV (PE) for *(2)*; 0.25 eV (MINDO/2) for *(3)*; 0.33 eV (PE) for *(5)* and *(6)*. The small differences and the tendency shown by this series of values unequivocally rule out a significant symmetry-allowed and likewise antibonding transannular d-π interaction (see the representation of this MO). On the contrary, model calculations taking account of d-AOs indicate a HOMO stabilization in agreement with a previously developed d-AO bonding model[13]. This result clearly shows that the d-AO participation in the HOMO is effective in the $-SiMe_2-$ ($-GeMe_2-$) bonds (bonding) and not in a transannular fashion (antibonding).

Received: July 11, 1972, [Z 689b IE]
German version: Angew. Chem. *84*, 899 (1972)

[*] Prof. Dr. A. Schweig and Dipl.-Chem. U. Weidner
Fachbereich Physikalische Chemie der Universität
355 Marburg, Biegenstrasse 12 (Germany)

Dr. G. Manuel
Laboratoire des Organométalliques
Université Paul Sabatier
118, route de Narbonne
F-31 Toulouse (France)

[1] Theory and Application of Photoelectron Spectroscopy, Part 14. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. The calculations were carried out at the Deutsches Rechenzentrum, Darmstadt. – Part 13: *W. Schäfer* and *A. Schweig*, Angew. Chem. *84*, 898 (1972); Angew. Chem. internat. Edit. *11*, 836 (1972).

[2] *L. A. Leites, T. K. Gar*, and *V. F. Mironov*. Dokl. Akad. Nauk SSSR *158*, 400 (1964).
[3] *J. Laane*, J. Chem. Phys. *50*, 776 (1969); *J. F. Blanke, T. H. Chao*, and *J. Laane*, J. Mol. Spectrosc. *38*, 483 (1971).
[4] *M. T. Tribble* and *N. L. Allinger*, Tetrahedron *28*, 2147 (1972).
[5] A synonymous designation of transannular d-π interaction would be d-π through-space interaction. For the concept of through-space interaction, see *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1971).
[6] CNDO/2 method, see *J. A. Pople* and *D. L. Beveridge*: Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970; MINDO/2 method, see *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.
[7] The same considerations apply to compounds *(2)* to *(4)* and *(6)*.
[8] *P. Bischof* and *E. Heilbronner*, Helv. Chim. Acta *53*, 1677 (1970).
[9] *H. Bock* and *W. Ensslin*, Angew. Chem. *83*, 435 (1971); Angew. Chem. internat. Edit. *10*, 404 (1971).
[10] *U. Weidner* and *A. Schweig*, Angew. Chem. *84*, 550 (1972); Angew. Chem. internat. Edit. *11*, 536 (1972).
[11] No unambiguous indication was hitherto available for the individual assignment of the MOs π_2, σ_1, and σ_2 to the three superposed bands in the second photoelectron peak. A similar situation applies to trimethylvinylsilane [14] and dimethyldivinylsilane [10].
[12] Observed shifts of the Ge-H MOs in GeH_4 relative to the Si-H MO in SiH_4: 0.38 eV; *B. P. Pullen, T. A. Carbon, W. E. Moddeman, G. K. Schweitzer, W. E. Bull*, and *G. F. Grimm*, J. Chem. Phys. *53*, 768 (1970).
[13] *U. Weidner* and *A. Schweig*, J. Organometal. Chem. *37*, C 29 (1972).
[14] *U. Weidner* and *A. Schweig*, J. Organometal. Chem. *39*, 261 (1972).
[15] the He-I (584 Å) photoelectron spectra were recorded with a PS 16 spectrometer produced by Perkin-Elmer Ltd., Beaconsfield (England).
[16] *O. Klemperer*: Electron Optics. University Press, Cambridge 1953, 414.

Synthesis of Dineopentyl Phosphorothiocyanatidate: The First Compound with the >P(O)S—C≡N Structure

By *Andrzej Łopusiński* and *Jan Michalski*[*]

Phosphoroisothiocyanatidates >P(O)N=C=S are stable and relatively readily accessible compounds[1]. In contrast the isomeric thiocyanatidates >P(O)S—C≡N have not, as yet, been described and characterized[2]. Recently, we have investigated a variety of reactions in which formation of the latter structure is to be expected. In this communication we describe the first authentic representative of this interesting series of compounds.

$$[(CH_3)_3C\text{-}CH_2\text{-}O]_2\overset{\overset{O}{\|}}{P}\text{-}S\text{-}Cl \quad (1)$$

$$\downarrow \begin{matrix}+AgCN\\-AgCl\end{matrix}$$

$$[(CH_3)_3C\text{-}CH_2\text{-}O]_2\overset{\overset{O}{\|}}{P}\text{-}S\text{-}C{\equiv}N \quad (2)$$

$$\downarrow$$

$$[(CH_3)_3C\text{-}CH_2\text{-}O]_2\overset{\overset{O}{\|}}{P}\text{-}N{=}C{=}S \quad (3)$$

Bis(neopentyloxy)phosphinoylsulfenylchloride[4] reacts with an excess of silver cyanide in methylene chloride solution at −5 °C to give the dineopentyl phosphorothiocyanatidate *(2)*, which can be isolated by removal of silver chloride and solvent at −5 °C [IR (film): 2170 cm^{-1} (sharp band, medium intensity) ($\nu_{-S-C\equiv N}$); ^{31}P-NMR: $\delta = -10.8$ ppm (H_3PO_4 as external standard)].

[*] Dipl.-Chem. A. Łopusiński und Prof. Dr. J. Michalski
Polska Akademia Nauk, Centrum Badań Molekularnych i Makromolekularnych Lódź,
Przedzalniana 72 (Poland)

At room temperature *(2)* isomerizes to the isothiocyanatidate *(3)*[4] [IR: 2010 cm^{-1} (very strong, broad band, $\nu_{-N=C=S}$); ^{31}P-NMR: $\delta = +17.5$ ppm (H_3PO_4, external)], which can also be prepared by condensation of dineopentylphosphorochloridate *(4)* with thiocyanates[5].

$$[(CH_3)_3C\text{-}CH_2\text{-}O]_2\overset{\overset{O}{\|}}{P}\text{-}Cl \xrightarrow[-Cl^{\ominus}]{+SCN^{\ominus}} \quad (3)$$

(4)

Received: June 28, 1972 [Z 682 IE]
German version: Angew. Chem. *84*, 896 (1972)

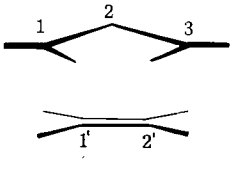
[1] *G. I. Derkatsch* and *S. M. Ivanowa*, Z. Chem. *9*, 369 (1969), and literature cited therein.
[2] Claims concerning the isolation of compounds of the type >P(X)S—C≡N (X—O, S) [*B. C. Saunders et al.*; J. Chem. Soc. *1948*, 699; *1949*, 2921; *G. Schrader*, German Patent 1240850; Chem. Abstr. *67*, 53729j (1967)] are, in the light of our unpublished results, erroneous.
[3] After several minutes at 25 °C only characteristic signals for *(3)* appear.
[5] All compounds mentioned were analyzed and characterized by their IR and NMR spectra.

Substituent Effects in 1,3-Dipolar Cycloadditions of Phenyl Azide

By *Reiner Sustmann* and *Heinrich Trill*[*]

In a model recently proposed[1, 2] for the effects of substituents in cycloadditions the separations of the highest occupied π-molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs) of the other system concerned provide a measure for the reactivity. This model is here placed on a quantitative foundation and tested experimentally for the example of cycloadditions of phenyl azide.

For 1,3-dipolar cycloaddition of an allyl anion 2nd order HMO perturbation theory[3, 4] provides equation (1) for the energy gain in bond formation between the centers 1 and 3 of the 1,3-dipole (A) and the atoms 1′ and 2′ of the olefin (O)[**]:



(A)

(O)

$$\Delta E = \frac{[(c_{Ho1}\cdot c_{Lu1} + c_{Ho2}\cdot c_{Lu3})\beta]^2}{E_{OHo} - E_{ALu}} + \frac{[(c_{Ho1}\, c_{Lu1'} + c_{Ho3}\, c_{Lu2'})\beta]^2}{E_{AHo} - E_{OLu}} \quad (1)$$

Simplifying, we now assume that the eigenvectors of the HOMOs and LUMOs in the numerator are independent of the 1,3-dipole and olefin concerned, *i.e.* the numerator is regarded as constant. This is valid for the contribution of a 1,3-dipole if its reactivity is studied with reference to a large number of olefins. Further, the contribution of the olefin should remain constant to a first approximation so

[*] Priv.-Doz. Dr. R. Sustmann und Dipl.-Chem. H. Trill
Organisch Chemisches Institut der Universität
44 Münster, Orléansring 23 (Germany)
[**] In the subscripts Ho denotes HOMO and Lu denotes LUMO.

long as the π-MO considered as the HOMO is localized mainly in the reacting double bond. With these assumptions the expression for ΔE is only a function of the differences in orbital energies (eq. 2).

$$\Delta E = A\beta^2 \left[\frac{1}{E_{\mathrm{OHo}} - E_{\mathrm{ALu}}} + \frac{1}{E_{\mathrm{AHo}} - E_{\mathrm{OLu}}} \right]. \qquad (2)$$

The case where $E_{\mathrm{OHo}} - E_{\mathrm{ALu}} = E_{\mathrm{AHo}} - E_{\mathrm{OLu}} = D$ will be discussed in more detail. A substituent introduced into O may increase or decrease D. If for a given substituent one assumes the same shifts in orbital energies for HOMO and LUMO (this is the case in a first order perturbation calculation) and denotes an increase in orbital energy of the olefin by $-x$ and a decrease by $+x$, then we have:

$$\Delta E = A\beta^2 \left[\frac{1}{D+x} + \frac{1}{D-x} \right]. \qquad (3)$$

Figure 1 illustrates the pattern of this function, where the broken curve shows superposition of the two full branches which represent $1/(D+x)$ and $1/(D-x)$ separately.

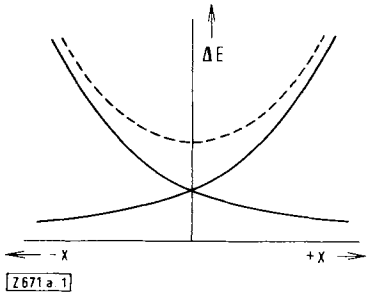


Fig. 1. Qualitative shape of the function (3). Broken line, total function; full lines, $1/(D+x)$ and $1/(D-x)$.

Three possibilities can be distinguished for the influence of substituents on the reaction rate, according to the relative positions of the frontier orbitals (Fig. 2). For case I the separation of HOMO (O) from LUMO (A) determines the reactivity, *i.e.* the first summand in equation (2) is dominant and the second can in a first approximation be neglected. In case III the situation is reversed; here it suffices to

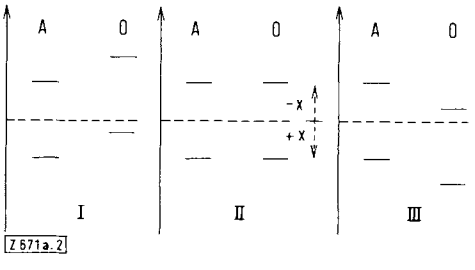


Fig. 2. Possible relative positions of frontier orbitals on cycloaddition of molecules A and O.

consider the second summand in equation (2) in order to determine the increase in reactivity caused by electron-attracting substituents in O. For type II, the separations of both HOMOs and LUMOs must be taken into account; it is always the separation that is reduced by substitution which becomes dominant. The character of a substituent is measured by its influence on the energy of HOMO and LUMO in ethylene. If the orbitals are lowered relative to ethylene, then the substituent is electron-attracting, and the reverse. This treatment takes into account the sum of inductive and mesomeric effects.

In 1,3-dipolar cycloadditions of phenyl azide[5] the reactivity is found to be increased both by electron-attracting and by electron-donating substituents, *i.e.* this system corresponds to type II of Figure 2. To prove the value of the model one must thus in principle know all the separations between HOMOs and LUMOs. However, since phenyl azide is a reactant throughout, its HOMO and LUMO energies give rise to a constant term in the calculation of the difference, and only the HOMOs and LUMOs of the olefins are needed for verification of the model. The energies of the HOMOs are determined from the photoelectron spectra of the olefins[6] or are taken from the literature[7]. The energies of the LUMOs are not known. Nevertheless, here one can use the fact that the energies of HOMOs and LUMOs are shifted in the same direction by any one substituent. So, in place of LUMO energies, the positions of the HOMOs of electron-poor olefins can be used as a measure for the decrease in the LUMO. It should thus be possible to confirm the model by plotting the ionization potentials of the highest occupied π-molecular orbitals against the logarithms of the rate constants for cycloadditions of phenyl azide to olefins. So far as Figure 1 is concerned this means following each rising branch of the hyperbola from the origin towards positive and negative x values instead of considering the superposition of the two stabilizations (broken curve).

Figure 3 shows the expected minimum in the region of the ionization potential of ethylene. That the correlation is sometimes only semiquantitative shows only that there are

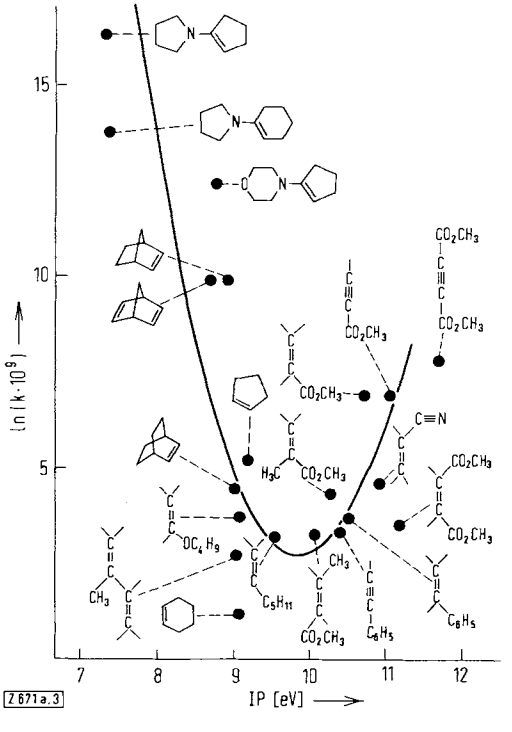


Fig. 3. Correlation of the logarithms of the rate constants for cycloaddition of phenyl azide with the ionization potentials of the highest occupied π-molecular orbitals of substitued olefins. Substituents denoted by bonds are hydrogen atoms.

also other factors affecting the rate of cycloadditions. The model considered here takes only electronic substituent effects into account. Steric influences, which are often very important for cycloadditions, cannot be incorporated in a model that uses only the properties of the isolated reactants as measure of the reactivity. Also electrostatic effects, which play a part in the interaction of polar reactants, do not enter into the correlation. It seems justified to interpret major deviations of individual olefins as a measure of the influence of non-electronic substituent effects. In this way it is possible to obtain an insight into the contribution of individual effects to the total substituent effect.

Received: May 30, 1972 [Z 671a IE]
German version: Angew. Chem. *84*, 887 (1972)

[1] *R. Sustmann*, Tetrahedron Lett. *1971*, 2717.
[2] *R. Sustmann*, Tetrahedron Lett. *1971*, 2721.
[3] *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw Hill, New York 1969.
[4] *E. Heilbronner* and *H. Bock*: Das HMO-Modell und seine Anwendung. Verlag Chemie, Weinheim 1968.
[5] *R. Huisgen*, *G. Szeimies*, and *L. Moebius*, Chem. Ber. *100*, 2494 (1967).
[6] *R. Sustmann* and *H. Trill*, unpublished.
[7] *P. Bischof*, *J. A. Hashmall*, *E. Heilbronner*, and *V. Hornung*, Helv. Chim. Acta *52*, 1745 (1969).

Substituent Effects in Diels-Alder Additions

By *Reiner Sustmann* and *Reinhard Schubert*[*]

Electronic substituent effects in cycloadditions can be interpreted by means of a model of the interaction of frontier orbitals[1–3] whose development goes back to *Fukui*[4, 5]. For the examples of Diels-Alder additions of maleic anhydride (MA) and of tetracyanoethylene (TCNE)[6, 7] to substituted butadienes it is shown that the qualitative reactivity model can be confirmed quantitatively by correlation of the separations of the highest occupied (HOMO) and the lowest unoccupied molecular orbitals (LUMO) with the logarithm of the rate constants for the cycloadditions. The reactions of these two dienophiles are "normal" Diels-Alder additions, in which the separations HOMO (diene)—LUMO(dienophile) determine the reactivity. The influence of the interaction HOMO(dienophile)—LUMO (diene) can thus be neglected in this work. The result of plotting the logarithms of the rate constants against the HOMO-LUMO separations is expected to be a hyperbola corresponding to one branch in Figure 1 of the preceding Communication[3].

The energies of the HOMOs of the diene skeleton of the substituted butadienes were determined by photoelectron spectroscopy[8]. The electron affinities of TCNE (1.7 eV) and MA (0.5 eV) were taken from the literature[9]. Figure 1 shows the result of the correlation. Even if the points do not all lie on the hyperbola drawn (because of the multiple approximations involved in the model this is not to be expected), expectation is still semiquantitatively fulfilled.

The deviations also allow recognition of other factors that are important for these cycloadditions. In both series, cyclopentadiene shows a reactivity that, measured by the energy of its HOMO is much too high. The fixed cisoid conformation and the short distance between the reacting centers caused by the clamping of positions 1 and 4 provide a simple explanation. If one assumes that the open-chain dienes exist to the extent of 1% or less in the cisoid form (this is so for unsubstituted butadiene[11]) and corrects the rate constants of cyclopentadiene, then this diene also moves

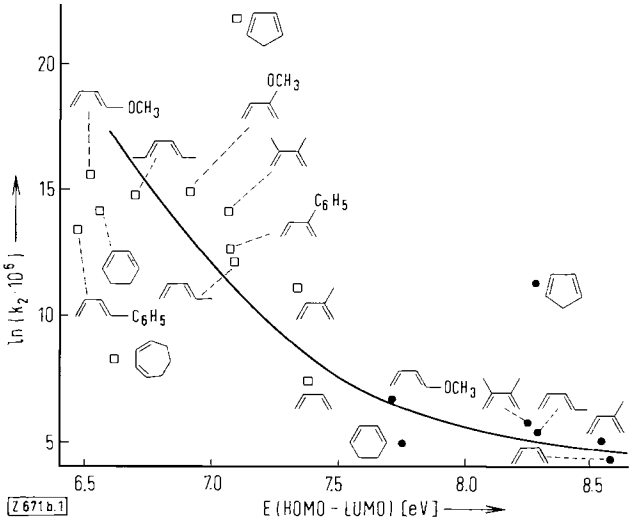


Fig. 1. Correlation of the rate constants of Diels-Alder additions of TCNE (□) and MA (●) to substituted butadienes. Open bonds in the formulas represent methyl groups.

to near the hyperbola drawn (a decrease of *ca.* 5 units on the logarithmic scale). Steric effects are also not taken into account in this model; deviations from the curve can also arise from this cause, as appears to be confirmed by the example of cycloheptadiene. As third factor, electrostatic interactions of polarized and unsymmetrical reactants may codetermine the reactivity, and can be responsible for deviations in some cases.

The kinetic data show that introducing a substituent into a diene has a greater effect on the rates of reactions of TCNE than on those of MA. This greater selectivity in spite of the greater reactivity follows naturally from the reactivity model. The smaller the HOMO-LUMO separation, the more a decrease in the separation caused by a substituent makes itself felt on the reactivity.

Received: May 30, 1972 [Z 671b IE]
German version: Angew. Chem. *84*, 888 (1972)

[*] Priv.-Doz. Dr. R. Sustmann and Dipl.-Chem. R. Schubert
Organisch Chemisches Institut der Universität
44 Münster, Orléansring 23 (Germany)

[1] *R. Sustmann*, Tetrahedron Lett. *1971*, 2717.
[2] *R. Sustmann*, Tetrahedron Lett. *1971*, 2721.
[3] *R. Sustmann* and *H. Trill*, Angew. Chem. *84*, 887 (1972); Angew. Chem. internat. Edit. *11*, 838 (1972).
[4] *K. Fukui*, Fortschr. Chem. Forschung *15*, 1 (1970).
[5] *W. C. Herndon*, Chem. Rev. *72*, 157 (1972).
[6] *J. Sauer*, Angew. Chem. *79*, 76 (1967); Angew. Chem. internat. Edit. *6*, 16 (1967).
[7] *Ch. Rücker*, Dissertation, Universität München 1969.
[8] *R. Sustmann* and *R. Schubert*, Tetrahedron Lett. *1972*, 2739.
[9] *G. Briegleb*, Angew. Chem. *76*, 326 (1964); Angew. Chem. internat. Edit. *3*, 617 (1964).
[10] A small inexactitude arises in that the kinetics for TCNE were determined at 20°C and those for MA at 30°C. Nevertheless, the error is probably negligible on the logarithmic scale.
[11] *J. G. Aston*, *G. Szasz*, *H. W. Woolley*, and *F. G. Brickwedde*, J. Chem. Phys. *14*, 67 (1946).

Single-Step Synthesis of 1,*n*-Dicarboxylic Diesters by Kolbe Electrolysis of Oxalic and Malonic Half Esters in the Presence of Olefins[**] [1]

By *Hans Schäfer* and *Rudolf Pistorius*[*]

Radicals of a great variety of structure are available by Kolbe electrolysis of carboxylates. Their preparative use has been almost exclusively for the preparation of dimers[2] whilst very little has been recorded on their addition to double bonds[3].

On electrolysis of ethyl hydrogen oxalate or methyl hydrogen malonate in the presence of mono- and di-olefins we have obtained the esters listed in Tables 1 and 2. The adducts were separated by gas chromatography and characterized by C, H analyses and NMR, IR, and mass spectrometry as well as by comparison with authentic samples.

The formation of the products can be explained in accordance with the annexed scheme (see over). The radicals *(3)* produced at the anode dimerize to *(1)* and/or add to the olefin (Ol), yielding *(4)*, which combines to give the dimer *(2)*, couples with *(1)* to give *(5)*, or to a small extent disproportionates to give *(6)* and *(7)*.

In experiments to date, dimers of type *(2)* are accessible in good yields from dienes and styrene, but the yields from

Table 1. Electrolysis of ethyl hydrogen oxalate in the presence of various olefins

Expt.	Olefin	Product	Product distribution [a] in dependence on current density i (A/cm^2)		
1	Butadiene [b]		$i=0.025$ (70%) [c]	$i=0.25$ (66%)	$i=0.66$ (24%)
		Diethyl 3-hexenedioate	6%	29%	60%
		Diethyl 3,7-decadienedioate	50%	34%	18%
		Diethyl 6-vinyl-3-octenedioate	37%	31%	12%
		Diethyl 3,4-divinyladipate	7%	6%	5%
		Diethyl 2-vinylsuccinate			5%
2	Isoprene		$i=0.85$ (64%)	$i=0.21$ (65%)	$i=0.148$ (50%)
		Diethyl 3-methyl-3-hexenedioate	37%	12%	8%
		Diethyl 3,8-dimethyl-3,7-decadienedioate	24%	20%	39%
		Diethyl 3,7-dimethyl-3,7-decadienedioate	22%	59%	46%
		Diethyl 3,6-dimethyl-6-vinyl-3-octenedioate	17%	9%	7%
3	Isobutene		$i=0.32$ (9%)		
		Diethyl 2,2-dimethylsuccinate			
4	Cyclohexene		$i=0.35$ (9%)		
		Diethyl *cis*-1,2-cyclohexanedicarboxylate	45%		
		Diethyl *trans*-1,2-cyclohexanedicarboxylate	55%		

[a] Determined by gas chromatography with the aid of known mixtures of adducts.
[b] See also: *R. V. Lindsey* and *M. L. Petersen*. J. Amer. Chem. Soc. *81*, 2073 (1959); *M. J. Fioshin, L. A. Mirkind, L. A. Salmin*, and *A. G. Konienko*, Zhur. Vses. Khim. Obshc. *10*, 238 (1965); Chem. Abstr. *63*, 15858 (1965).
[c] Percentages in parentheses = total yield based on ethyl hydrogen oxalate used.

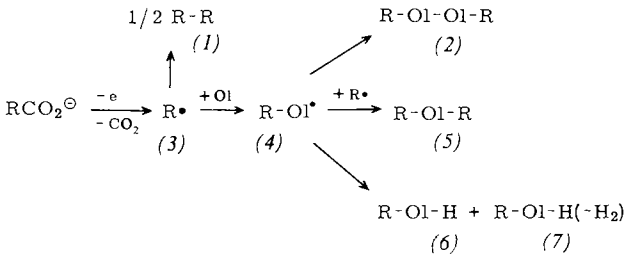
Table 2. Electrolysis of methyl hydrogen malonate in the presence of various olefins.

Expt.	Olefin	Product	Product distribution in dependence on current density i (A/cm^2)	
1	Butadiene		$i=0.218$ (35% [a]; 17% [b])	
		Dimethyl 4-octenedioate	28.5%	
		Dimethyl 3-vinylhexanedioate	19.5%	
		Dimethyl 4,8-dodecadienedioate	26 %	
		Dimethyl 7-vinyl-4-decenedioate	22.5%	
		Dimethyl 3,4-divinylsuberate	3.5%	
2	Styrene		$i=0.03$ (58%; 7%)	$i=0.26$ (42%; 12%)
		Methyl 4-phenylbutyrate *(8)*	15.5%	15%
		Methyl 1-phenyl-1-butenoate *(9)*	12.5%	16%
		Dimethyl 3-phenylhexanedioate *(10)*	6%	6%
		Dimethyl 4,5-diphenyloctanedioate *(11)*	66%	63%
3	Isoprene		$i=0.218$ (64%; 14%)	
		Dimethyl 3-methyl-3-vinylbutanedioate	1.5%	
		Dimethyl 3-isopropenylhexanedioate	0.5%	
		Dimethyl 4,7-dimethyl-7-vinyl-4-octenedioate	18 % [c]	
		Dimethyl 4,9-dimethyl-4,8-dodecadienoate	49.5%	

[a] Total yield based on the methyl hydrogen malonate used.
[b] Yield of dimethyl succinate *(12)*.
[c] 25.5% of isomeric dimers were also isolated; their structures were not determined.

[*] Doz. Dr. H. Schäfer and R. Pistorius
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

unconjugated monoenes are still unsatisfactory. The proportions of *(2)* : *(5)* (Table 1, expts. 1 and 2) and of the isomers *(2)* (Table 1, expt. 2) can be modified by varying the current density.



Electrolysis of methyl hydrogen malonate in the presence of styrene:

A solution of styrene (80 ml), methyl hydrogen malonate (30 g, 0.26 mol), and potassium methyl malonate (8 g, 51 mmol) was electrolyzed at 0 °C at a cylindrical platinum gauze anode (effective surface area 2.3 cm^3) with 0.6 A and a terminal voltage of 60 V to consumption of 0.336 F. Distillation of the crude product up to 40—135 °C/0.2 torr afforded 9.4 g, from which compounds *(8)* to *(10)* and *(12)* were separated by gas chromatography at 200 °C (column: 8 m, 10% of Apiezon M on Chromosorb P). The distillation residue (15.5 g) consisted to 93% of sublimable *(11)*.

Received: June 28, 1972 [Z 676 IE]
German version: Angew. Chem. *84*, 893 (1972)

[1] Anodic Oxidation of Organic Compounds, Part 10.—Part 9: *H. Schäfer* and *A. AlAzrak*, Chem. Ber. *105*, 2398 (1972).
[2] *L. Eberson* and *H. Schäfer*, Fortschr. Chem. Forsch. *21*, 1 (1971), Table 11.
[3] See [2], Table 7; *M. Chkir* and *D. Lelandais*, Chem. Commun. *1971*, 1369.

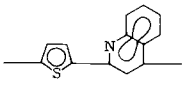
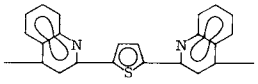
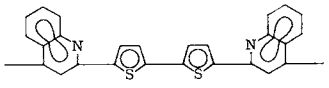
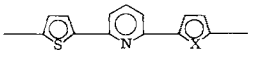
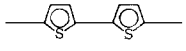
Linkage of Alkyl Groups through Arenofunctional Groups[1] [**]

By *Thomas Kauffmann* and *Annegret Woltermann*[*]

Alkyl groups are often linked through functional groups; some important types of such linkage are shown in Table 1. On the basis of the arenology principle[2] we have investigated the possibility of effecting corresponding linkages also through suitable hetarenes ("arenofunctional groups"[2]), and we have succeeded with types A, B, C, and E but surprisingly not with D.

Type A (—Nu—El—): This type of linkage of alkyl groups by classical functional groups occurs readily. With arenofunctional groups, however, a difficulty arises: the slight reactivity of nucleophilic hetarenes[3] towards electrophilic hetarenes requires that they be first activated by lithiation. However, since just in those electrophilic alkylhetarenes that are readily accessible by synthesis the alkyl groups in the α-position are relatively acidic, an undesired transmetalation occurs easily, with subsequent aromatic substitution according to or analogous to the change *(1)* → *(2)* (in THF at −65 to +60 °C)[4], *i.e.* there is an "arenological Claisen reaction", as can be readily appreciated by comparing the two sets of following formulas [yield of *(2)*, *ca.* 80%; m.p. of *(2)*; 81 °C].

Table 1. Important types of linkage for alkyl groups (Nu = nucleophilic, El = electrophilic center).

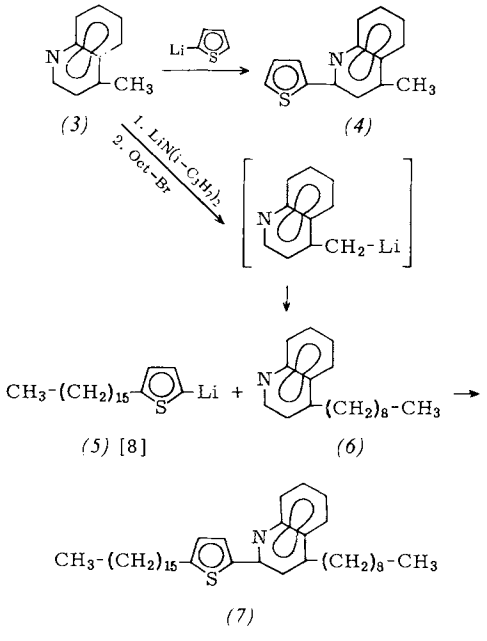
Type	(—— = alkyl)	Through classical functional groups	Through arenofunctional groups
A	——Nu—El——	*e.g.* esters O ‖ ——O—C——	*e.g.* 
B	——El—Nu—El——	acid anhydrides O O ‖ ‖ ——C—O—C——	
C	——El—Nu—Nu—El——	diacyl peroxides O O ‖ ‖ ——C—O—O—C——	
D	——Nu—El—Nu—— ——Nu—El—Nu'——	carbonic acid esters/urethanes O ‖ ——O—C—X—— (X = O or NH)	 (X = S, O)
E	——Nu—Nu——	disulfides ——S—S——	

The bicyclic 10π-electron system of quinoline, with the relatively high double-bond character of its C—N bond, is suitable for linkages of this type, for its electrophilic activity

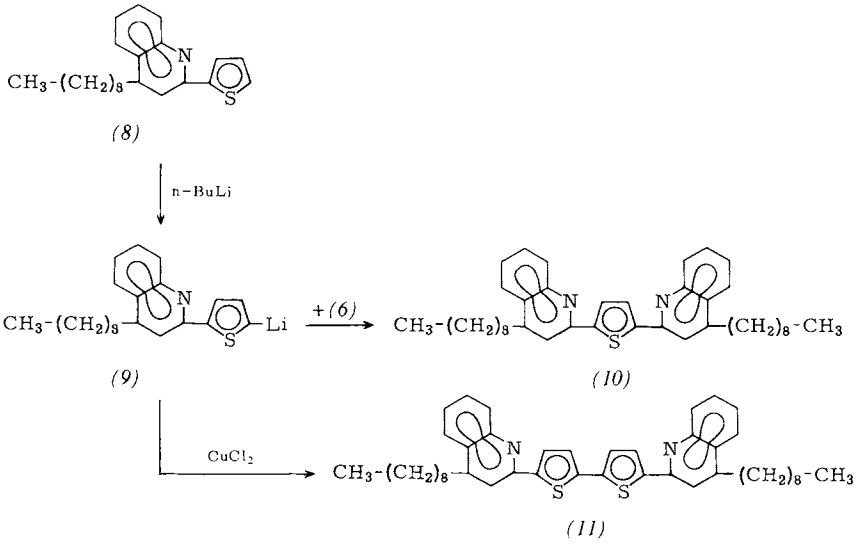
[*] Prof. Dr. Th. Kauffmann and A. Woltermann
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Landesamt für Forschung des Landes Nordrhein-Westfalen, and the Fonds der Chemischen Industrie.

resembles that of a 2π-electron system such as >C=N— or >C=O more than that of the 6π-electron system of pyridine. Unlike *(1)* or 2-methylpyridine[5], 4-methylquinoline *(3)* reacts with 2-lithiothiophene to give *(4)* smoothly in ether/hexane (4 : 1) at 5 °C[6, 7]. Further, in THF at −60 °C it is lithiated by Li diisopropylamide almost quantitatively at the methyl group and can then be alkylated by alkyl halides to afford 4-alkylquinolines [synthesis of *(5)*: in THF at −60 °C]. These compounds can be linked to 2-hexadecylthiophene[8], as shown by the example *(5)* → *(7)* (in ether at 35 °C) [*(4)*: yield 36%, m.p. 120—121 °C[7]; *(6)*: yield 79% b.p. 158—159 °C/0.01 torr; *(7)*: yield 63%, m.p. 34 °C].



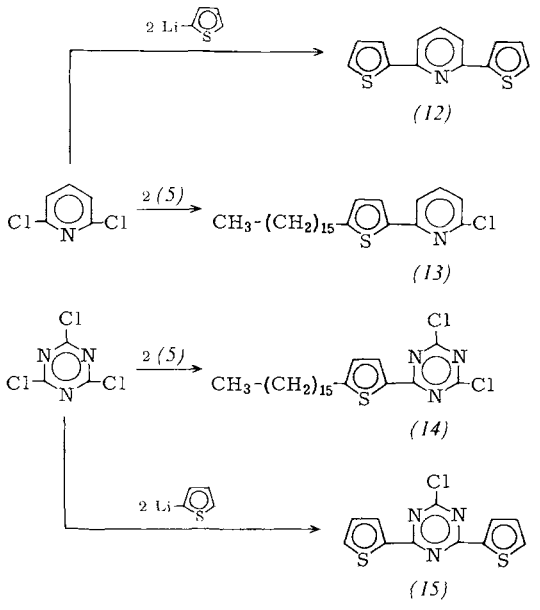
Types B and C (—El—Nu—El— and —El—Nu—Nu—El—): 4-Nonylquinoline *(6)* reacts with 2-lithiothiophene in ether/hexane (5 : 1) at 0—36 °C to give 58% of *(8)*, m.p. 43 °C. The lithium compound *(9)* obtained therefrom by *n*-BuLi in ether at 5 °C (yield >45%, proved by addition to benzophenone; m.p. of the alcohol obtained, 120—121 °C) was treated with 1 mol of 4-nonylquinoline



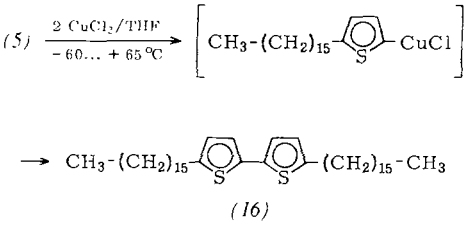
(in ether at 5 °C, after distillation of the ether in di-*n*-butyl ether at 120 °C). A surprisingly low yield (4%) of *(10)* (m.p. 70 °C, yellow) was thus obtained, together with unchanged starting material. However, the action of 2 mol of $CuCl_2$ on *(9)* (in ether at 5 °C after distillation of the ether in di-*n*-butyl ether at 140 °C) led to a 24% yield of *(11)*, yellow, m.p. 84—85 °C.

Type D (—Nu—El—Nu—): Since alkyl groups attached to *nucleophilic* hetarenes at the α-position are not acidic, the difficulty (transmetalation and secondary reaction) mentioned above need not be feared for this type. We attempted such a linkage by treating 2 mol of the 2-alkyl-5-lithiothiophene *(5)* with 2,6-dichloropyridine in ether at 35 °C and with 2,4,6-trichloro-*s*-triazine in ether/THF (2 : 1) at −25 °C. Unlike the analogous treatments with 2-lithiothiophene which gave *(12)* (yield 18%[9] or *(15)* (yield 52%, m.p. 147 °C[10]), this reaction stopped at the biaryl stage *(13)* (yield 28%, 46 °C) or *(14)* (yield 82%, m.p. 67—68 °C). The further reaction with *(5)*, which could not be forced under more severe conditions, is clearly hindered sterically by the long alkyl groups.

Type E (—Nu—Nu—): Except with thiols, oxidative coupling plays only a small role for compounds Alk—Nu—H (Nu = O, NH, or S) because of interfering side reactions and subsequent reactions. With the corresponding arenofunctional compounds such couplings become more important, since nucleophilic hetarenes mostly undergo satisfactory oxidative coupling through organocopper



compounds, and by the synthesis of *(16)* (yield 66%, m.p. 77 °C) we could show that long alkyl groups hardly hinder this type of coupling at all.



The compounds prepared, whose structural formulas are in accord with elemental analyses and spectra (MS, NMR, UV, IR), all melt sharply and usually in a favorable range; they are readily soluble in organic solvents and crystallize well. Working with such arenofunctional compounds is only little more difficult (chromatography in place of distillation) than with normal functional compounds.

Received: July 5, 1972 [Z 677a IE]
German version: Angew. Chem. *84*, 824 (1972)

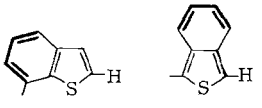
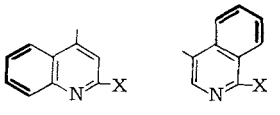
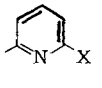
[1] Protophanes and Polyarenes, Part 7.—Part 6: *Th. Kauffmann*, Tetrahedron, in press; Part 5: *Th. Kaufmann, J. Jackisch, H.-J. Streitberger*, and *E. Wienhöfer*, Angew. Chem. *83*, 799 (1971); Angew. Chem. intern. Edit. *10*, 744 (1971).
[2] *Th. Kauffmann*, Angew. Chem. *83*, 798 (1971); Angew. Chem. internat. Edit. *10*, 743 (1971). Expanded treatment: *Th. Kauffmann*, Chimia, in press.
[3] *A. Albert* (Heterocyclic Chemistry. 2nd Edit., Athlone Press, London 1968; Chemie der Heterocyclen. Verlag Chemie, Weinheim 1962) recognized the two main categories of hetarenes and designated them by the additions "π-electron excess" and "π-electron deficiency". Insofar as the hetarenes act as functional groups we prefer the designations "nucleophilic" and "electrophilic". These expressions have no absolute significance but denote the prevailing character.
[4] First observed (yield 85%) for the action of Li diisopropylamide on *(1)* in ether at 35 °C: *H. Fischer*, Dissertation, Universität Münster 1972.
[5] Is metalated by 2-lithiothiophene on the methyl group: *C. G. Screttas, J. F. Eastham*, and *C. W. Kamienski*, Chimica 24, 109 (1970).
[6] In nucleophilic substitutions with quinoline derivatives, hydrolysis was always followed by heating at 60 °C with nitrobenzene to ensure rearomatization.
[7] *J. Jackisch*, Dissertation, Universität Münster 1972.
[8] Preparation according to *E. Campaigne* and *J. L. Dietrich*, J. Amer. Chem. Soc. *70*, 391 (1948), metalation by *n*-BuLi.
[9] *Th. Kauffmann, E. Wienhöfer*, and *A. Woltermann*, Angew. Chem. *83*, 796 (1971); Angew. Chem. internat. Edit. *10*, 741 (1971).
[10] *W. Brinkwerth*, Diplomarbeit, Universität Münster 1972.

Protophanes by Oxidative Coupling of "Transposed Dithiols"[1][**]

By *Thomas Kauffmann, Jörg Jackisch, Annegret Woltermann*, and *Peter Röwemeier*[*]

According to the arenology principle[2,3] classical functional groups of organic chemistry such as —O—H, —S—H, —CO—X, —CS—X, *etc.*, can be regarded as the first members of homologous series whose higher members (6 or 10π-electrons, *etc.*) consist of "arenofunctional groups", *i.e.* nucleophilic or electrophilic hetaryl groups with suitable substituents (H or X[3]) (examples: Table 1). In their relevant properties[3], the higher members resemble the initial members that are poorer by one or more units of 4π-electrons (printed bold in Table 1), as shown by the comparison in Table 2. It seems reasonable, therefore, to "transpose"[4]

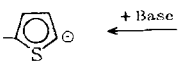
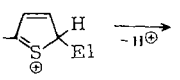
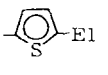
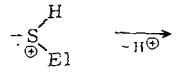
Table 1. Arenology principle for functional groups (examples) [6].

Stage	Nucleophilic groups	Electrophilic groups
10-π		
6-π		
2 [p/π]	-S-H	

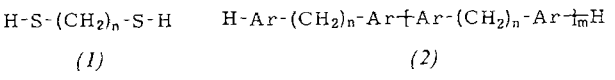
[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. J. Jackisch, A. Woltermann, and P. Röwemeier
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

the important compound types containing functional groups into their higher π-electron analogs and to explore the scopes of the compounds thus obtained.—While the extreme importance of functional groups in organic chemistry renders the possibility of "pole reversal" in such groups[5] most valuable, the much broader possibility of modifying them whilst retaining the fundamental character of nucleophile and electrophile discussed here is certainly not less valuable.

Table 2. Comparison of functional groups/arenofunctional groups.

Deprotonatable, nucleophilic, and regenerative					
	+ Base		+ El⊕		
$-S^{\ominus}$	+ Base	−S−H	+ El⊕		−S−El

Transposing the dithioles *(1)* to the 6π-electron stage leads to α,ω-dithienylalkanes *(3)*. Since thienyl groups attached to an alkyl group[2], like thiol groups, are readily made to undergo oxidative coupling, we first coupled α,ω-dithienylalkanes in this way and thus obtained the first examples of the protophane type *(2)*, which, when Ar = nucleophilic hetarene, belongs to probably the most easily prepared types of protophanes.

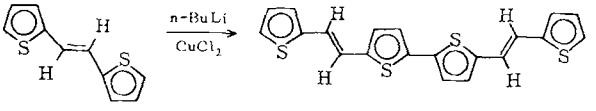


(1) *(2)*

In detail, the dithienylalkanes *(3)*, $n = 2$[7], $n = 6$[8], and $n = 9$ (Table 3) were treated with 1 mol of *n*-BuLi in THF at 0—5 °C and then with 3 mol of $CuCl_2$ at −65 °C. Since the mono- *(4)* and di-lithium compounds *(5)* are always obtained side by side on lithiation, the coupling always leads to a mixture of protophanes from which the tetranuclear *(6)* and the hexanuclear *(7)* product can be separated by extracting the solid reaction product (freed from solvent) with ethanol and benzene, respectively.

This is true also for the protophanes *(7)*, $n = 6$ and 9 (signals at $\tau = 7.8$ and 8.7).

Unlike the compounds *(3)*, *trans*-1,2-dithienylethylene *(8)*[10] is almost exclusively monolithiated (metalation yield *ca.* 80%) by 1 mol of *n*-BuLi in THF at 0—5 °C. Coupling with 3 mol of $CuCl_2$ at −65 °C therefore leads only to *(9)* [*trans,trans*: in KBr out-of-plane vibration at 950 cm^{-1}, as for *(8)*], along with resins.

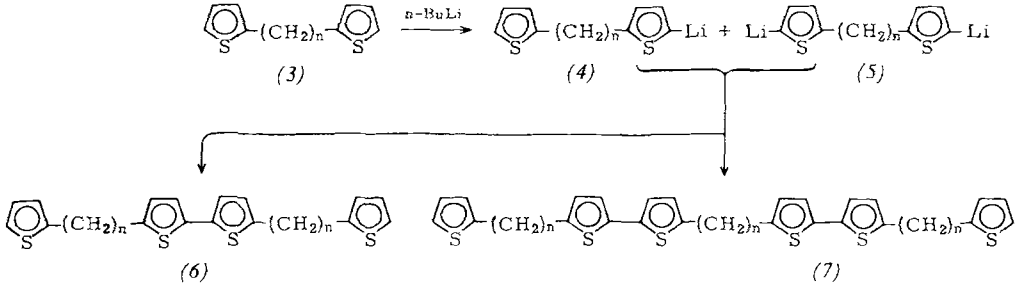


(8) *(9)*

Table 3. New compounds prepared.

Compound	M.p. [°C] b.p. [°C/torr]	Yield [%]
(6), $n = 2$	108—109	32
(7), $n = 2$	145—146	7
(6), $n = 6$	68–70	40
(7), $n = 6$	107—109	7
(3), $n = 9$	185–189/0.5	63
(6), $n = 9$	47–48	33
(7), $n = 9$	77	6
(9)	216–217	28

The structures and configurations of the newly prepared compounds are in accord with elemental analyses and spectra (NMR, IR, UV, MS).



(3) *(4)* *(5)* *(6)* *(7)*

In the NMR spectrum (Varian T 60; $CDCl_3$; TMS) of *(7)*, $n = 2$, the signals of the aliphatic protons coincide to give a singlet at $\tau = 7.0$, as they do for *(6)*, $n = 2$. In this respect, therefore, there is no noticeable difference between the central aliphatic bridge and the peripheral bridges[9].

Received: July 5, 1972 [Z 677b IE]
German version: Angew. Chem. *84*, 826 (1972)

[1] Protophanes and Polyarenes, Part 8. Part 7: [2].
[2] *Th. Kauffmann* and *A. Woltermann*, Angew. Chem. *84*, 824 (1972); Angew. Chem. internat. Edit. *11*, 842 (1972).

[3] *Th. Kauffmann*, Angew. Chem. *83*, 798 (1971); Angew. Chem. internat. Edit. *10*, 743 (1971).
[4] By "transposing" (in music: transfer from one key into another) is meant the transfer of a functional or arenofunctional group from the one π-electron stage (2[p/π]-, 6π-, 10π-, *etc.*) into another without changing the hetero atoms in the nucleophilic or electrophilic center of the group (*e.g.* —O— or a furan nucleus) or introducing new ones.
[5] *E. J. Corey*, Pure Appl. Chem. *14*, 19 (1967); *D. Seebach*, Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969).
[6] It is equally as correct to describe groups such as —S—H and >C=N— as 2p- or 2π-electron systems as to describe thiophene or pyridine as 6π-electrons; with respect to the substituent X cf. [3]; the free valence is drawn arbitrarily at the position to which an alkyl group is most readily attached.
[7] *F. F. Blicke* and *J. H. Burckhalter*, J. Amer. Chem. Soc. *64*, 477 (1942).
[8] *S. Z. Taits* and *Y. L. Goldfarb*, Izv. Akad. Nauk SSSR, Ser. Khim. *1963*, 1289; Chem. Abstr. *59*, 13990 (1963).
[9] The situation is different with pyridine protophanes having central and peripheral ethylene bridges; *W. Jenny* and *H. Holzrichter*, Chimia *23*, 158 (1969).
[10] *Y. K. Yurev* and *D. Eckhardt*, Zh. Obshch. Khim. *31*, 3536 (1961); Chem. Abstr. *57*, 4621 (1962).

Synthesis and Properties of Azole-Pyridine Combinations: Problem of the Hydrolytic Cleavage of Hetarene Combinations[1] [**]

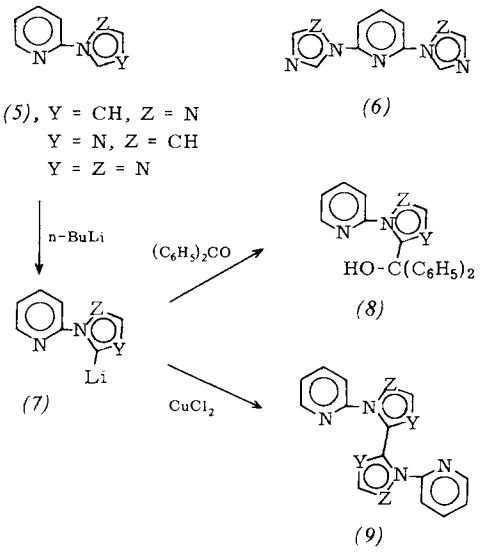
By *Thomas Kauffmann*, *Jochen Legler*, *Elisabeth Ludorff*, and *Heinz Fischer*[*]

The arenofunctional groups so far used (cf.[2]) have one considerable disadvantage compared with classical functional groups, namely, that the bond between the directly linked arenofunctional groups is not amenable to hydrolysis by normal means, so that it is necessary to seek heterocyclic groups that are more favorable in this respect.

Azolides (*i.e. N*-acylazoles) are interesting in this connection[3]: replacing the amino group of *(1)* or *(2)* by azole groups containing two or more N atoms [*e.g.* compounds *(3)* and *(4)*] leads to a drastic increase in the susceptibility to hydrolysis.

Alk-CO-NH_2 *(1)*	H_2N-CO-NH_2 *(2)*
Alk-CO-azole *(3)*, Y = CH, Z = N; Y = N, Z = CH; Y = Z = N	azole-CO-azole *(4)*

The diarenes *(5)*, which can be considered as arenologs of the azolides *(3)*, have been described but not studied in detail[4]. For a test of their susceptibility to hydrolysis we have prepared these compounds, more simply than recorded in the literature, by treating 2-chloropyridine with the azoles at 190°C (autoclave, no solvent)[5]. Also, the hitherto unknown triarenes *(6)* (Table 1) have been synthesized analogously from 2,6-dichloropyridine.



All these compounds proved resistant to 2 N NaOH or 2 N HCl at 100°C. Even the strongly nucleophilic *n*-butyllithium did not cleave the internuclear C—N bond; the diarenes were lithiated by this reagent [in ether or ether/THF (1 : 1) at 20°C], giving *(7)*. This permitted synthesis of the colorless tetraarenes *(9)* by oxidative coupling of *(7)* with 2 mol of $CuCl_2$ (in ether/THF (1 : 1) at 0—50°C) as well as the preparation (in ether at 20°C) of the alcohols *(8)* (Table 1).

Table 1. Compounds synthesized.

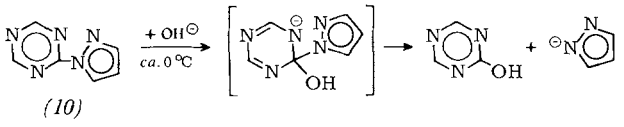
Compound	M.p. [°C]	Yield [%]	Compound	M.p. [°C]	Yield [%]
(6), Z = CH	152	28	*(9)*, Y = CH, Z = N	136—137	21
(6), Z = N	217	21	*(9)*, Y = N, Z = CH	138	18
			(9), Y = Z = N	143	18
(8), Y = N, Z = CH	158	46	*(11)* (yellow)	235—237	82
(8), Y = Z = N	184	70	*(12)* (yellow)	270—273	25

The resistance of the diarenes *(5)* and the triarenes *(6)* to boiling sodium hydroxide solution and hydrochloric acid is at first sight surprising in view of the sensitivity of the corresponding azolides[3] to hydrolysis, but is ascribed by us to the inability of the pyridine system, unlike the carbonyl group, to add weak nucleophiles. This interpretation is favored by the fact that the known diarenes *(10)*[6], whose electrophilic group (*s*-triazine) is scarcely inferior to the carbonyl group in electrophilic activity, is cleaved by dilute sodium hydroxide solution at as low a temperature as *ca.* 0°C and indeed even by aniline at 20°C[6]. Since azolides usually react with nucleophiles by the AE

[*] Prof. Dr. Th. Kauffmann, Dr. J. Legler, E. Ludorff, and Dipl.-Chem. H. Fischer
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Landesamt für Forschung des Landes Nordrhein-Westfalen, and the Fonds der Chemischen Industrie.

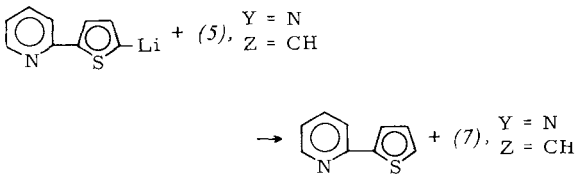
mechanism[3], this mechanism is also probable for the above cleavages[7].

Hetarene combinations that can be cleaved by hydrolysis will in general presumably be obtained if the azoles are linked, as in *(10)*, by a C—N bond to a strongly electrophilic hetarene.

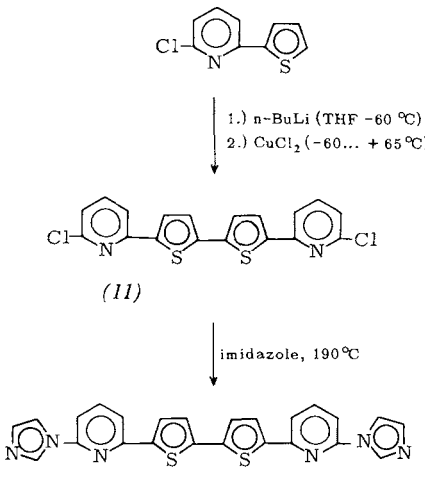


(10)

That *n*-butyllithium neither adds to the diarenes *(5)* nor cleaves them may well be due to the relatively high acidity of *(5)*. This was indicated by transmetalation of *(5)*, Y = N, Z = CH, which occurs almost quantitatively within a few minutes in ether at 20 °C.



In our experience it is generally difficult to prepare oligoarenes containing more than four hetarene nuclei by means of organo-lithium and -copper compounds. It is therefore valuable that the autoclave reaction used for preparation of the di- and tri-arenes can also be applied to chain extension of tetraarenes *(11)*.



(11)

The structural formulas above are in accord with analytical values and spectra (MS, NMR, IR).

Received: July 5, 1972 [Z 677c IE]
German version: Angew. Chem. *84*, 828 (1972)

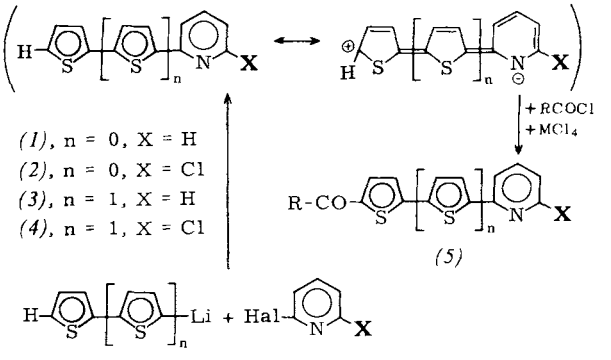
[1] Protophanes and Polyarenes, Part 9.—Part 8: [2].
[2] *Th. Kauffmann, J. Jackisch, A. Woltermann*, and *P. Röwemeier*, Angew. Chem. *84*, 826 (1972); Angew. Chem. internat. Edit. *11*, 844 (1972).
[3] *H. A. Staab*, Angew. Chem. *74*, 407 (1962); Angew. Chem. internat. Edit. *1*, 351 (1962).
[4] *M. A. Khan* and *J. B. Polya*, J. Chem. Soc. *C 1970*, 85.
[5] Yields obtained: *(5)*, Y = CH, Z = N, 83%; *(5)*, Y = N, Z = CH, 60%; *(5)*, Y = Z = N, 61% (recorded m.p.'s confirmed).
[6] *H. Bredereck, F. Effenberger*, and *M. Hajek*, Chem. Ber. *98*, 3178 (1965).
[7] We are studying the mechanism.
[8] *Th. Kauffmann* and *A. Woltermann*, unpublished work.

Long-Range Substituent Effects in Acylation of Thiophene-Pyridine Combinations

By *Thomas Kauffmann, Alfred Mitschker*, and *Hans-Joachim Streitberger*[*]

As a result of the mesomerism shown in the formula scheme the nucleophilicity of the terminal thiophene nucleus in the arene combinations *(1)* to *(4)*[2] would be expected to be lower than that of thiophene, and this has been confirmed by the results of acylation experiments.

When acylation in fact occurs—as expected, it takes place always in the α-position of the terminal thiophene ring —the yields (Table 1) are always distinctly lower than for unsubstituted thiophene.



(1), n = 0, X = H
(2), n = 0, X = Cl
(3), n = 1, X = H
(4), n = 1, X = Cl

(5)

Whereas there was no acylation of *(1)* or *(3)* by 1 mol each of acylating agent and Lewis acid ($SnCl_4$ or $TiCl_4$) under conditions that led to almost quantitative reaction of thiophene, it does result with the chloro derivatives *(2)* and *(4)* (Table 1). Further, with two mol each of acylating agent and Lewis acid results were, with one exception [benzoylation of *(4)*], better than for the non-chlorinated arene combinations (Table 1). In none of these cases was there any reaction other than monoacylation.

We interpret the easier electrophilic substitution at the α-position of the terminal thiophene nucleus due to a chlorine atom in the α-position of the pyridine nucleus in the following way: An electrophile (R—CO—Cl, $R—CO^+$, or MCl_4) present in the reaction mixture attacks primarily the pyridine nitrogen atom of the arene combinations *(1)* and *(3)*. Owing to the mesomerism *(6)* the positive charge thus induced in the aromatic system then makes it more difficult for electrophilic attack to occur on the terminal thiophene nucleus[4]. However, in the chloro compounds *(2)* and *(4)* the electron density on

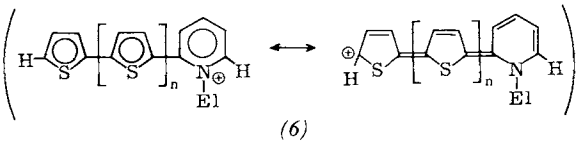
[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. A. Mitschker, and Dipl.-Chem. H.-J. Streitberger
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)
[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Landesamt für Forschung des Landes Nordrhein-Westfalen, and the Fonds der Chemischen Industrie.

Table 1. Acylation of thiophene and thiophene-pyridine combinations with 1 mol each of acylating agent and Lewis acid (in parentheses: with 2 mol each).

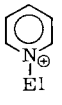
Reagents	Conditions	2-Acyl-thiophene	Yields and m.p.'s of the products (5), n = 0 X = H	(5), n = 0 X = Cl	(5), n = 1 X = H	(5), n = 1 X = Cl
CH_3COCl + $SnCl_4$	3 h in benzene, 20 °C (5 h in benzene, 80 °C) [a]	96 (98)%	0 (0)%	16 (45)%	0 (60)%	35 (77)%
			—	115—116 °C	178—179 °C	169—170 °C
C_6H_5COCl + $TiCl_4$	5 h in benzene, 80 °C	98 (98)%	0 (21)%	18 (48)%	< 1 (68)%	24 (62)%
			118—120 °C	128—130 °C	177—179 °C	204—206 °C

[a] Conditions for reaction with two mol each of acylating agent and catalyst.

the pyridine nitrogen is decreased by the −I effect of the chlorine to such an extent that electrophiles no longer add so readily to the pyridine nitrogen; and additionally the chlorine atom exerts steric hindrance.



(6)



(7)

This interpretation is supported by the fact that on titration in acetic anhydride with 0.1 N perchloric acid (added in glacial acetic acid) the chlorinated compounds *(2)* and *(4)* proved clearly less basic[5] than *(1)* and *(3)* and, correspondingly, unlike *(1)* and *(3)*, do not form picrates with ethanolic picric acid.

It is to be expected that such substituent effects will often play a role in reactions of substituted polyarenes consisting of nucleophilic and electrophilic hetarenes and will also be effective, though to a smaller degree, over more than three nuclei.

Received: July 5, 1972 [Z 677d IE]
German version: Angew. Chem. *84*, 829 (1972)

[1] Protophanes and Polyarenes, Part 10.—Part 9: *Th. Kauffmann, J. Legler, E. Ludorff*, and *H. Fischer*, Angew. Chem. *84*, 828 (1972); Angew. Chem. internat. Edit. *11*, 846 (1972).

[2] The new arene combinations *(3)* (m.p. 118–120 °C; 49%) and *(4)* (m.p. 121 °C; 44%) were prepared, analogously to the lower homologs *(1)* and *(2)* [3], by treatment of 5-lithio-2,2'-bithiophene with, respectively, 2-fluoropyridine at 100 °C in di-*n*-butyl ether/hexane (2 : 1) and 2,6-dichloropyridine at 45 °C in ether/hexane (1 : 1).

[3] *Th. Kauffmann, E. Wienhöfer*, and *A. Woltermann*, Angew. Chem. *83*, 796 (1971); Angew. Chem. internat. Edit. *10*, 741 (1971).

[4] It is known that, analogously, electrophilic attack at the β-position of the pyridine is made much harder by formation of an electrophile/pyridine adduct *(7)*: *H. C. Brown* and *B. Kanner*, J. Amer. Chem. Soc. *75*, 3865 (1953); *H. C. van der Plas* and *H. J. Den Hertog*, Tetrahedron Lett. *1960*, 13.

[5] Basicity constants (pK_B): pyridine 8.7; 2-chloropyridine 13.3; *(1)* 10.3; *(2)* 14.9; *(3)* 10.5; *(4)* 15.4. These values were obtained by potentiometric measurements in acetic anhydride/glacial acetic acid with a glass electrode and extrapolation to an aqueous medium as described by *C. A. Streuli*, Analytic. Chem. *30*, 997 (1958).

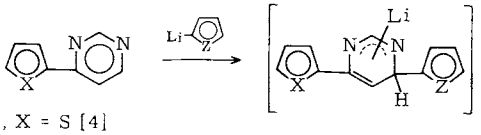
Triarenes of the Type Nucleophile-Electrophile-Nucleophile Containing Pyrimidine or *s*-Triazine as Central Nucleus[1][**]

By *Thomas Kauffmann, Patricia Bandi, Wolfgang Brinkwerth*, and *Bernhard Greving*[*]

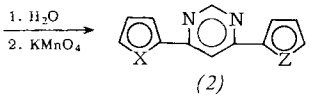
Systems Nu—El—Nu composed of nucleophilic (Nu) and electrophilic (El) groups of the 2[p/π]-electron level[2] are important in organic chemistry both for syntheses (HO—CO—OH, H_2N—CO—NH_2, H_2N—CS—NH_2, H_2N—CNH—NH_2) and as linking member between carbon chains (low- and high-molecular carbonic acid esters and urethanes). On the basis of the arenology principle (cf. [2]) we are interested in systems Nu—El—Nu of the 6π-electron level. In particular, we envisage them as useful units in polyarene syntheses.

As first representative we were able to prepare 2,6-di-(2-thienyl)pyridine, but only in 18% yield in spite of systematic experiments[3]. The electrophilic activity of the pyridine nucleus of 2-chloro-6-(2-thienyl)pyridine, weakened by internuclear electron exchange, obviously does not suffice for smooth reaction with 2-lithiothiophene. More strongly electrophilic nuclei should thus be more suitable as central nucleus, and this has been confirmed.

By starting from the diarenes *(1)*, which are accessible from pyrimidine and 2-lithio-thiophene, -1-methylpyrrole [*(1)*, X = NCH_3; m.p. 74—75 °C], or -furan in 46, 35, and 53% yield[4,5], respectively, the pale yellow triarenes *(2a)—(2f)* (Table 1) could be obtained, in some cases in satisfactory yield, by the action of a molar amount of each lithium compound (in ether at −30 °C)[6].



(1), X = S [4]
X = NCH_3 [5]
X = O [4]



(2)

[*] Prof. Dr. Th. Kauffmann, P. Bandi, Dipl.-Chem. W. Brinkwerth, and B. Greving
Organisch-Chemisches Institut der Universität
44 Münster, Orléans-Ring 23 (Germany)

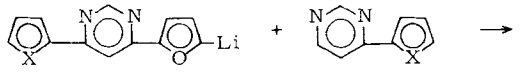
[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Landesamt für Forschung des Landes Nordrhein-Westfalen, and the Fonds der Chemischen Industrie.

The yields stated were obtained when 1-methylpyrrole [for *(2d)*] or furan [for *(2e)* and *(2f)*] were first linked to pyrimidine, giving *(1)* as precursor. The reverse route of synthesis led to larger amounts of by-products, of which the yellow pentaarenes (of type Nu—El—Nu—El—Nu) rimidine nucleus according to *(1)* is surprisingly seen only in the shift of the H_d resonance to higher field. The shift in the H_e resonance in the opposite direction can be explained as van der Waals repulsion or as an anisotropy effect starting from the peripheral nuclei.

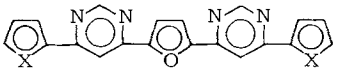
Table 1. Triarenes with pyrimidine as central nucleus.

	X	Z	Yield [%]	M.p. [°C]		X	Z	Yield [%]	M.p. [°C]
(2a)	S	S	35	136—142	*(2d)*	NCH_3	S	48	106—106.5
(2b)	NCH_3	NCH_3	25	135—136	*(2e)*	O	S	20	95—98
(2c)	O	O	15	95—97	*(2f)*	O	NCH_3	12	84—85

(4) (m.p. 208—210 °C, 5%) and *(5)* (m.p. 172—174 °C, 4%) could be isolated in pure form; their structures still await confirmation by independent synthesis. A product of type *(3)* or a dihydro derivative thereof is assumed as intermediate in the formation of the pentaarenes.

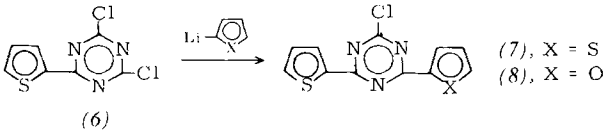


(3)



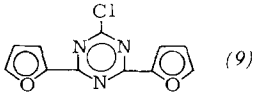
(4), X = S
(5), X = NCH_3

Combinations of *s*-triazine with two thiophene nuclei are also much more easily accessible than those with two furan nuclei. The diarene *(6)* was prepared in 84% yield from cyanuric chloride and 2-thienylmagnesium bromide in ether/THF (2 : 1) at 50—60 °C—it was previously prepared by a quite different route[7]—and, on treatment with 2-lithiothiophene [in ether/THF/*n*-hexane (2 : 1 : 1) at −20 °C] or with 2-lithiofuran [in ether/di-*n*-butyl ether/THF/*n*-hexane (4 : 2 : 1 : 2) at −25 °C] *(6)* afforded the pale yellow triarenes *(7)* (m.p. 147 °C, 59%) and *(8)* (m.p. 159 °C, 23%), respectively. Compound *(7)* can also be obtained from cyanuric chloride and 2 mol of 2-lithiothiophene [in ether/THF/*n*-hexane (4 : 3 : 2) at −15 °C, 52%]. The furan derivative *(9)* (m.p. 200—201 °C, 8%) was obtained analogously by using 1 mol (2 mol caused resinification) of 2-lithiofuran [in ether/THF (1 : 2) at −25 °C].



(6)

(7), X = S
(8), X = O



(9)

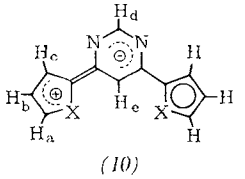
The NMR spectra (Table 2) of the triarenes prepared show the expected electron deficiency in the peripheral nuclei; pyrimidine and *s*-triazine nuclei exert approximately equal effects. The expected electron enrichment in the py-

In the mass spectra (70 eV, 300 mA, source 200 °C) of all the compounds prepared the base peak is the (M − 1) ion (if 1-methylpyrrole is a component) or the molecular ion.

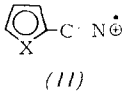
Table 2. Chemical shifts relative to thiophene, furan, or pyrimidine [ppm, $CDCl_3$, *ca.* 100 mg/ml, 20 °C; proton indices as in *(10)*].

Triarene	H_a	H_b	H_c	H_d	H_e
(2a)	−0.53	−0.10	−0.43	+0.21	−0.44
(2c)	−0.36	−0.38	−1.09	+0.20	−0.55
(7)	−0.59	−0.12	−1.17	—	—
(9)	−0.25	−0.27	−1.30	—	—

On fragmentation, the intranuclear bonds are broken preferentially; peaks indicating fission of internuclear bonds are weak or absent. The commonest fragment is always of type *(11)* [68—72% relative intensity for the triarenes *(7)* to *(9)*, 10—15% for the triarenes *(2)*, 8—10% for the pentaarenes].



(10)



(11)

The structural formulas ascribed accord with analytical results and spectra (MS, NMR, IR).

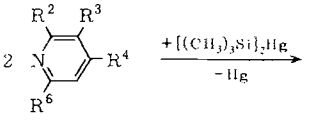
Received: July 5, 1972 [Z 677e IE]
German version: Angew. Chem. *84*, 830 (1972)

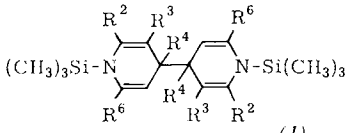
[1] Protophanes and Polyarenes, Part 11.—Part 10: *Th. Kauffmann, A. Mitschker,* and *H.-J. Streitberger*, Angew. Chem. *84*, 829 (1972); Angew. Chem. internat. Edit. *11*, 847 (1972).
[2] *Th. Kauffmann, J. Jackisch, A. Woltermann,* and *P. Röwemeier*, Angew. Chem. *84*, 826 (1972); Angew. Chem. internat. Edit. *11*, 844 (1972).
[3] *Th. Kauffmann, E. Wienhöfer,* and *A. Woltermann*, Angew. Chem. *83*, 796 (1971); Angew. Chem. internat. Edit. *10*, 741 (1971).
[4] *H. Bredereck, R. Gompper,* and *H. Herlinger*, Chem. Ber. *91*, 2832 (1958).
[5] *B. Greving*, Diplomarbeit, Universität Münster 1972.
[6] To ensure rearomatization of the pyrimidine nucleus, hydrolysis was always followed by oxidation with potassium permanganate (in acetone). This is not necessarily required in all cases.
[7] By cyclization of the side chain of a thiophene derivative: French Pat. 1387435; Chem. Abstr. *62*, 16276d (1965).

1,4-Dihydro-1-silylpyridyls—A New Class of Stable Radicals

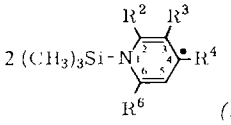
By *Bernd Schroeder, Wilhelm P. Neumann*[*], *Jochen Hollaender*[**], and *Hans-Paul Becker*[***]

1,1',4,4'-Tetrahydro-1,1'-bis(trimethylsilyl)-4,4'-bipyridines *(1)* have been described recently[1]. In the same way or by use of $(CH_3)_3SiCl/Li$[1,2] we have prepared the compounds *(1a)* to *(1g)*.





(1)



(2)

(a), $R^2 = R^3 = R^4 = R^6 = H$
(b), $R^2 = CH_3$, $R^3 = R^4 = R^6 = H$
(c), $R^3 = CH_3$, $R^2 = R^4 = R^6 = H$
(d), $R^4 = CH_3$, $R^2 = R^3 = R^6 = H$
(e), $R^4 = CN$, $R^2 = R^3 = R^6 = H$
(f), $R^2 = R^6 = CH_3$, $R^3 = R^4 = H$
(g), $R^2 = R^4 = CH_3$, $R^3 = R^6 = H$

We now find that these compounds dissociate reversibly into very stable radicals *(2)* when heated with exclusion of air. Thus, for example, *(2a)* can be heated without decomposition in decalin for 3 h at 150 °C. Well resolved ESR spectra can be obtained above 70 °C (Table 1); these accord with expectations. For example, the simulated stick spectrum obtained for *(2a)* using the measured coupling constants agrees well with the recorded spectrum; of the 54 expected lines, the 46 most intense are readily found. Similarly for *(2b)* and *(2c)* one finds 67 and 98 of 192 respectively, and for *(2d)* 92 out of 108 expected lines.

The enthalpies ΔH for *(1)* $\rightleftharpoons$ 2 *(2)* could be calculated (Table 1) by following the intensity of a sharp ESR line; they are equivalent to the dissociation energies for *(1)*. Using literature values[3] we calculated the spin densities (Table 1); the high densities at C-2, C-4, and C-6, and the low densities on the nitrogen atom should be noted (cf. 1,4-dihydropyridyl[4]).

1,4-Dihydropyridyl is extremely unstable; its spectrum has been recorded only at −196 °C. Corresponding 1-alkyl derivatives could not be prepared[5]; however, derivatives with conjugating π-systems (*e. g.* CN, COOR, COR) in the 4-position are relatively stable[3,6]. The stability of *(2)* probably arises from the strong electron attraction of the silyl group. That the electron density on N is low, at least in compounds of type *(1)*, follows from the absence of a shift of the N-H and C-D bands in the IR spectra of pyrrole or $CDCl_3$ when mixed with *(1)* (solid or in CCl_4 solution).

When the known and the new stabilizing principles are combined, by reacting 4-cyanopyridine in benzene with $[(CH_3)_3Si]_2Hg$, the deep green solution that at once results contains radicals *(2e)* that are very sensitive to air but are otherwise stable. This radical apparently does not dimerize at all at room temperature, since temperature changes between 20 and 60 °C have no effect on the intensity of the ESR signal.

Received: July 7, 1972 [Z 679 IE]
German version: Angew. Chem. *84*, 894 (1972)

Table 1. Properties of the 1,4-dihydropyridyl radicals *(2a)* to *(2e)*.

		ESR spectra, coupling constants *a* [G] and spin densities ρ						Temp. [°C] [b]	*g* Factor	ΔH [kcal/mol]
		N	C-2	C-3	C-4	C-5	C-6			
(2a)	*a*	4.20	6.26	1.38	11.55	1.38	6.26	110	2.0037	30 at 104—122 °C
	ρ	0.131	0.278	−0.061	0.513	−0.061	0.278			
(2b)	*a*	3.70	6.11[a]	1.65	11.49	1.70	6.28	170	2.0040	[c]
	ρ	0.116	0.218	−0.073	0.510	−0.076	0.279			
(2c)	*a*	4.16	6.52	1.44[a]	11.03	1.23	5.90	118	2.0039	≥24 at 113—131 °C
	ρ	0.130	0.290	−0.051	0.492	−0.055	0.262			
(2d)	*a*	3.86	6.24	1.57	12.30[a]	1.57	6.24	90	2.0040	29 at 86—104 °C
	ρ	0.121	0.278	−0.070	0.439	−0.070	0.278			
(2e)	*a*	4.28	4.69	0.18	1.98[a]	0.18	4.69	20		*ca.* 10 at 20 °C [d]
	ρ	0.134	0.208	−0.008	0.105	−0.008	0.208			

[a] a_{CH_3} or a_{CN}.
[b] *(2a)* to *(2d)* in decalin, *(2e)* in benzene.
[c] Could not be measured, presumably because an equilibrium exists between α- and γ-linked tetrahydropyridyl derivatives.
[d] Estimated (almost 100% dissociation).

[*] Dipl.-Chem. B. Schroeder and Prof. Dr. W. P. Neumann, Lehrstuhl für Organische Chemie der Universität 46 Dortmund, August-Schmidt-Str. 6 (Germany)
[**] Dr. J. Hollaender
Present address: Lehrstuhl für Organische Chemie II der Universität
463 Bochum-Querenburg (Germany)
[***] Dr. H.-P. Becker
Present address: Catholic University of America Washington, D. C. 20017 (USA)

This work was supported by the Deutsche Forschungsgemeinschaft.

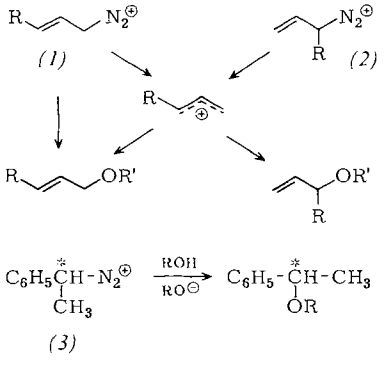
[1] *H.-P. Becker* and *W. P. Neumann*, J. Organomet. Chem. *20*, P 3 (1969); *37*, 57 (1972).
[2] In analogy to *R. A. Sulzbach*, J. Organomet. Chem. *24*, 307 (1970).
[3] Review: *K. Scheffler* and *H. B. Stegmann*: Elektronenspinresonanz. Springer-Verlag, Heidelberg 1970. We used: $Q_N = 32$, $Q_{CH} = -22.5$, $Q_{CN} = 18.8$, $^1/_2 B^H_{C-CH_3} = 28$ (values in Gauss).
[4] *C. J. Chachaty*, J. Chim. Phys. *64*, 608 (1967).
[5] *E. Weitz*, Angew. Chem. *66*, 658 (1954).
[6] *E. M. Kosower* and *E. J. Poziomek*, J. Amer. Chem. Soc. *86*, 5515 (1964); *M. Itoh* and *S. Nagakura*, Bull. Chem. Soc. Jap. *39*, 369 (1966).

Concerted and Non-Concerted Deamination Reactions

By *Wolfgang Kirmse*[*]

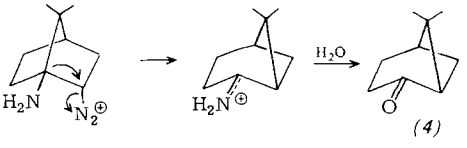
Deamination reactions have been carried out in alcoholic alkaline solution by cleavage of nitrosoacylamines or sulfonylhydrazones in order to study the influence of strong nucleophiles on the decomposition of aliphatic diazonium ions.

For *intermolecular* substitutions it has been proved that the nucleophile participates in the removal of nitrogen from primary allylic diazonium ions *(1)*. For secondary allylic diazinium ions *(2)*, however, the product distribution is independent of the base; with the α-methylbenzylic diazonium ions *(3)* the amount of configurational inversion was not influenced by the concentration of alkoxide.



(3)

Concerted reactions were observed in the following cases of *intramolecular substitution* (= displacement of the diazonium nitrogen by the migrating alkyl group): with the *endo*-bornyl and norbornyl diazonium ions strong electron-donors in position 1 cause concerted rearrangement to the bicyclo[3.1.1]heptane series *(4)*.



(4)

By comparison of decomposition and deuterium exchange it was shown that bicyclo[*n*.1.0]alkane diazonium ions ($n = 3$ or 5) undergo preferentially a concerted ring fission to give cycloalkenyl cations. However, 2-phenylcyclopropane diazonium ions react by way of a phenylcyclopropyl cation as intermediate (identical product mixtures are formed from *cis/trans*-isomeric starting materials).

Concerted reactions can also be detected with aliphatic diazonium ions: the boundary between concerted and non-concerted decomposition is, however, shifted to more energetic carbonium ions in comparison with weaker leaving groups (halide or sulfonate).

Lecture at Bonn on May 16, 1972 [VB 344 IE]
German version: Angew. Chem. *84*, 833 (1972)

[*] Prof. Dr. W. Kirmse
Abteilung für Chemie der Ruhr-Universität Bochum
Lehrstuhl für Organische Chemie II
463 Bochum-Querenburg (Germany)

Structural Aspects of Metal Ion-Ligand Interaction

By *Helmut Sigel*[*]

The problem of metal ion-ligand interaction with regard to the specificity of biochemical reactions can be resolved into three questions: (i) What factors determine the coordination tendency between ligand groups on the one hand and a certain metal ion on the other? [Or: Why is it that the "right" metal ion capable of activating an enzyme coordinates with that enzyme?]—(ii) How great is the coordination tendency of free (hydrated) coordination sites of a metal ion whose coordination sphere is already partially [as in an enzyme-metal ion complex] saturated by a ligand?—(iii) Does the first ligand coordinated to a metal ion exert any influence on the nature of the second ligand? [Or: Why does the "right" substrate coordinate with a certain enzyme-metal ion complex?]

Disregarding the "lock and key" concept[1] and the possiblity of forming distorted coordination spheres by binding of metal ions to proteins[2] the following essential points remain:

Regarding (i): In accord with *Pearson*'s rule— "hard acids prefer hard bases and soft acids soft bases" —Mg^{2+}, for example, preferentially coordinates with an R—O^- group, while Cu^+ definitely prefers R—S^-. Moreover, the coordination tendency of the metal ions of the Irving-Williams series towards N and O donors is known to vary. Thus, for instance, the ions Ba^{2+}, Sr^{2+}, Ca^{2+}, Mg^{2+}, and Mn^{2+} form relatively stable complexes with CH_3COO^-, and the ions Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} give more stable complexes with NH_3. The stability of the Fe^{2+} complex is about the same with both ligands. In both series, in accord with *Irving* and *Williams*, the Cu^{2+} complex is the most stable. A further important aspect is the pH dependence of most complexation reactions. Thus, for example, the competition between protons and metal ions to coordinate with NH_3 (and ligand groups derived therefrom) is very pronounced at pH 7, while it plays only a subordinate role in the case of imidazole, owing to its lower basicity, and is completely negligible in the case of acetate[3]. Correspondingly, *e.g.* Cu^{2+} coordinates preferentially to the glycinate-like group of L-dopa at pH < 8, while at pH > 8 preferential coordination to the pyrocatecholate-like group occurs. The "critical" pH value for Fe^{3+} is about 4.

Regarding (ii): Surprisingly, a ternary metal-ion complex consisting of an aromatic amine and a ligand having an O donor is frequently more stable than the binary complex —at least with Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}. This means, that contrary to the general rule $K^{M}_{ML} > K^{ML}_{ML_2}$, positive values are obtained for[4]

$$\Delta \log K = \log K^{MA}_{MAB} - \log K^{M}_{MB}$$

in other words, the equilibrium

$$MA + MB \rightleftharpoons MAB + M$$

is shifted to the right.

[*] Priv.-Doz. Dr. Helmut Sigel
Institut für Anorganische Chemie der Universität
CH-4056 Basel, Spitalstrasse 51 (Switzerland)

Regarding (iii): If the first ligand coordinated is an aromatic amine, the binary complex of Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} possesses discriminating properties, *i. e.* a ligand having an O donor will be coordinated preferentially to a ligand with an N donor. This is mainly attributable to the π-acceptor qualities of the aromatic amine (*e.g.* of pyridine and imidazole groups) and only to a limited extent to the compensation of charge in the ternary complex[4]. Thus the equilibrium constant of the reaction

$$MA_2^{2+} + MB_2^{2-} \rightleftharpoons 2MAB$$

for the 2,2'-bipyridine-Cu^{2+}-pyrocatecholate system is 1.4×10^6 and only 450 for the ethylenediamine-Cu^{2+}-pyrocatecholate system, both constants being greater than the statistically predicted value of 4.

Additionally, with regard to biological systems the "kind of structure" of a ternary complex is important. For example, coordination of the nucleic bases is prevented in 2,2'-bipyridine-Cu^{2+}-nucleoside triphosphate complexes[5]. Such factors have an effect on the reactivity; *e.g.* the deprotonation of the amide group occurs at pH *ca.* 8 in 2,2'-bipyridine-Cu^{2+}-oligoglycine complexes whereas the same reaction takes place at pH 7 and 4, respectively in Cu^{2+}-glycinamide and Cu^{2+}-glycylglycine[6]. Similar effects are manifested in catalytic processes: 2,2'-bipyridine-Cu^{2+} is a more effective catalyst, as compared to Cu_{aq}^{2+}, both for the decarboxylation of acetonedicarboxylate and for the disproportionation of H_2O_2[3,4].

Lecture at Konstanz, Germany, on May 4, 1972 [VB 346 IE]
German version: Chem. *84*, 833 (1972)

[1] *R. D. Gillard*, Inorg. Chim. Acta Rev. *1*, 69 (1967).
[2] *R. J. P. Williams*, Inorg. Chim. Acta Rev. *5*, 137 (1971).
[3] *H. Sigel* and *D. B. McCormick*, Accounts Chem. Res. *3*, 201 (1970).
[4] *R. Griesser* and *H. Sigel*, Inorg. Chem. *9*, 1238 (1970); *10*, 2229 (1971).
[5] *H. Sigel*, Eur. J. Biochem. *3*, 530 (1968).
[6] *H. Sigel*, *R. Griesser*, and *B. Prijs*, Z. f. Naturforschg. *27b*, 353 (1972).

Malate-Lactate Transhydrogenase

By *S. H. George Allen*[*]

Malate-lactate transhydrogenase catalyzes the following reaction:

L-lactate + oxaloacetate $\rightleftharpoons$ pyruvate + L-malate

It has been purified and shown to be a single protein having a molecular weight of 70000. Spectroscopic and fluorescence analysis of the native enzyme reveal an absorbance band at 350 nm, and a fluorescence peak at 440 nm. Addition of L-malate or L-lactate causes an increase in these peaks while addition of either pyruvate or oxaloacetate to the enzyme eliminates them. Treatment of the native enzyme in 7M urea or 5M guanidinium chloride removes the prosthetic group which cannot be removed by other methods. The prosthetic group has been resolved from the apoenzyme by gel filtration. The isolated cofactor exhibited coenzyme activity with lactate dehydrogenase and is chromatographically identical with NADH. The apoenzyme is very insoluble and cannot be reactivated even in the presence of cofactor. This protein could be solubilized in 7M urea with 0.1% mercaptoethanol or by succinylation. Molecular weight determination of the apoenzyme by sedimentation and diffusion in the analytical ultracentrifuge gave a molecular weight of 40000. The equivalent weight per coenzyme binding site as measured by absorbance at 350 nm yields a value of 35000. Thus the transhydrogenase is similar in structure to the mitochondrial malate dehydrogenase and has the same equivalent weight per coenzyme binding site as lactate dehydrogenase which is a tetramer rather than a dimer.

Malate-lactate transhydrogenase reacts according to a modified "ping pong mechanism". The reaction can be shown to proceed in two separate steps. First by:

$$[2\text{-}^3H]\text{-L-lactate} + \text{E-NAD}^+ \rightarrow \text{pyruvate} + \text{E-}[^3H]\text{-NADH}$$

If this reaction is carried out using stoichiometric amounts of enzyme then equivalent amounts of pyruvate can be isolated by ultrafiltration, and if tritium labeled lactate is used then the radioactive enzyme can be isolated on a gel filtration column. If this radioactive enzyme is then incubated with oxaloacetate, and again subjected to gel filtration all the radioactivity is released from the enzyme and appears with the low molecular weight substances as labeled malate in the second step:

$$\text{oxaloacetate} + \text{E-}[^3H]\text{-NADH} + H^+ \rightarrow [^3H]\text{-L-malate} + \text{E·NAD}^+$$

The results of kinetic analysis at low substrate concentrations are in agreement with this mechanism. At higher substrate concentrations however substrate inhibition occurs and the kinetics become complex.

Lecture at Konstanz on April 27, 1972 [VB 347 IE]
German version: Angew. Chem. *84*, 901 (1972)

[*] Dr. S. H. G. Allen
Fachbereich Biologie der Universität
775 Konstanz (Germany), P.O. Box 733

α-Chloroenamines: New Reagents for Organic Synthesis

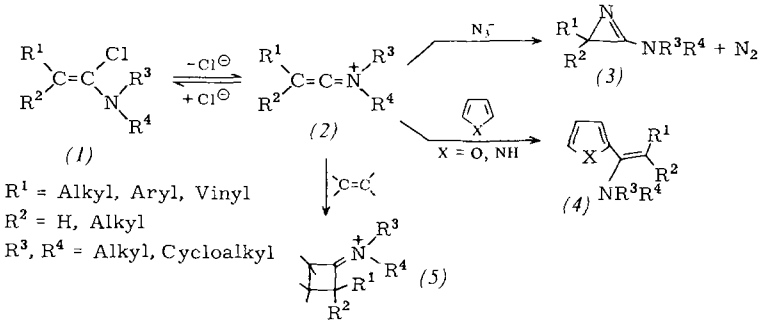
By *Léon Ghosez*[*]

The presence of an electron donating group and a suitable leaving group on an sp^2 carbon atom is expected to confer a versatile chemical behavior to the unsaturated system. α-Chloroenamines *(1)* are interesting representatives of this class which can be readily obtained from tertiary amides and phosgene followed by elimination of HCl with triethylamine.

In contrast to ordinary vinyl halides they show a remarkably high reactivity toward nucleophilic reagents. The results are best explained by prior ionization to a keteneimmonium ion *(2)* followed by attack of the nucleophilic reagent. This behavior is illustrated by the reaction of α-chloroenamines with sodium azide which yields quantitatively aminoazirines *(3)*, a new class of cyclic amidines which show interesting properties.

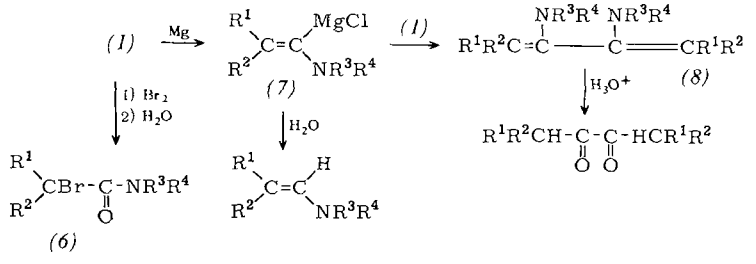
[*] Prof. Dr. L. Ghosez
Laboratoire de Chimie Organique de Synthèse—U.C.L.
Naamsestraat, 96
B-3000 Louvain (Belgium)

Furthermore, alkylsubstituted α-chloroenamines react readily with electron-rich aromatics in electrophilic substitutions without the need of an acid catalyst. This reaction, called aminoalkenylation, allows for the specific and direct introduction of enamine functional groups on nucleophilic carbon centers *(4)*.



Keteneimmonium salts *(2)* cycloadd to various unsaturated substrates to give four-membered rings *(5)* in high yields. Even with ethylene the reaction takes place at room temperature with high yield. All additions are directio- and stereospecific.

Like enamines, α-chloroenamines *(1)* also react as nucleophiles at the β-carbon atom with various electrophilic reagents, *e. g.* Br_2, to yield compounds of type *(6)*.



Furthermore, with magnesium in boiling THF they form a new type of Grignard reagent *(7)* which can be hydrolyzed to enamines or coupled with *(1)* to give a new class of activated dienes *(8)*.

Lecture at Stuttgart an May 18, 1972 [VB 348 IE]
German version: Angew. Chem. *84*, 901 (1972)

Synthesis of Ethylene-Olefin Copolymers by Means of Soluble Organometal Catalysts

By *Hans Schnecko*[*]

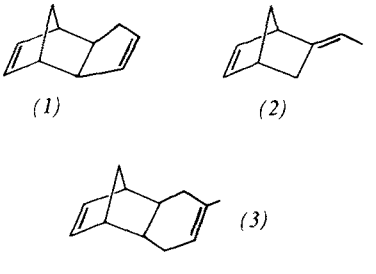
Besides the known ethylene-propylene copolymers and the terpolymers of these two monomers with small amounts of non-conjugated dienes (EPDM) it is possible also to prepare copolymers from ethylene and these dienes [especially bicyclic derivatives of norbornene such as dicyclopentadiene *(1)* and ethylidenenorbornene *(2)* or hexahydromethyl-1,4-methanonaphthalene *(3)*] in any desired molar ratio, and also terpolymers with diene contents appreciably higher than customary hitherto (*i.e.* up to > 60 wt.-%).

[*] Prof. Dr. H. Schnecko
Dunlop-Forschung
645 Hanau (Germany)

Combinations of the known vanadium halides with organoaluminum compounds are particularly suitable as catalyst systems. It is assumed that the active species are relatively short-lived soluble complexes of trivalent vanadium (half-life < 10 min, according to the aluminum compound used). Further, the activity of the catalyst is dependent on the amount and the nature of the diene.

The synthesis is best carried out in a closed system under slight excess pressure (< 5 atm). Addition of the reactants must be controlled. The molecular weight is regulated by H_2.

In ethylene-diene copolymers it was found that the polyethylene crystallinity decreases continuously with increase in the proportion of diene and that with 45—50 wt.-% of diene the polymers are amorphous. The modulus-temperature curves pass through a minimum at *ca.* 50—60 wt.-% of diene. Owing to the rigidity of the ethylene



comonomers the glass transition temperature T_G lies in the region of 0 °C, whereas with propylene as comonomer customary values of *ca.* −55 °C are found for T_G. Thus terpolymers starting from equimolar amounts of ethylene and propylene plus diene are characterized by appreciably lower softening ranges (*ca.* −45 °C), which, however, are shifted upwards again with increasing diene content; at > 30 wt.-% of diene the T_G values once more rise above 0 °C.

From IR spectra and measurement of oxygen uptake it can be shown that autoxidative cross-linking of the pro-

ducts readily occurs, this leading to insolubility. Polymers of this type can thus, for instance, be used as coatings, and pigmented or colorless lacquers with good properties can be obtained.

Lecture at Clausthal-Zellerfeld on June 2, 1972 [VB 350 IE]
German version: Angew. Chem. *84*, 902 (1972)

Chirooptical Properties of the Cystine Disulfide Bond

By *R. Schwyzer*[*]

In synthetic [2,7-cystine]gramicidin S the cyclodecapeptide is bridged by a disulfide group. NMR studies show that, as in gramicidin S, the peptide chain of the compound exists in the antiparallel β-conformation. Shielding effects indicate *P*-helical[1] chirality for the disulfide bridge. In molecular models the dihedral angle φ amounts to about 120°. According to theory[2] the *P*-helical arrangement, linked with $|90°| < |\varphi| < |180°|$, requires that the contribution of the longest-wavelength absorption band to the rotation should be negative, and we have confirmed this experimentally by measurement of the circular dichroism (λ_{min} = 271.5 nm, rotational strength $R = -12.3 \times 10^{-40}$ erg cm^3). In addition, the theoretically required second Cotton effect with the opposite sign can be clearly seen for this compound (λ_{max} = 230 nm, $R = +58.6 \times 10^{-40}$; measurement in ethanol).

[*] Prof. Dr. R. Schwyzer
Institut für Molekularbiologie und Biophysik der Eidgenössischen Technischen Hochschule
CH-8049 Zürich (Switzerland)

Theory further requires that disulfide bonds with $\varphi = \pm 90°$ absorb at *ca.* 250 nm, and also that when the arrangement of the disulfide bond is chiral none of the optical activity inherent in the disulfide bond should appear. This requirement seems to be satisfied with cyclo-L-cystine. According to ^{1}H- and ^{13}C-NMR measurements the molecule has a diketopiperazine ring in the chair form and a chiral disulfide bridge. In molecular models $\varphi = 90°$. In the ultraviolet spectrum, absorption is observed at 247 nm, but there is no long-wave Cotton effect. We assign a strong negative Cotton effect at 228 nm (CD in ethanol) to the n, π* transition of the peptide-carbonyl group. We interpret the sign and rotatory power ($R = 45.5 \times 10^{-40}$) of this band as indicating the existence of cyclo-L-cystine as the *P*-helical diastereomer, but this would require confirmation by other techniques.

These investigations support the theoretical treatment and confirm the quadrant rule: $0° < \varphi < 90°$, $180° < \varphi < 270°$: $R(+) \equiv P$-helical; $90° < \varphi < 180°$, $270° < \varphi < 360°$: $R(+) \equiv M$-helical. The chirality of the disulfide bond cannot be deduced from measurements of the circular dichroism (CD) and rotatory dispersion (ORD) alone without a knowledge also of the (approximate) dihedral angle.

Lecture at Freiburg on May 29, 1972 [VB 354 IE]
German version: Angew. Chem. *84*, 902 (1972)

[1] *R. S. Cahn, Sir Christopher Ingold,* and *V. Prelog,* Angew. Chem. *78*, 413 (1966); Angew. Chem. internat. Edit. *5*, 385 (1966).

[2] *J. Linderberg* and *J. Michl,* J. Amer. Chem. Soc. *92*, 2919 (1970).

[3] *U. Ludescher* and *R. Schwyzer,* Helv. Chim. Acta *54*, 1637 (1971); *B. Donzel, B. Kamber, K. Wüthrich,* and *R. Schwyzer, ibid. 55*, 947 (1972).—See also *M. Carmack* and *L. A. Neubert,* J. Amer. Chem. Soc. *89*, 7134 (1967); *D. L. Coleman* and *E. R. Blout, ibid. 90*, 2405 (1968).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The properties of collagen and gelatin in the solid state are reviewed in an article by *I. V. Yannas*. The structural unit of solid collagen in its various forms is the tropocollagen "molecule", a right-handed superhelix itself consisting of three left-handed protein helices connected by N—H···O bridges. Furthermore, these protein chains are apparently built up from two alternating types of subunits, one of which is rich and the other poor in imino acids (proline, hydroxyproline). Gelatin is the amorphous form of collagen. The report contains sufficient relative data, summarized and in some cases also interpreted, to form a basis for an adequate physico-chemical description of collagen and gelatin in the solid state. [Collagen and Gelatin in the Solid State. Rev. Macromol. Chem. *8*, 49—104 B (1972); 190 references]

[Rd 525 IE–G]

The labeling of receptor sites in biological material with photochemically generated reagents is the theme of a report by *J. R. Knowles*. This method aims to simulate the natural situation

receptor + ligand ⇌ [receptor·ligand]

with a reagent that structurally resembles the ligand and interacts specifically with the receptor. In the reaction

[receptor·ligand] → [receptor – ligand]

the reagent should not behave specifically; it must be capable of insertion into C—H bonds. These conditions are fulfilled by photochemically generated carbenes and nitrenes. Examples of applications are the labeling of antidinitrophenyl- and anti-2-nitro-4-azidophenyl anti-

bodies. [Photogenerated Reagents for Biological Receptor-Site Labeling. Accounts Chem. Res. *5*, 155—160 (1972); 45 references]

[Rd 523 IE –L]

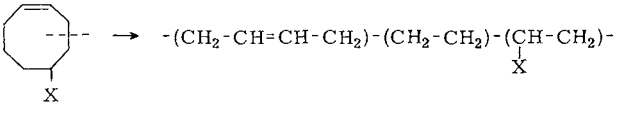
Carbenoids, carbenes, and nitrenes as polymerization initiators are described in a report by *M. Imoto* and *T. Nakaya*. The polymerizations of ethylene, methyl methacrylate, and vinyl monomers are described. Despite the same type of initiator being used, these polymerizations proceed partly by radical and partly by ionic mechanisms. The first two sections of the report constitute a review of the polymerizations of diazoalkanes and bisdiazo compounds. [Polymerization by Carbenoids, Carbenes, and Nitrenes. Rev. Macromol. Chem. *8*, 1—48 (1972); 64 references]

[Rd 524 IE –G]

Polymerizations of cycloolefins which proceed *via* ring opening are summarized in a report by *N. Calderon*. Processes of this type can be considered as reactions involving bond rearrangement since for each bond cleaved in the monomer there is formed a bond of similar type in the polymer. The analogy between these reactions and olefin metathesis

$$2R^1{-}CH{=}CH{-}R^2 \rightleftharpoons R^1{-}CH{=}CH{-}R^1 + R^2{-}CH{=}CH{-}R^2$$

is thus clear, and it is not by chance that the latter owes its discovery to efforts made in elucidating the mechanism of polymerization. Ring-opening polymerization of cycloolefins is the only process a available for preparation of copolymers exhibiting exact alternation:



[Ring-Opening Polymerization of Cycloolefins. Rev. Macromol. Chem. *8*, 105—159 (1972); 86 references]

[Rd 526 IE –G]

The thermodynamics of polymerization are outlined in a progress report by *H. Sawada*. The author limits this discussion to cationic reactions, *i.e.* to processes in which the growing polymer carries a positive charge. Ionic polymerizations can be divided into (i) the initial dissociation step, in which the active polymerization ion is formed, (ii) chain growth, the mechanisms of which resemble those of free-radical polymerization, (iii) growth termination, for example by loss of a proton, and (iv) transfer of charge to another molecule (usually a monomer). Data are given, on the basis of examples, regarding the magnitude of various thermodynamic parameters that are characteristic of these reaction steps. [Thermodynamics of Polymerization. Rev. Macromol. Chem. *8*, 161—187 (1972); 30 references]

[Rd 527 IE –G]

The electronic theory of cyclic $(pd)_\pi$-systems is dealt with in a review article by *G. Häfelinger*. The work is concerned with the question of what happens to the ground state of an aromatic π-electron system when p_π-orbitals are replaced by d-orbitals that can form π-bonds. Is an exceptional stabilization of the ground state, *i.e.* aromaticity, to be expected? This question is dealt with both theoretically and experimentally, in the latter case with regard to transition-metal chelates containing aliphatic 1,2-diimine ligands. It is found that in cyclic $(pd)_\pi$-systems a cyclic electron delocalization is possible, which could lead to enhanced stability. However, in not one case of such a system alone can it be proved that there is such an unusual stabilization of the ground state which could be looked upon as aromatic. [Theoretical Considerations for Cyclic $(pd)_\pi$-Systems. Fortschr. Chem. Forsch. *28*, 1—39 (1972); 129 References]

[Rd 531 IE –G]

Organic syntheses with transition metal complexes are reviewed by *J. Tsuji*. Many reactions of this type can be considered to proceed in three steps: formation of a σ-bond between the metal and hydrogen, carbon, oxygen, nitrogen, or halogen; insertion of groups with multiple bonds or of carbenes into this bond; and finally, detachment of the resulting molecule from the metal. The role of the metal in cyclization reactions is more complex, since, in this case, both π-bonding as well as σ-bonding to the metal are of importance. [Organic Synthesis by Means of Transition Metal Complexes. Fortschr. Chem. Forsch. *28*, 41—84 (1972); 173 References]

[Rd 532 IE –G]

The stereochemistry of double bonds, especially its determination by NMR spectroscopy, is the subject of a review by *G. J. Martin* and *M. L. Martin*. Double bonds of the type C=C, C=N, and N=N in organic compounds are dealt with, but not structural elements in which only partial double bond character occurs, as, for instance, in carboxamides of azoxy compounds. Various methods by which the configurations of double bonds can be determined NMR spectroscopically are described and values for chemical shifts and coupling constants are tabulated. [The Stereochemistry of Double Bonds. Prog. Nucl. Magn. Resonance Spectrosc. *8*, 163—259 (1972); 445 References]

[Rd 535 IE –G]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i.e.* provisionally published specifications as filed with the German Patent Office

Improved polyester fibers suitable for dyeing under high-temperature conditions are obtained by spinning polyesters with an oligomer content of less than 1.1%, preferably 0.3—0.8%, and a relative viscosity of 1.55—1.7. The oligomer content is reduced *e.g.* by extraction of the granulated polymer before spinning. The new polyester fibers exhibit a reduced tendency to give thread breaks during twisting, as well as less abrasion than conventional polyester fibers dyed under high-temperature conditions. [DOS 2000359; Glanzstoff AG, Wuppertal]

[PR 3 IE –A]

Crosslinked, carbon-loaded polyolefin textile fibers are produced by extrusion of substantially uncrosslinked mixtures of 20—80 wt.% of polyolefin, 80—20 wt.% of an electrically conducting carbon black, and 0.01 to 5 wt.% of an organic peroxide to form substantially uncrosslinked fibers, cooling the uncrosslinked fibers to temperatures below the melting point of the polyolefin, supporting the cooled fibers, and then passing the cooled fibers through an electromagnetic field having a frequency of between 8.9×10^2 and 1×10^{12} Hz. During the final phase, the temperature of the fibers is raised at least to the decomposition point of the peroxide, and at the same time at least to the melting point of the polymer. The polyolefin fibers have a tensile strength of at least 0.3 g/den and an elongation at break of at least 10%, so that they can be woven. [DOS 2123281; Beaunit Corp., New York]

[PR 6 IE -A]

New biologically active heptapeptides having the formula *(1)* are characterized by an action on the system's pressure

X—Trp—Ala—Val—Gly—His—Leu—Met—NH_2 *(1)*

X = H, carboxylic acid, amino acid, or dipeptide residue or protected derivatives or salts.

and a stimulatory action on the uterus, intestine, and gastric secretion, and they also increase the blood sugar level. They are prepared by known methods. [DOS 2137971; Societa Farmaceutici Italia, Milan]

[PR 11 IE -N]

Insulin derivatives that cause only slight immunization and a method for their preparation are claimed. In these insulin derivatives (bovine and pig insulin), the terminal amino residue of the B chain (B_1, phenylalanine) is protected by an acyl residue or other blocking residue; the amino residue of the A chain (A_1, glycine) is either free or protected by an acyl residue or other blocking residue. Monosubstituted derivatives protected at B_1 are preferred. The protection can be readily achieved by known acylation processes, the content of acylating agent being kept low to obtain maximum yields of B_1-acylated insulin. [DOS 2023447; National Research Development Corp., London]

[PR 12 IE -N]

Monoacyl derivatives of insulin *(1)* **with improved physicochemical properties** are obtained as follows:

H—Gly—Ile— ..... (A-chain) ...
A—Phe—Val— ..... (B-chain) ... } *(1)*

A = alkanoyl, phenylalkanoyl, benzoyl, alkyloxycarbonyl, aralkyloxycarbonyl, aminoacyl.

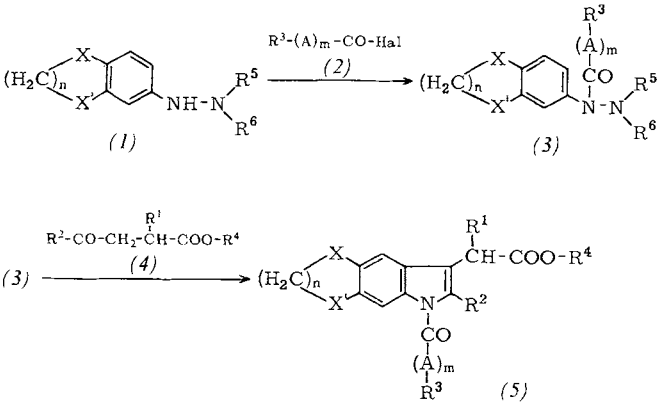
Insulin (preferably bovine and/or pig insulin) is treated with a mixture of an *N,N*-dialkylcarboxamide and an aqueous buffer solution (pH = 8.0—9.0) and an excess of *tert*-butyloxycarbonyl azide, and is then allowed to react with 2 to 4 equivalents of an activated ester of a carboxylic acid A—OH. The reaction product is then treated with a strong acid, *e.g.* trifluoroacetic acid. The new compounds, which are characterized *e.g.* by modified solubility coupled with full insulin activity, allow the production of preparations containing a component that dissolves more readily and one that dissolves less readily, so that a desired time-effect relationship can be produced. [DOS 2038121; Farbwerke Hoechst AG, Frankfurt/Main-Höchst]

[PR 14 IE -N]

A preparation containing L-3-(4-hydroxy-3-methoxyphenyl)-alanine and having an antiparkinsonian action is claimed. The active substance, which may also be present as a salt or hydrate, has a lower toxicity than L-dopa and a depot effect. By addition of one or more inhibitors of the peripheral decarboxylase, it is possible to reduce the quantity of active substance that must be administered. A process for the production of the preparation and a method for the treatment of parkinsonism are included in the idea of the invention. [DOS 2131616; F. Hoffmann-La Roche and Co. AG, Basel]

[PR 16 IE -N]

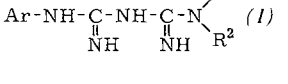
Antiphlogistic *N*-acyl-3-indolylacetic acid derivatives *(5)* are prepared by reaction of phenylhydrazine derivatives *(1)* with acyl halides *(2)* to form N^1-acyl compounds *(3)*, which are condensed with aliphatic keto acid derivatives *(4)*. The compounds *(5)* have antipyretic, analgesic, and antiphlogistic properties coupled with low toxicity. X, X' = —O—, —CH_2—; $m = 0, 1$; $n = 1,2$; A = substituted or unsubstituted saturated or unsaturated hydrocarbon residue



(up to C_5); R^1, R^2 = H, alkyl; R^3 = alkyl (C_{1-4}), cycloalkyl (C_{3-7}), unsubstituted or substituted aryl, monoalicyclic or polyalicyclic residue, heterocyclic residue; R^4 = H, alkyl (C_{1-4}), any cation; R^5, R^6 = H, protective group. [DOS 2142196; Sumitomo Chemical Co., Ltd., Osaka]

[PR 18 IE -N]

New biguanides *(1)* are prepared by condensation of an amine having the formula $ArNH_2$ or R^1R^2NH with a dicyanodiamide or an aryl derivative thereof. They have hypoglycemic and anorectic effects. Ar is a trifluoromethyl-



phenyl residue, which may be halogen-substituted. Possibilities for R^1 and R^2 are: R^1 and R^2 are H or a linear or branched alkyl residue containing 1—12 C atoms; R^1 is H, and R^2 is a cyclohexyl residue or a heterocyclic residue, which may be substituted with halogen atoms, lower alkyl residues, lower alkoxy residues, fluoroalkyl residues, tri-

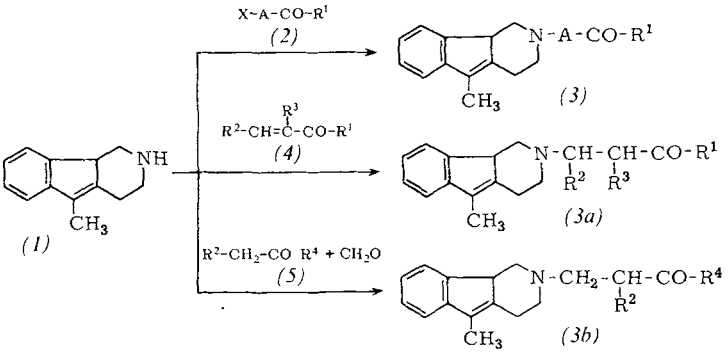
haloalkyl residues, and/or nitro residues; R^1 and R^2 together with the nitrogen atom form a heterocycle. [DOS 1693036; Laboratories Laroche, Navarron]

[PR 19 IE -K]

The contraceptive reliability of the minipill can be improved by the daily administration of a combination of a progestagen and a progestin (ratio 10—30:1) instead of a gestagen. 17α-Ethynyltestosterone derivatives or 19-nortestosterone derivatives are regarded as progestins, and progesterone or retroprogesterone derivatives as progestagens. The dose of each component is lower than the dose of the same component that is required for reliable contraception when used alone as a minipill. [DOS 2146239; CIBA-Geigy AG, Basel]

[PR 27 IE -N]

1,3,4,9b-Tetrahydro-2*H*-indeno[1,2-*c*]pyridines *(3)* and their acid adducts are characterized by a pronounced inhibitory effect on open aggression in doses such that general depression of the central regulations is not yet detectable. They can be used for the treatment of hereditary or congenital disturbances of personality and for the prevention and treatment of mental illnesses. The compounds *(3)* can be obtained by reaction of the indenopyridines *(1)* with ketones *(2)* in the presence of an acid-binding agent. The compounds *(3a)* and *(3b)* can be obtained by reaction of *(1)* with the alkenes *(4)* in the presence of a base or by reaction of *(1)* with formaldehyde and the ketones *(5)* under the conditions of a Mannich reaction.



R^1 = lower alkyl, cycloalkyl, (substituted) aryl; A = alkylene (C_1—C_4)
X = acid residue of a reactive ester; R^2, R^3 = H, alkyl (C_1,C_2)
R^4 = lower *tert*-alkyl, (substituted) aryl.

[DOS 2046298; Sandoz AG, Basel]

[PR 26 IE -N]

BOOK REVIEWS

Biochemisches Praktikum (Manual of Practical Biochemistry). By *S. Heilenz, W. Höfner,* and *K. H. Neumann*. Bibliographisches Institut, Mannheim 1970. 1st Edit., 239 pp., 27 figures, bound, DM 8.90.

This laboratory course manual presents a collection of classical and modern methods of quantitative analysis for students of agricultural, forestry, and food sciences. It is intended to be covered in a two-semester course of 5 hours per week, and to provide students with a grasp of the possibilities for dealing quantitatively with their specific problems. The selection of methods is therefore almost entirely confined to the narrow field of fertilizer and plant ash analysis.

The first few sections, which are clearly based on direct practical experience, provide very exact and detailed introductions to the methods of gravimetric and volumetric analysis, flame photometry, and colorimetry. A few practical exercises are set in each case, but these are sometimes, as in the case of the colorimetric determination of Cu, highly colored by the circumstances of the particular application, or else the authors, as in the discussion of the further possibilities of spark spectroscopy or atomic absorption spectroscopy, have allowed their enthusiasm to carry them far beyond the bounds of a course manual. The presentation of the theoretical principles is readily comprehensible.

The chromatographic experiments are weak, the methods that are most important at present, such as gas chromatography, merely being reported. The radiochemical experiments are poorest of all. One receives the impression that these later parts of the book, which are treated unfeelingly, are too short, because of lack either of material or of time, and that they have been included mainly for show, though they constitute the most "biochemical" material of the entire course, since such an introduction becomes a handbook of practical biochemistry only if the biological aspect is not ignored. It is time for biochemists to resist the widespread misuse of their name. Where in this course is anything said about the living or surviving object? Only in the very briefly mentioned uptake of ^{32}P and ^{59}Fe in plant material. However, once the biochemist has overcome this disappointment and accepted the entire book as a slightly modified manual of practical analysis, it is a well-intentioned and well-produced book, from which the student and even the course supervisor can learn a great deal.

L. Jaenicke [NB 62 IE]

Foreign Compound Metabolism in Mammals. Vol. 1. Specialist Periodical Reports. Published by The Chemical Society, London, 1970. 1st Edit., iii, 455 pp., numerous figures and tables, bound £ 11.00.

The question of the metabolic fate of drugs, food additives, and pesticides has always been raised by biochemists and pharmacologists, but is also increasingly stirring the public conscience, following recent incidents that have shown the serious consequences, both for the individual

and for the community, that can result from the indiscriminate recommendation and use of such substances.

Toxicologists and clinical pharmacologists have the responsible task of investigating not only the mode of action but also the side reactions and breakdown of chemicals before they are placed on the market, and of pointing out possible dangers. In this work they make use of modern biochemical procedures and analytical methods, as well as their knowledge of biochemistry as a fundamental science. The information that has been acquired and collected here frequently allows *a priori* prediction of possible harmful effects and carcinogenic action, whether direct or *via* breakdown and transformation products. Nevertheless, there have been many surprises, which show the need for constant watchfulness, particularly since it is too easy to forget that extrapolations from one species of animal to another, or even to man, are unreliable, and that differences due to sex and condition exist even within the same species.

The present volume, which is the first of a series of progress reports on the metabolism of foreign compounds in mammals, deals with the absorption, distribution, and excretion of drugs, the kinetics of these processes, and the experimental labeling methods for the investigation of these pharmacodynamically important problems, as well as the transformations and transformation pathways of drugs in the mammalian organism as a function of age, sex, and state of development. It presents a modern and extremely topical survey of the pharmacological and other relevant literature of the 1960's. The publications, which were often widely scattered, have been collected, sorted, and above all presented critically and understandably from the chemist's point of view by several authors. The report does not mention the latest techniques of gas chromatography and mass spectrometry, which promise, individually and in combination, to become an important aid in the statics and dynamics of drug metabolism, or the bioactivation of drugs and inhibitors as an essential factor in their biological and therapeutic activity; however, the material presented is very carefully balanced in itself.

This work will be extremely useful to all clinical pharmacologists, toxicologists, and biochemists, as well as to interested chemists, as an up-to-date reference work. It also provides interesting reading, and goes into the principles and the development of the problems, so that it may provide the biologically less experienced chemist with new insights.

L. Jaenicke [NB 61 IE]

Radiochemie (Radiochemistry). By *W. Schulze*, Walter de Gruyter & Co., Berlin 1971. 1st Edit., 157 pp., 33 figures, stitched DM 7.80.

The book provides an introduction to the types of nuclear radiation, the interaction of radiation with matter, the measurement of radiation, working rules, and working methods of radiochemistry, as well as the preparation of radionuclides. Most radiochemical problems and some of the problems of nuclear chemistry are presented in a readily understandable fashion. The strength of the book lies in the concise manner in which the basic principles are presented. The text is well supported by tables and figures. The book is particularly suitable for chemistry students desiring an introduction to the field of radiochemistry, but will also be extremely useful to other scientists who wish to familiarize themselves with the fundamentals of radiochemistry. The subject index could have been somewhat more detailed; moreover, familiarization with the field would have been facilitated by a list of further reading.

Knut Bächmann [NB 63 IE]

Chemical Energetics. By *N. J. Selley*. Edward Arnold Ltd., London 1971. 1st Edit., ix, 209 pp., numerous tables, bound £ 3.20.

The author of this little book attempts to give an introduction to chemical thermodynamics, *e.g.* within the scope of a first course with exercises on general chemistry. The book contains many exercises (with solutions at the end of the book), fully worked examples, and instructions for practical experiments, as well as a (rather skimpy) subject index, a table of four-figure logarithms, and tables of atomic weights, bond energies, redox potentials, *etc.* It is therefore a textbook and a laboratory manual all in one.

The book is practically free from printing errors and is well laid out. Unfortunately, it has little pedagogical value and the writing is sloppy in places. It may be pardonable, when symbols like +ve (for "positive") or RMS (for "root mean square") are not explained anywhere in the book, since these are probably familiar to the English readers for whom the book was written. However, inadequacies stand out when definitions become ambiguous (*e.g.* on p. 9, $1\ \text{eV} = 1.6 \times 10^{-19}$ J is followed by 1 eV/mol $= 96487\ \text{J mol}^{-1}$) or when concepts are obscured (as *e.g.* van der Waals forces on p. 49). It almost seems to be a principle of the author to use a new concept first and to explain it later (*e.g.* the relation $\Delta G = -2.3\ RT \log K$ on p. 31 or the salt bridge on p. 36). Also awkward is the introduction of the entropy concept ($\Delta G = \Delta H - T \cdot$ something), and inept wording is too common to be overlooked (*e.g.* on p. 40 "... the sign of ΔS cannot be predicted, but is probably small..." or on p. 69 "As the efficiency of the harnessing of the work of reaction is made more efficient, the net gain of entropy is reduced", *etc.*). And that the reaction rate be proportional to $e^{-1/T}$ (p. 85) or that the kinetic energy be quantized (p. 59) can at best be described as misleading.

At most, therefore, the book has some value as a collection of exercises. However, in view of the outstanding books on chemical thermodynamics that already exist in German and in English, it cannot really be recommended to anyone.

Günther v. Bünau [NB 64 IE]

Organic Photochemical Syntheses. Vol. I. By *R. Srinivasan* and *T. D. Roberts*. Wiley-Interscience, New York—London 1971. 1st Edit., x, 108 pp., numerous figures and tables, bound £ 4.75.

The present volume, which is the first of a planned series, corresponds in style and layout to the well-tried pattern of "Organic Syntheses". A brief introduction to photochemical techniques, with mention of a number of safety precautions (17 pages), which is not intended to replace the study of more comprehensive systematic monographs (*e.g. A. Schönberg, G. O. Schenck,* and *O. A. Neumüller*: Preparative Organic Photochemistry. Springer, Berlin 1968), is followed in varied succession by 39 detailed procedures from 28 research groups, nearly all of which have been independently checked. This provides even the non-photochemist with easy access to 20 products containing four-membered rings and five products with three-

membered rings. The other examples deal with syntheses of products containing five-membered (three cases), six-membered (two cases), and eight-membered rings (one case), four isomerizations without ring formation in the end product, three oxidations, and one aromatic substitution.

The arrangement into structural formulas, authors, "Procedure", "Notes", "Methods of Preparation", and "Merits of the Preparation" in many cases enables the reader to find information that is not contained in the original publications. The concluding "References" cannot give complete coverage of the literature, which is unfortunate, since a complete collection of all the procedures published so far (*e.g.* including *H. M. Frey*, J. Chem. Soc. *1964*, 365, for the synthesis of quadricyclane) could be particularly useful to the non-photochemist, as the equipment listed in the examples in the volume may be unavailable in many cases.

It is to be hoped that further photochemists will be prepared to help with the later volumes, and that the selection of the examples will be based mainly on preparative considerations. "Organic Photochemical Syntheses" will then prove useful both in practical instruction and in research, and should be available in any library where these aspects are important.

Gerd Kaupp [NB 65 IE]

Polymer Networks—Structural and Mechanical Properties. By *A. J. Chompff* and *S. Newman*. Plenum Press, New York—London 1971. 1st Edit., xiv, 493 pp., numerous figures, bound $ 31.50.

The book contains 22 papers presented at a Symposium of the American Chemical Society in Chicago in September 1970 by distinguished scientists such as *P. J. Blatz*, *K. Dušek*, *M. Gordon*, *R. F. Landel*, *W. Prins*, and *M. L. Williams* on the subject of "Highly Crosslinked Polymer Networks". The discussions are appended to the papers.

The first ten papers are concerned with the network as a continuum. They deal with the kinetics of the crosslinking processes, the macrothermodynamics and the microstatic mechanics of networks, and the influence of the network structure and intermolecular forces on the glass transition temperature and the mechanical properties. The next twelve papers deal with the particularly important question of the inhomogeneities and heterogeneities of networks in a wide variety of forms. Four papers discuss the methods for the characterization of such networks by means of birefringence and light scattering. The importance of the microstructure to swelling and to the stress-strain behavior up to breakage is finally discussed in several papers.

The proceedings of the ACS Symposium do not have the character of a textbook with the integrated form of a monograph. Their main significance is the topicality of the various contributions. The book, a remarkable review of the most important developments in the field of crosslinked polymers, includes many results of recent research and provides an excellent supplement to former publications, *e.g.* to those by *Kuhn*, by *Treloar* and *Dušek*, and by *Prins*. Chemists, physicists and engineers with the necessary background find up-to-date information of research and development in the field of crosslinked polymers.

Dieter Heinze [NB 66 IE]

Organic Peroxides. Vol. 2. By *D. Swern*. Wiley-Interscience, New York—London 1971. 1st Edit., ix, 963 pp., numerous figures and tables, bound £ 19.00.

The new volume of *Swern's* work has followed the first[1] in a gratifyingly short time. Of the eight chapters in the volume, those by *Mair* and *Hall*: "Determination of organic peroxides by physical, chemical, and colorimetric methods" and by *Silbert*: "Physical properties of peroxides" deserve special mention because of their general interest, particularly since there were no similar modern reviews of these fields.

However, the other chapters (*Hiatt*: Hydroperoxides, *Sosnovsky* and *Rawlinson*: The chemistry of hydroperoxides in the presence of metal ions, *Sosnovsky*: Metal-ion catalyzed reactions of hydrogen peroxide and peroxydisulfate, *Davies*: Formation of organometallic peroxides by autoxidation, *Swern*: Organic peroxy acids as oxidizing agents. Epoxidation, and *Hiatt*: Acyl peroxides) are also valuable and exhaustive monographs on these fields, which are of great interest in part even to the inorganic chemist. Lavish use has been made of figures and tables throughout. An example is provided by a list of all expoxidations carried out since 1952, amounting to about 1600, arranged according to the peracid used. The total of almost 4000 references evaluated and the 32-page subject index also testify to the diligence of the authors and of the editor.

This work, which is practically free from errors and excellent in its presentation, is a necessity for any library. It is with keen anticipation that we look forward to the third and final volume.

Rudolf Criegee [NB 68 IE]

Crystal Chemistry and Semiconduction. By *J. P. Suchet*. Academic Press. New York—London 1971. 1st Edit., xvii, 380 pp., numerous figures, bound $ 22.—.

The book was written to provide scientists working on semiconductors in university polytechnics and in industry with a survey of the developments of the past 20 years and of the present research position in the difficult field of semiconducting binary compounds of the transition metals, the lanthanoids and the actinoids. The author is a chemist, and he can thus appreciate the great variety of the compounds investigated and their properties, and present the material in an orderly fashion.

The first 80 pages are spent in laying the theoretical foundations for the description of the bonding in crystals. In earlier years the author built up a classification that is partly his own, and this forms the basis of the book. The language is thus defined, and the reader is then in a position to translate a described situation into concepts with which he is familiar.

In the second part of the book (200 pages), the relationships between crystal structure, chemical bonding, and physical properties are discussed. The presentation intentionally avoids what the author, with some justification, calls the often "esoteric" tendencies of solid-state physicists. There are frequent hints of the author's own experience and of his familiarity with experimental work. The treatment of the compounds with IIIB, IVB, and VB elements is fairly short (45 pages); this is a reflection of the large amount of investigation that still remains to be carried out on these compounds. Considerable space (80 pages) is devoted to the oxides, while the chalcogenides occupy 50

pages. The topics discussed include the phase relations, the crystal structures, the electric, magnetic and sometimes also the optical properties. Conflicting experimental and theoretical results are considered critically. Observations for which no explanation has been found are also mentioned. The author expresses himself very briefly. He evidently places special value on complete coverage of the literature, since more than 1000 original publications to which the reader can and should refer are cited in this second part of the book.

The third part (60 pages) deals with some problems of major interest and with future applications, particularly with magnetic properties in their relation to electric and optical properties.

Comprehensive formula, author, and subject indexes enhance the value of the book.

The book has filled a need, since there had previously been no survey of the results obtained in this field. It can serve as an introduction for those with sufficient background knowledge, while it should stimulate experimental and theoretical workers to further research.

One disadvantage should not pass without mention. The captions to the figures, most of which have been taken from the literature, are frequently too brief, and the meanings of the symbols are often not explained.

Heinz Krebs [NB 69 IE]

The Alkaloids. Vol. 1. Specialist Periodical Reports. Published by The Chemical Society, London 1970. 1st Edit., xiii, 505 pp., numerous figures, bound £ 11.—.

The well-known series of reviews now examines another field of the chemistry of natural products, *i.e.* the chemistry of the alkaloids. The present book in every respect maintains the high standard set by earlier volumes (*e.g.* in the series: Amino Acids, Peptides, and Proteins). It covers works from the entire field of alkaloid chemistry in 1969 and in the first half of 1970; only publications on steroid alkaloids from the families *Solanum* and *Veratrum* have not been considered. The book also contains chapters on the biosynthesis of the indole alkaloids and also of the other alkaloids.

For the specialist, the volume is a valuable source of references (even to less readily accessible periodicals) and of detailed information. Chemists who are interested in natural products in general will also find this review very useful. The main directions that have been taken in recent years by the chemistry of the alkaloids are pointed out.

The volume reviewed here and the series that it introduces will be essential to all those who are concerned with natural products. It is to be hoped that the new publication will find many attentive readers.

Karel Bláha [NB 70 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 40 36/40 37, Telex 46 55 16 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (06201) 40 31, Telex 46 55 16 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 10
October 1972
Pages 861–948

International Edition in English

^{1}H-NMR Spectra of the AA'XX' and AA'BB' Type – Analysis and Classification[**]

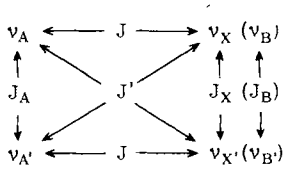
By Harald Günther[*]

It is shown how the secular determinant for the general four-spin case can be greatly simplified in the case of NMR spectra of the AA'XX' and AA'BB' type on the basis of molecular symmetry and with the aid of the so-called X approximation. The methods for the direct analysis of these spectra are presented, and the relations between the type of spectrum and the chemical structure are discussed in detail for selected examples. In an appendix, parallels are pointed out between the formalism of the Hückel MO theory and the calculation of the eigenvalues and eigenfunctions of nuclear spin systems.

1. Introduction

The theory of high resolution NMR spectra of nuclei with spin $^1/_2$ is now substantially complete, and numerous methods are available for the analysis of these spectra[2]. Analytical methods that are particularly important in practice are those that enable the desired information about the resonance frequencies and coupling constants of a spin system to be obtained directly from the observables, *i.e.* the line frequencies and intensities. However, the application of these *direct methods* is generally confined to spin systems with less than five nuclei, and a certain molecular symmetry is usually required.

Among the more complicated spectra for which direct analysis is possible are those of AA'XX' and AA'BB' spin systems. They are characterized by two resonance frequencies ν and four coupling constants J, *i.e.* the A and the X(B) nuclei are chemically, but not magnetically equivalent:



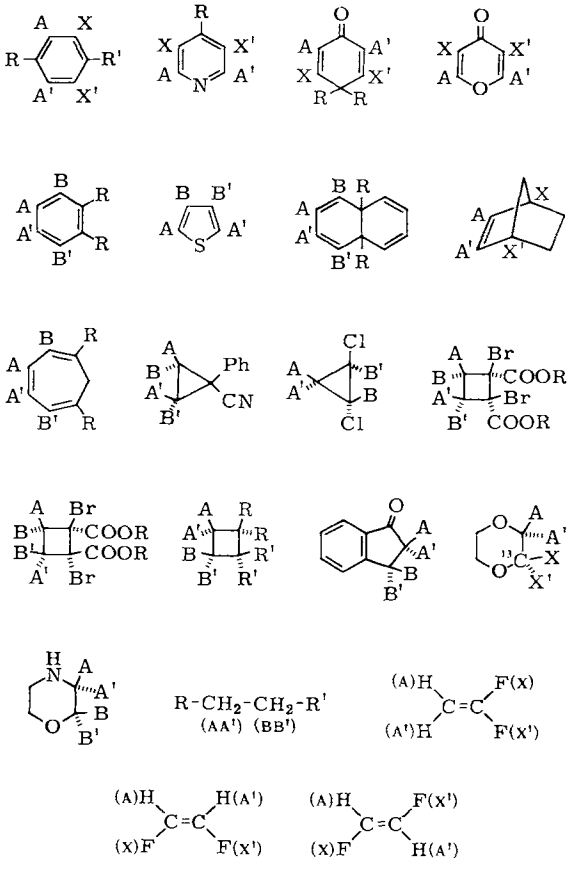
As can be seen from Table 1, these types of spectra are of wide occurrence for organic molecules; their analysis provides valuable information about the structure, configuration, and conformation of the compounds in question.

The mathematical formalism necessary for the *synthesis* of an NMR spectrum—*i.e.* the calculation of line frequencies and intensities from a set of resonance frequencies ν_i and coupling constants J_{ij}—also forms the basis of the HMO model[3], which rightly occupies an important place at present in chemical education. This parallel, which is almost trivial as far as the theory is concerned,

[*] Prof. Dr. H. Günther
Institut für Organische Chemie der Universität
5 Köln, Zülpicher Strasse 47 (Germany)

[**] This review supplements the earlier progress report in this journal by *Dischler*[1].

Table 1. Molecules with NMR spectra of the AA'XX' or AA'BB' types.



but which is only rarely recognized because of the still prevalent unfamiliarity with quantum-mechanical principles, will be shown in an appendix (Section 4). It will suffice for the present to point out that for the direct *analysis* of an NMR spectrum, *i.e.* the determination of the parameters ν_i and J_{ij} from the observed line frequencies, the mere reversal of the mathematical formalism mentioned, which at first seems the obvious course, is possible only in the two-spin case. In this case, the solution of the secular determinant[4] leads to quadratic equations, which can be explicitly solved. This leads to the well-known relations for the AB system[1]:

$$\delta\nu = \nu_A - \nu_B = \sqrt{(J_4 - J_1)(J_3 - J_2)} \quad (1)$$

$$|J| = J_4 - J_3 = J_2 - J_1 \quad (2)$$

All spin systems with more than two nuclei, on the other hand, have secular determinants of higher order, which generally no longer allow the derivation of similar equations. It is therefore an important object of the direct spectral analysis to simplify the secular determinant in such a way that it can be factorized into subdeterminants of the order two[5]. This can be achieved in favorable cases on the basis of the symmetry of the spin system or with the aid of the "X approximation"[6].

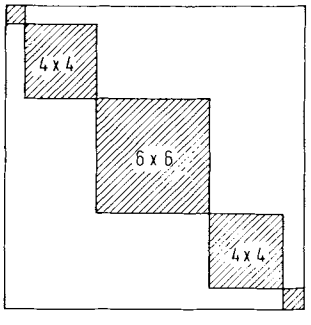
The significance of these principles will be illustrated below for AA'XX' and AA'BB' systems. By their application, the more complicated AA'XX' four-spin system may be regarded as a superposition of a_2 and ab subspectra—*i.e.* simple two-spin systems. On the one hand, a direct analysis is possible in this way, and on the other, the diversity of the experimental spectra can be systematically discussed, to a close approximation even for the AA'BB' case. For the derivation of a series of concepts that will be used in the next section, the reader is referred to the introductory article by *Dischler*[1] and to the appendix (Section 4).

2. Direct Analysis of AA'XX' and AA'BB' Systems

For the general four-spin case, the basis functions for the characterization of the spin states are, as usual, the products φ_k of the spin functions α and β, of which there is a total of 16 in the present case:

$m_T = +2$	$m_T = +1$	$m_T = 0$	$m_T = -1$	$m_T = -2$
(1) αααα	(2) βααα	(6) ββαα	(12) βββα	(16) ββββ
	(3) αβαα	(7) βαβα	(13) ββαβ	
	(4) ααβα	(8) βααβ	(14) βαββ	
	(5) αααβ	(9) αβαβ	(15) αβββ	
		(10) αββα		
		(11) ααββ		

The secular determinant that is derived on the basis of the variation method[3, 52] using eq. (A 2) and the Hamiltonian operator eq.(A6) is therefore of the order 16. Since only basis functions with the same total spin m_T mix with one another, it factorizes into subdeterminants of the order 1, 4, 6, 4, and 1:



(3)

For the AA'XX' system, much greater simplification results from the additional consideration of the symmetry and the application of the "X approximation".

First, instead of using the usual product functions as the basis, it is possible to use the products of the symmetry functions s_{+1}, s_0, s_{-1} and a_0, such as are known for the A_2 system[2] (cf. Appendix), and which are valid here for the AA' and for the XX' nuclei. If the resulting basis functions are arranged according to the total spin $m_T(X)$ of the XX' group, one obtains Scheme 1. A similar result is obtained if the functions are arranged according to $m_T(A)$ instead of $m_T(X)$.

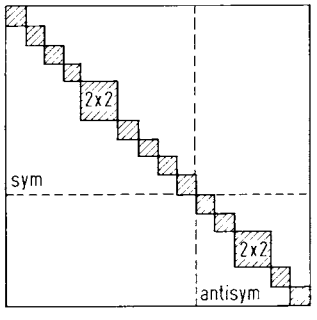
The result of this consideration is:

1. The separation of the basis functions into a symmetric and an antisymmetric set, between which transitions are forbidden by symmetry[2, 54].

	Symmetric product functions		
m_T			
+2	(1) $s_{+1}(A)\ s_{+1}(X)$		
+1	(2) $s_0\ (A)\ s_{+1}(X)$	(4) $s_{+1}(A)\ s_0(X)$	
0	(3) $s_{-1}(A)\ s_{+1}(X)$	(5) $s_0(A)\ s_0(X)$ (6) $a_0(A)\ a_0(X)$	(8) $s_{+1}(A)\ s_{-1}(X)$
−1		(7) $s_{-1}(A)\ s_0(X)$	(9) $s_0\ (A)\ s_{-1}(X)$
−2			(10) $s_{-1}(A)\ s_{-1}(X)$
$m_T(X)$	+1	0	−1
	Antisymmetric product functions		
m_T			
+1	(11) $a_0(A)\ s_{+1}(X)$	(12) $s_{+1}(A)\ a_0(X)$	
0		(13) $a_0(A)\ s_0(X)$ (14) $s_0(A)\ a_0(X)$	
−1		(15) $s_{-1}(A)\ a_0(X)$	(16) $a_0(A)\ s_{-1}(X)$
$m_T(X)$	+1	0	−1

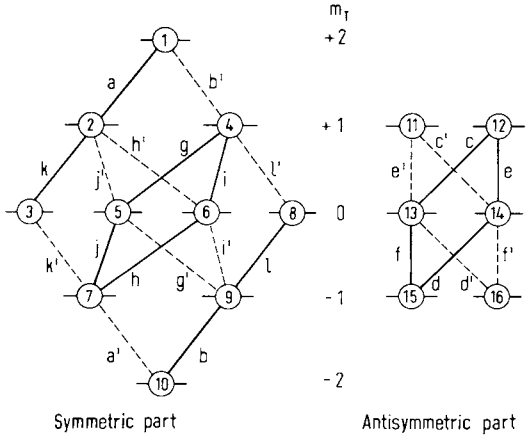
Scheme 1. Products of the symmetry functions s_{+1}, s_0, a_0 and s_{-1} of the A_2 system (cf. Section 4). The symmetry of the products obeys the general rule that products of functions of like symmetry are symmetrical, while those of functions of unlike symmetry are antisymmetrical.

2. The extensive factorization of the secular determinant on the basis of the "X approximation", according to which states with different $m_T(X)$ (or $m_T(A)$) values do not mix[2, 6]. The corresponding offdiagonal elements are therefore zero. The secular determinant (3) thus simplifies to (4), and apart from twelve subdeterminants of the order 1, whose elements H_{kk} are already correct eigenvalues of the AA'XX' system, it now contains only two subdeterminants of the order 2:



(4)

The simplification resulting from this treatment becomes particularly clear when one arranges the functions of Scheme 1 or the eigenfunctions calculated in accordance with (4) in an energy level diagram. Considering the transitions possible on the basis of the selection rules[1, 2],



Scheme 2. Energy level diagram of the AA'XX' and AA'BB' systems.

the structures of simple systems of the A_2 and AB types (Scheme 2) are immediately recognized. The AA'XX' system is thus reduced in the AA' and XX' parts to two a_2 and two ab subsystems each, which can be analyzed directly. They are represented in Figure 1 for a typical example by the line pairs a, k, and b, l, and by the quartets c, d, e, f and g, h, i, j.

The quantitative treatment[6], which we shall not give here, provides proof that the subsystems mentioned are in fact spectra of the A_2 and AB type. Moreover, it also leads to the relations between the effective spectral parameters of the subsystems, the shift differences N and L and the coupling constants K and M as defined in Figure 1, and the data for the AA'XX' system:

$$N = J + J';\ L = J - J';\ K = J_A + J_X;\ M = J_A - J_X \tag{5}$$

With the aid of the expressions (1) and (2), the following equations are derived for the direct analysis of the AA'XX' system:

$$N = a - b \tag{6}$$

$$L = \sqrt{(c-f)(d-e)} = \sqrt{(g-j)(h-i)} \tag{7}$$

$$K = g - h = i - j \tag{8}$$

$$M = c - d = e - f \tag{9}$$

As expected, because of the "X approximation", $\delta\nu(AX)$ does not appear in these relations. The AA'XX' system is thus independent of the relative chemical shift between A and X nuclei. The spectrum is symmetrical with respect to $(\nu_A + \nu_X)/2$, and each half spectrum is symmetrical with respect to ν_A or ν_X. The analysis does not allow the assignment of the resonance frequencies that are determined directly as center of the AA'- and XX'-part, respectively, or of the coupling constants J and J' or J_A and J_X, since the spectrum is unaffected by an interchange of the nuclei within one group or of the A and X nuclei, *i.e.* it is independent of the relative signs of N and L as well as K and M. It is therefore necessary to make use of the empirical relations between coupling constants and chemical structure, which give a conclusive answer in practically every case. For the resonance frequencies, the necessary clue is often provided by an asymmetry of the spectrum due to long-range coupling. Since N may be differentiated from

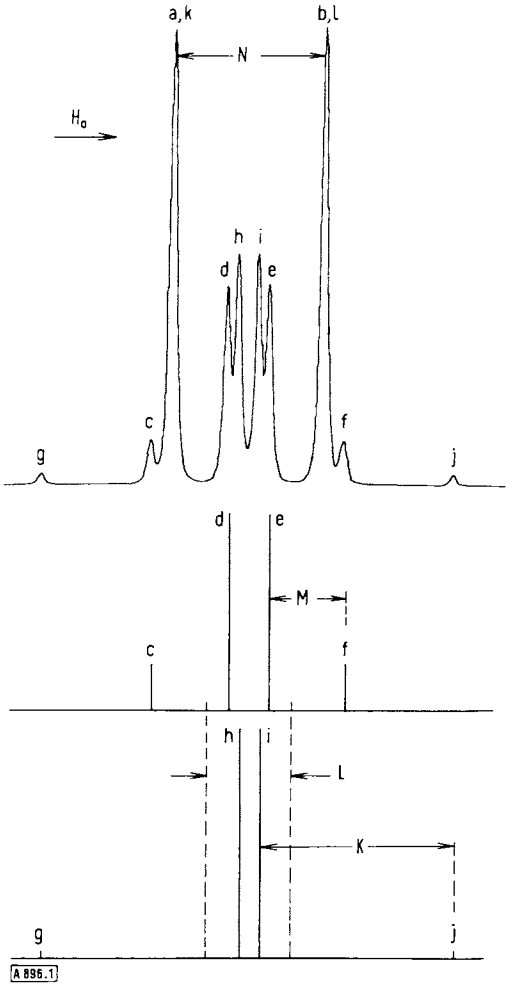
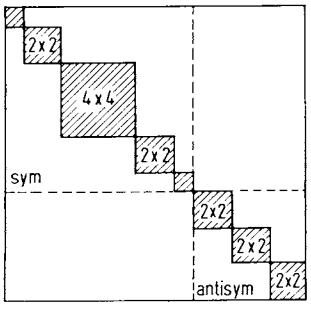


Fig. 1. Half-spectrum of an AA'XX' system ($J = 8.0$, $J' = 2.0$, $J_A = 9.0$, and $J_X = 4.0$ Hz) with antisymmetrical (c, d, e, f) and symmetrical (g, h, i, j) ab subspectra. Line designation after [9].

L, however, the relative signs of J and J' are obtained. For $|N| > |L|$, the signs are like, while for $|L| > |N|$ they are unlike. Equation (7) is decisive for the assignment of lines to the symmetrical and the antisymmetrical quartets, though the origin of the ab subspectra in the experimental spectrum may not be recognized. K and M cannot, therefore, be distinguished without further experiments (cf. Section 3.7), and the relative signs of J_A and J_X remain undetermined.

If we consider the AA'BB' system, the direct analysis is complicated by the fact that the spectrum now depends on the parameter $\delta\nu$(AB). The "X approximation" can no longer be applied, and the classification of the basis functions according to m_T(B) is lost. The secular determinant has the following form:



(10)

In the symmetrical part of the spectrum, therefore, the subdeterminant of order 4 prevents a simple solution. However, if one makes use of the theorem that the trace of the secular determinant is zero, *i.e.*

$$H_{44}+H_{55}+H_{66}+H_{77} = E_4+E_5+E_6+E_7$$

then equations can also be derived for the direct analysis of AA'BB' spectra[7–9]. These equations are given in Table 2. Further equations for special cases in which not all of the transitions are observed, as well as intensity relations[9, 10], are also known.

Table 2. Equations for the direct analysis of AA'BB' systems (after [9]). Line frequencies have to be measured with respect to the center of the spectrum at $(\nu_A+\nu_B)/2$.

$$\begin{aligned}
\delta\nu &= +\sqrt{4\,ab} \\
&= +\sqrt{2(ce+df)} \\
N &= a-b \\
K &= g+i+k-2a-l \\
&= 2b+k-h-j-l \\
&= b+g+k-a-h-l \\
&= b+i+k-a-j-l \\
M &= (ce-df)/\delta\nu \\
L &= +\sqrt{(c-e)^2-M^2} \\
&= +\sqrt{(d-f)^2-M^2}
\end{aligned}$$

An important difference between the AA'XX' system and the AA'BB' system is that in the latter case, the line groups a,k/b,l and c,d,e,f/g,h,i,j can no longer be regarded as a_2 or ab subsystems. The degeneracy of the line pairs a,k and b,l is lost, and the half-spectrum consists of twelve transitions. These are no longer symmetrical with respect to ν_A or ν_B, but the spectrum is still symmetrical with respect to the center $(\nu_A+\nu_B)/2$ (cf. *e.g.* Fig. 3). For very small $\delta\nu$(AB), the half-spectra may partly overlap, and the assignment of the lines will then be more difficult. The following distance relations still exist for the line groups of the symmetric and antisymmetric quartets

$$c-d=e-f \quad \text{and} \quad g-h=i-j.$$

Furthermore

$$g-a=b-j \quad \text{and} \quad a-i=h-b.$$

The direct analysis here yields definite values for the parameters $\delta\nu$, N, L, K, and M, and in addition the relative signs of K and N. The relative signs of all the coupling constants are therefore obtainable. The assignments of the resonance frequencies and of the coupling constants J and J' on the one hand and J_A and J_B on the other, however, are still undetermined. The variety of the possible types of spectra and their relations to chemical structure are discussed in the next section.

3. Classification of Spectra of the AA'XX' and AA'BB' Types

The central problem of the direct analysis of AA'BB' spectra is to find the correct line assignment. Computers[11, 12] or experimental aids (cf. Section 3.7) may be used for this

purpose. However, it is important to recognize the relations between the expected coupling parameters, *i.e.* ultimately the chemical structure, and the type of spectrum. The reduction of the AA'XX' four-spin system to a_2 and ab subspectra allows the systematic discussion of these relations. With regard to proton resonance, however, it should be noted that the AA'XX' type is only approximately realized here, since the differences in the shifts are strictly speaking too small for the "X approximation" to be valid, that is fully acceptable only in the case of heteronuclear spin systems, such as ^1H, ^{13}C or ^1H, ^{19}F combinations. Nevertheless, the AA'XX' approximation is adequate here for a qualitative discussion, if it is realized that the AA'BB' treatment must always be used for accurate analysis in the case of homonuclear spin systems. Furthermore, efforts will always be made to check the line assignment derived by the calculation of a test spectrum using one of the relevant programs[11]. Misassignments may thus be avoided by a careful comparison of calculated frequencies and intensities with the experiment. In addition, an improvement of the parameters may be obtained in most cases by the application of an iterative computing process[11], since in this case all the experimental information is used likewise. In contrast, the direct analysis is based mainly on the lines a—f (cf. Table 2).

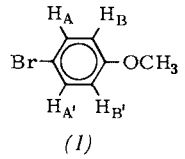
3.1. *p*-Disubstituted Benzenes of the Type XC_6H_4Y

The typical appearance of the spectrum for this group of substances[13] and for a series of other compounds such as 4-pyrone[14, 15], 2,5-cyclohexadienones[16], and 4-substituted pyridines[17] is illustrated in Figure 2 by the spectrum of *p*-bromoanisole *(1)*[13]. It is easy to interpret if the coupling constants to be expected for the molecule, all of which are positive, are considered: Here $J \gg J'$, J_A, and J_B.

The parameter N then consists of the relatively large *ortho* coupling (J) and the smaller *para* coupling (J'). The two a_2 subspectra are thus separated by about 7—9 Hz, and can be immediately assigned to the strong lines 1 and 2. A value of about 5—7 Hz is then found for the parameter L. On the other hand, the effective coupling parameters K and M of the ab subsystem are very different in the present case, since the remaining two *meta* couplings (J_A and J_X) are similar in magnitude. M is therefore generally smaller than 1 Hz, whereas a magnitude of about 4—6 Hz is to be expected for K. The symmetrical ab quartet (g, h, i, j) is clearly visible, whereas only the inner lines (d, e) of the antisymmetric quartet can be recorded. The outer transitions (c, f) coincide with the a_2 subsystems, and the parameter M can therefore be determined only inaccurately. In the case of the 2,5-cyclohexadienones, on the other hand, the lines c and f can be satisfactorily measured[16].

3.2. *o*-Disubstituted Benzenes of the Type $C_6H_4X_2$

Here one finds spectra that differ considerably from the AA'XX' limit in the majority of cases, since the relative chemical shift is generally small. For the coupling parameters the relation $J, J_A \gg J', J_B$, that is $N \approx L$ and $K \approx M$, holds. The result is that the lines a,k and b,l are no longer



(1)

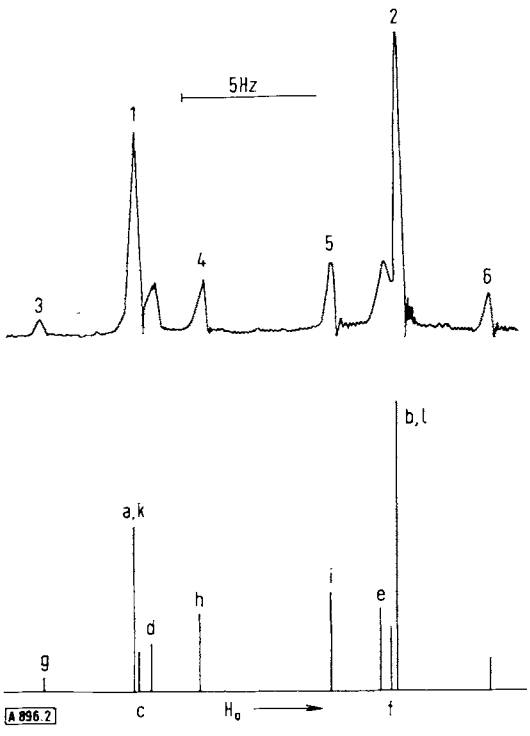
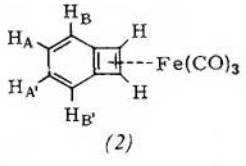


Fig. 2. Half-spectrum (AA' part) of the AA'BB' system of the aromatic protons in *p*-bromoanisole *(1)*: spectrometer frequency 60 MHz. The analysis gave $\delta\nu = 37.8$, $K = 5.6$, $L = 8.4$, $M = 0.5$, and $N = 9.0$ Hz (after [13]).

degenerate, and the A lines f and j are displaced in some cases past the center, *i.e.* into the B part. Moreover, the intensities of the lines c and g are greatly reduced. Figure 3 shows the spectrum of the six-membered ring protons in benzocyclobutadienetricarbonyliron *(2)*[18], as obtained with decoupling of the two four-membered ring protons.



(2)

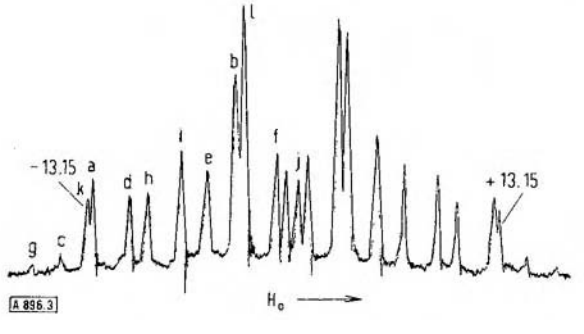
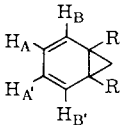
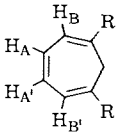


Fig. 3. AA'BB' system of the six-membered ring protons in benzocyclobutadienetricarbonyliron *(2)* with decoupling of the four-membered ring protons; spectrometer frequency 100 MHz. The analysis of the spectrum gave: $\delta\nu = 13.50$, $J = 8.61$, $J' = 0.69$, $J_A = 6.78$, and $J_B = 1.57$ Hz (after [18]).

Similar systems are found for thiophene[15, 19] and for substituted cyclohexadienes[20]. It is relatively simple here to determine the parameter N, since the strong lines a and b can be easily located. This information proves to be an important aid in the assignment of structures for norcaradiene-cycloheptatriene isomers, since N values of 9—11 and 5—6 Hz are found for systems of the types *(3)* and *(4)*, respectively, because of the different positions of the double bonds.

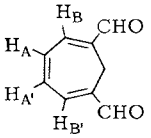


(3)



(4)

For strongly coupled spin systems, *i.e.* systems with small $\delta\nu$, according to *Dischler*, the assignment[9] is often possible by calculation of the A_4 and the AA'XX' limiting cases with estimated parameters and examination of the frequency changes of the various lines. Comparison of this interpolation between A_4 and AA'XX' systems with the experimental spectrum then shows the extent to which line superpositions occur or the regions in which lines of low intensity may be expected. This method was used, as shown in Figure 4, in the analysis of the four-spin system of the olefinic protons in cycloheptatriene-1,6-dialdehyde *(5)*[21], where, because of the large vicinal coupling $J_{3,4}$, the parameters K and M (12.27 and 10.93 Hz respectively) are much larger than the parameter L (5.31 Hz). One obtains $\delta\nu = 11.83$, $J_A = 11.60$, $J_B = 0.67$, $J = 6.03$, and $J' = 0.72$ Hz.



(5)

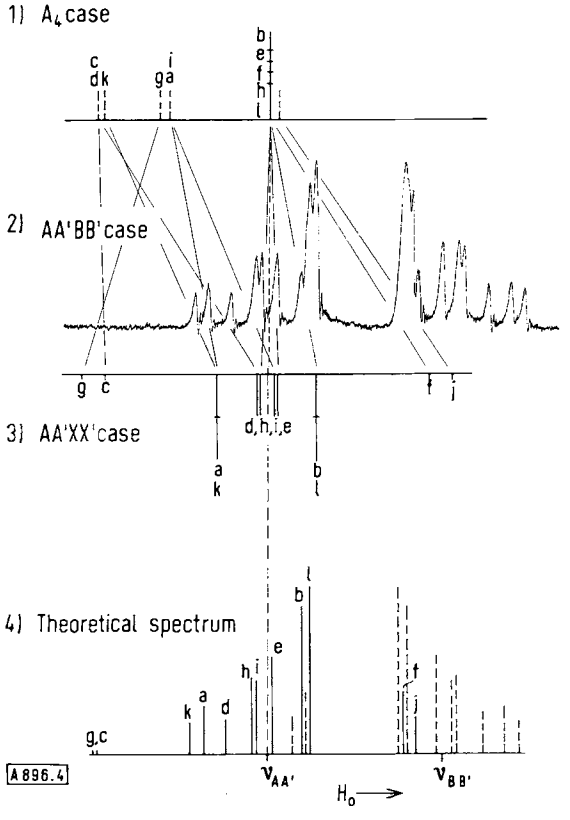
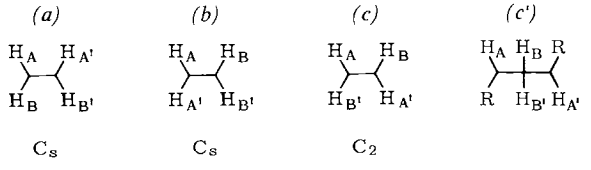


Fig. 4. AA'BB' system of the olefinic protons in cycloheptatriene-1,6-dialdehyde *(5)* with A_4 and AA'XX' limiting cases; spectrometer frequency 100 MHz (after [21]). The definite assignment h > i is possible here only on the basis of the iterative computer analysis.

3.3. Substituted Cyclopropanes, Cyclobutanes, and Five-Membered Rings

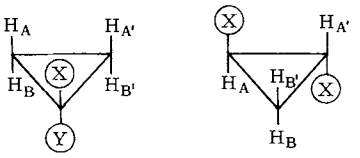
Depending on substitution, a CH_2-CH_2 fragment is expected to give one of three types of AA'BB' systems, which differ in their coupling parameters because of differences in local symmetry (C_s or C_2):



Three-membered rings normally give spectra of type *(a)* and, in addition, those of type *(c')*. Thus for 1,1-disubstituted cyclopropanes [*(6)*, type *(a)*][22], the magnitudes of the *cis* coupling constants are similar, so that a large difference exists between the parameters K and M in the sense $|K| \gg |M|$. Because of the negative sign of the geminal spin-spin interaction, moreover, $|N| \ll |L|$. As is shown in Figure 5 for 1,2-bis-(1-cyanocyclopropyl)ethylene, therefore, the lines a and b are situated close together, as are the lines c and d as well as e and f. The outer lines of the symmetrical quartet (g, j) are difficult to locate, since g has a low intensity and j is displaced past the center.

For the type *(c')* [*(7)*], in contrast with the case described above, $|K| \ll |M|$ and $|N| \gg |L|$[23, 24], so that an entirely different appearance is found. Finally, the type *(b)* is found for the ^{13}C satellite spectra of 1,1-disubstituted cyclopropanes with X = Y. In this case, $J_A = J_X$, *i.e.* $M = 0$. If K is also very large, the half-spectrum consists of five lines having an intensity ratio 2 : 1 : 2 : 1 : 2, as is found for the ^{13}C-satellites of the ^{19}F resonance of 1,1-dichloroperfluorocyclopropane[25].

The symmetry in four-membered rings is again either C_s or C_2 [*(8)* or *(9)*], depending on the substitution type. However, the resulting spectra do not differ appreciably, and resemble the spectrum of *(6)*[26]. In the case *(8)*, the parameters N and L are found to be $^2J \pm {}^3J_{trans}$, and in case *(9)* $^2J \pm {}^3J_{cis}$; the corresponding expressions for K and M are $^3J_{cis} \pm {}^3J_{cis}$ and $^3J_{trans} \pm {}^3J_{trans}$, respectively. Another substitution type with C_s symmetry [*(10)*] leads to spectra of a type that has been discussed in detail for indanone *(11)*[27]. In this case $N = {}^3J_{cis} + {}^3J_{trans}$, $L = {}^3J_{cis} - {}^3J_{trans}$, $K = {}^2J_A + {}^2J_B$, and $M = {}^2J_A - {}^2J_B$. It was found for *(11)* that $\delta\nu = 33.04$, $K = -37.13$, $L = 5.12$, $M = 1.79$, and $N = 12.10$ Hz, so that only the lines h and i are measured for the symmetrical quartet, as shown in Figure 6.



(6) (7)

3.4. Larger Ring Systems

Because of the conformational mobility of ring systems with more than five members, some of the measured coupling parameters are time averages. If we consider the ethane fragment in morpholine in a Newman projection,

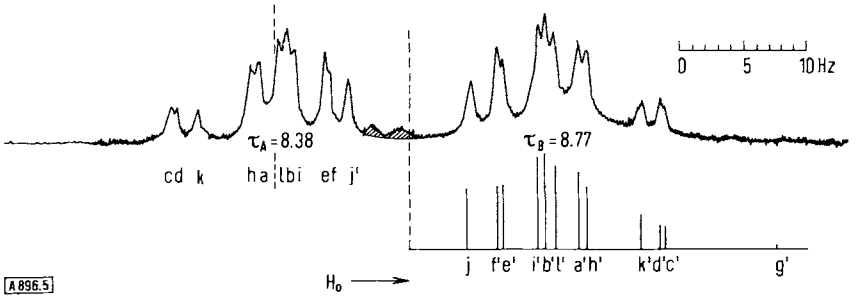
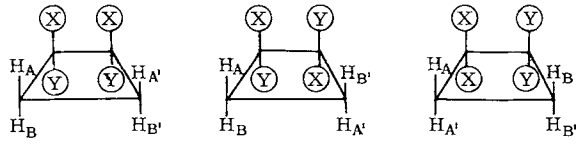


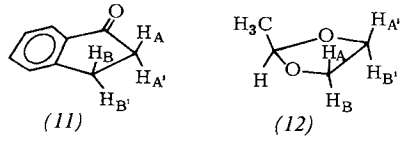
Fig. 5. 60 MHz AA'BB' spectrum of the three-membered ring protons in 1,2-bis(1-cyanocyclopropyl)-ethylene. The analysis gave: $\delta\nu = 39.1$, $J = -5.0$, $J' = 7.6$, $J_A = 9.6$, and $J_B = 9.2$ Hz (after [9]).

A type of spectrum that is similar to the type found for the disubstituted cyclopropane *(6)* is observed for 2-methyl-dioxolane *(12)*[28] and for ethylene sulfite[29]. In this case,



(8) (9) (10)

$J_A \approx J_B$, so that M is approximately zero. The AA'BB' half-spectrum generally consists of only ten lines, since the line pairs c,d and e,f may be resolved only under optimum conditions[2c].



(11) (12)

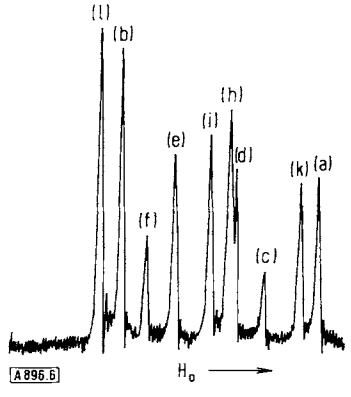
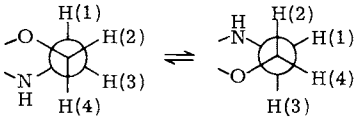


Fig. 6. Half-spectrum (BB' part) of the CH_2-CH_2 grouping in indanone *(11)*; spectrometer frequency 60 MHz (after [27]).

it is clear that the fast reversible ring inversion leads to a transition from the ABCD to the AA'XX' type of spectrum:



(13) *(14)*

The protons H(1) and H(3) on the one hand and H(2) and H(4) on the other change their positions, so that effectively $\nu_1 = \nu_3 = \nu_A$ and $\nu_2 = \nu_4 = \nu_X$. For the coupling constants, in addition to the two geminal interactions $J_{1,3} = J_A$ and $J_{2,4} = J_X$, only two other constants are found on time average, *i.e.*

$$J = 1/2[J_{1,4}(13) + J_{1,4}(14)] = 1/2(J_{trans} + J_{gauche}) = 1/2[J_{2,3}(13) + J_{2,3}(14)] = 1/2(J_{gauche} + J_{trans}) \quad (11)$$

$$J' = 1/2[J_{1,2}(13) + J_{1,2}(14)] = 1/2(J'_{gauche} + J''_{gauche}) = 1/2[J_{3,4}(13) + J_{3,4}(14)] = 1/2(J''_{gauche} + J'_{gauche}) \quad (12)$$

The criteria for an AA'XX' system are thus satisfied. The appearance of the spectrum is again determined in this case by the large geminal coupling constants, which have values of about -10 to -12 Hz. As in the case of *(11)*, the parameter K is therefore very large and the parameter M, as the difference between two large values, is relatively small. Since $J > J'$, moreover, $N > L$. Of the ab subspectra, therefore, in the case of the symmetrical quartet only the inner lines h and i can be observed without difficulty (and may appear as a singlet), while the antisymmetrical quartet should approach an AX system[30]; in the case $M \approx 0$, it degenerates to a doublet. The parameter K frequently cannot be determined, so that only the difference (M) between the coupling constants J_A and J_X is obtainable (Fig. 7). Despite the fact that the coupling constants J and J' measured in these systems do not allow direct determination of the parameters J_{trans}, J_{gauche}, J'_{gauche}, and J''_{gauche} that are characteristic for the conformation, their ratio,

the so-called R-value ($= J/J'$), proves to be a useful source of information in this respect[58].

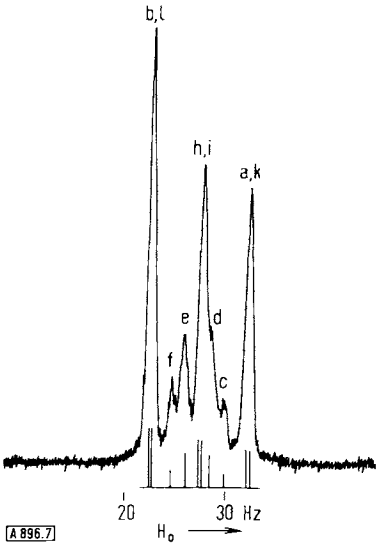
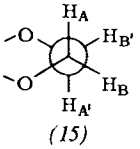


Fig. 7. Half-spectrum (BB' part) of the protons in morpholine, solution in benzene, at 60 MHz. The analysis gave: $\delta\nu = 54.3$, $N = 9.7$, $L = 3.6$, and $|M| = 1.5$ Hz (after [30]). The values found for the pure substance were: $\delta\nu = 81.0$, $J = 6.7$, $J' = 2.8$, $J_A = -12.2$, and $J_B = -11.1$ Hz [9]. At increased sensitivity it is also possible to measure line j [2b].

In symmetrical systems, such as 1,4-dioxane, fast ring inversion causes the spectrum to degenerate to the A_4 case, and the coupling parameters must be determined from the ^{13}C satellites, which give the desired AA'XX' system[31, 54]. The type of spectrum is the same as that of morpholine, except that because of the symmetry of the system (C_s, type *(b)* of the possibilities mentioned in Section 3.3), $M = 0$ and $J'_{gauche} = J''_{gauche}$.



(15)

On the other hand, an entirely different appearance is to be expected for a 1,4-dioxane *(15)* fixed in the chair form, since the CH_2-CH_2 fragment in this case has C_2 symmetry (type *(c)*), and $J = {}^2J$, $J' = {}^3J''_{gauche}$ (J_{ae}), $J_A = {}^3J_{trans}$ (J_{aa}), and $J_B = {}^3J_{gauche}$ (J_{ee}). Such a spectrum has been observed at -103 °C for the ethane fragment in [D_8]-cyclohexane[32] (Fig. 8). It is noteworthy here that because of the negative N value the transitions a and k lie closer to the center than b and l.

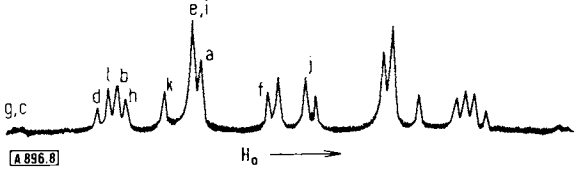
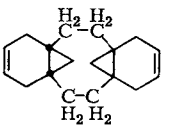
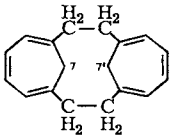


Fig. 8. AA'BB' system of the ethane fragment in [D_8]-cyclohexane at -103 °C with decoupling of the deuterons. The analysis gave: $\delta\nu = 28.76$, $J = -13.05$, $J' = 3.65$, $J_A = 13.12$, and $J_B = 2.96$ Hz (after [32]).

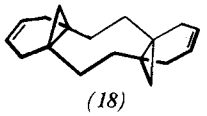
The connection between the type of spectrum of an ethane fragment and the dynamic behavior of the molecule in question is impressively demonstrated by the pair of compounds *(16)* and *(17)*[33]. For *(16)* one observes an AA'BB' system, whose analysis gives the following data: $J = {}^2J = -14.53$, $J' = {}^3J''_{gauche} = 2.21$, $J_A = {}^3J_{trans} = 10.61$, and $J_B = {}^3J_{gauche} = 5.58$ Hz.



(16)



(17)



(18)

The central eight-membered ring thus exists in a rigid chair conformation *(18)*. The compound *(17)*, on the other hand, gives an A_4 system for the ethane bridges between the cycloheptatriene fragments at room temperature. A fast consecutive inversion of the two cycloheptatriene rings must therefore be assumed for the molecule. As is shown by the experiments, it is only below -10 °C that this conformational transition becomes sufficiently slow on the NMR time scale to allow the observation of an AA'BB' system[*].

3.5. 1,2-Disubstituted Ethanes

As is shown by the Newman projections *(19)*—*(21)*, in addition to the conformational equilibrium already discussed for morpholine [cf. *(13)* $\rightleftharpoons$ *(14)*], 1,2-disubstituted ethanes exhibit a third component, *i.e.* the *trans* form *(19)*. Since an AA'BB' system is to be expected for this conformation as well as for the equilibrium *(20)* $\rightleftharpoons$ *(21)*, the type of spectrum remains unchanged, but the average values are now:

$$J = p_t J_{1,4}(19) + (1 - p_t)\,[J_{1,4}(20) + J_{1,4}(21)]/2 \quad (13)$$

$$J' = p_t J_{1,2}(19) + (1 - p_t)\,[J_{1,2}(20) + J_{1,2}(21)]/2 \quad (14)$$

where p_t is the mole fraction of the *trans* conformation *(19)*. Moreover:

$$J_A = p_t J_{1,3}(19) + (1 - p_t) J_{1,3}(20) \quad (15)$$

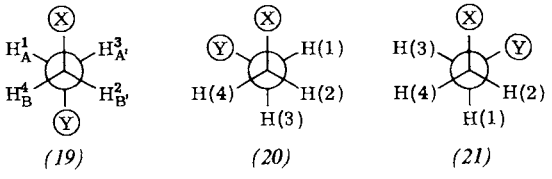
$$J_B = p_t J_{2,4}(19) + (1 - p_t) J_{2,4}(20) \quad (16)$$

Against the four observables J, J', J_A, and J_B, therefore, including the mole fraction p_t, there are eleven unknowns, so that the analysis of the spectrum does not provide direct information regarding the conformation of the ethane in question. Under the simplifying assumption that only *two* different vicinal coupling constants—namely $^3J_{trans}$ and $^3J_{gauche}$—exist for a given compound, it is possible to deduce

[*] This dynamic process is also recognizable by changes in the spectrum of the methylene protons on C(7) and C(7'), which transforms from the A_2 to the AB type.

from equations (13) and (14) that the expression $3/2N + 1/2L$ is constant and independent of the conformational equilibrium[34].

Further, because ${}^3J_{trans} > {}^3J_{gauche}$ it follows that for $L > 0 p_t < 1/3$. In this case, the *gauche* conformers *(20)* and *(21)* are more stable than the *trans* conformer *(19)*. $L = 0$ and a spectrum of the A_2B_2-type (cf Section 3.8) is obtained for $E_{trans} = E_{gauche}$, whereas $L < 0$ means $p_t > 1/3$ and thus $E_{trans} < E_{gauche}$.



(19) *(20)* *(21)*

Of the various spectral parameters, K, as the sum of the geminal interactions, has the largest magnitude for the 1,2-disubstituted ethanes. Since L is small, the lines g and j are only rarely observed because of their low intensity. Various situations are found for the antisymmetric quartet (c, d, e, f). For $M \approx 0$, it degenerates to two lines (c+d and e+f), while for $M \gg L$, only one line (d+e) is found. The lines a, k, and b, l are generally well separated and strong, and since $N \gg L$, they flank the lines c, d, e, f, and h and i.

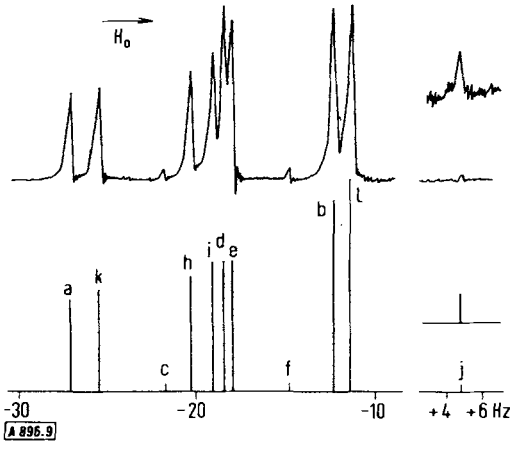


Fig. 9. Half-spectrum (AA' part) of the ethane protons in 1-phenyl-2-chloroethane; spectrometer frequency 60 MHz. The analysis gave: $\delta\nu = 36.54$, $J = 8.22$, $J' = 6.45$, $J_A = -10.66$, and $J_B = -13.84$ Hz (after [35]).

To illustrate the situation described, Figure 9 shows the spectrum of 1-phenyl-2-chloroethane[35]. Further examples have been described in detail[35, 36].

3.6. Deceptively Simple Spectra

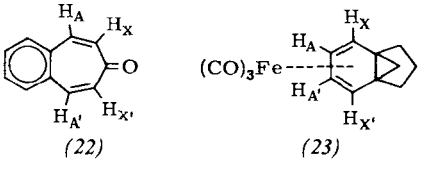
The sensitivity and the resolution of the spectrometer determine whether all the theoretically expected transitions of a spin system can be measured experimentally. If there are weak or closely spaced lines, one often observes spectra whose appearance resembles that of a simpler type of spectrum because of the apparent deficiency of lines. The analysis of such "deceptively simple" spectra may then be incorrect.

A well-known case is the deceptively simple AA'XX' system of the protons in furan[13], whose half-spectrum degenerates to a triplet. Since $L \ll K$, the symmetrical ab subspectrum approaches the a_2 type. The lines of the antisymmetric quartet coincide on the one hand (d, e) with h, i, and on the other, (c, f) with a, k, and b, l. A triplet is also found for the ^{19}F resonance of *trans*-1,2-dichloroperfluorocyclopropane[25], where K and M are very much larger than L. In both cases, therefore, the spectrum is not of the A_2X_2-type and the conclusion $J = J'$ suggested by its appearance is incorrect.

On application of the rules derived in the AB case for deceptively simple spectra, *i. e.* in this case A_2-like systems with $\delta\nu \ll J$, to the ab subspectra of the AA'XX' case, one obtains[37]

$$\Delta > L^2/2M \quad \text{or} \quad > L^2/2K$$
$$i > L^2/2M^2 \quad \text{or} \quad > L^2/2K^2$$

where Δ (the half-width of the single line) characterizes the resolution and i (the smallest line intensity that is still measurable) the sensitivity of the spectrometer. The experimental aids therefore have the object of improving these instrument characteristics. In addition to the CAT storage instruments used for the detection of weak lines, a



(22) *(23)*

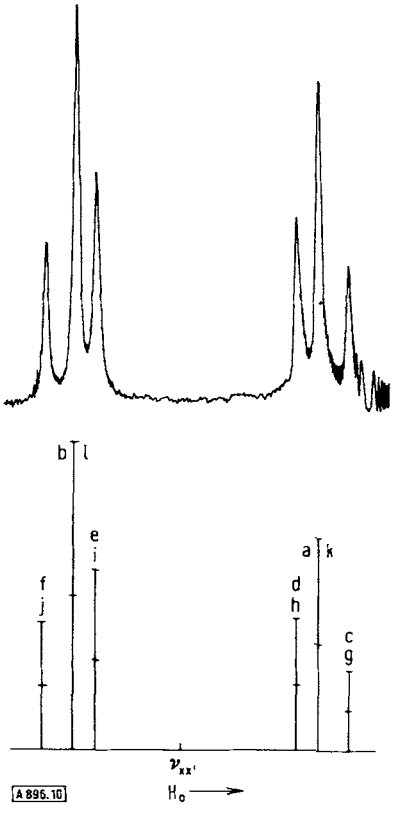


Fig. 10. 100 MHz half-spectrum (XX' part) of the seven-membered ring protons in 4,5-benzotropone *(22)* with decoupling of the aromatic protons. The analysis gave: $\delta\nu = 66.90$, $J = 12.64$, $J' = -0.11$, $J_A \leq 0.2$, and $J_X \approx 2.7$ Hz (after [21]).

very promising method is now available in Fourier transform spectroscopy[38, 39], which also allows the improvement of the resolution[40].

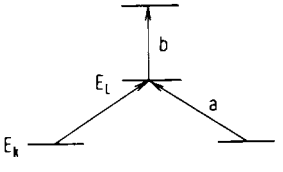
Another case of a deceptively simple four-spin system is found in the AA'XX' spectrum of the olefinic protons of 4,5-benzotropone *(22)*[21]. The coupling J_A here is very small, so that to within the accuracy of the measurements, $K = M$. Consequently, the two ab subspectra are degenerate, and only six lines are observed in the half-spectrum, which thus becomes similar to the X part of an ABX spectrum. According to the analysis, $|L| > |N|$, so that a negative sign results for J'. The limiting value for J_A can be estimated from the line width of the observed signals (Fig. 10). Deceptively simple six-line half-spectra of this type are also observed for a number of carbonylmetal complexes with cyclic diene ligands such as *(23)*[18, 41].

Finally, superposition of the inner quartet lines d, h and e, i can occur in the AA'XX' system for $K \approx M$ and $L < K, M$. The experimental half-spectrum then consists of eight transitions[42]. The olefinic protons of norbornene (Table 1) and similar unsaturated bicycles may give rise to such spectra, since in this case $J_X \ll J_A$.

3.7. Experimental Aids in Line Assignment

The line assignment for the direct analysis of AA'XX' or AA'BB' systems can be checked experimentally in many cases by spin tickling experiments[43, 44] or by the observation of double-quantum transitions[9, 15]. Reliable line assignment is often possible only with the aid of this additional information.

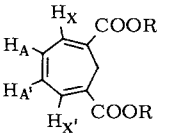
As is well known, in spin tickling experiments a transition $E_k \rightarrow E_l$ is irradiated with a second RF field of frequency ν_2 by selective double resonance; this leads to splitting of all lines that have an eigenvalue in common with the irradiated



transition. From the nature of the splitting (resolved or unresolved), moreover, it is possible to tell whether the line in question is regressively (a) or progressively (b) connected to the perturbed transition.

As can be seen from a glance at the energy level diagram of the AA'XX' and AA'BB' system (Scheme 2), spin tickling experiments should be useful here for distinguishing between symmetrical and antisymmetrical transitions and for the localization of subspectra. In this way it is possible even in the AA'XX' case to distinguish definitely between the line groups c, d, e, f and g, h, i, j, and hence between the parameters M and K. The relative signs of J_A and J_X are thus obtainable. Figure 11 illustrates such an experiment in the case of the cycloheptatriene-1,6-dicarboxylic ester *(24)*[21]. Irradiation was carried out in the XX' part at the line pair a', k'. In addition to the nuclear Overhauser effects[44] for the line pairs a, k and b, l due to the change in the Boltzmann distribution, one observes splitting of an inner and an outer line of the ab subspectra. The lines of the symmetrical quartet then flank those of the antisymmetrical quartet. Thus $K > M$, *i.e.* J_A and J_X have the same sign, which is positive in this case.

The nuclear Overhauser effect is often sufficient, with its characteristic intensity changes, to verify the line assignment[45]. Transitions of two or more quanta can be found at very high amplitudes of the observation field H_1, *i.e.* under saturation conditions for the one-quantum transi-



(24)

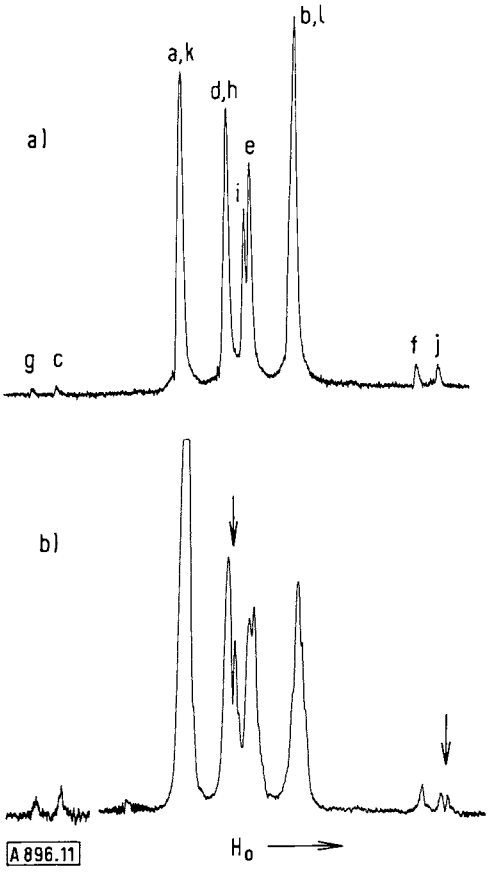


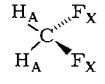
Fig. 11. Spin tickling experiment in the AA'XX' system of the olefinic protons of the cycloheptatriene-1,6-dicarboxylic ester *(24)*; spectrometer frequency 100 MHz. a) Single resonance spectrum (AA' part); b) double resonance spectrum (AA' part) with $\nu_2 = a'$, k' (after [21]). Result of the analysis: $J_A = 11.22$, $J_X = 0.82$, $J = 6.08$, $J' = 0.67$ Hz.

tions. They appear in the center of the ab subspectra and at $(\nu_A + \nu_B)/2$[9, 15]. In the case of AA'BB' spectra, whose appearance is influenced by the shift difference $\delta\nu$(AB), the recording of the spectrum at different field strength H_0 is often useful, since a superposition of lines may be detected in this way.

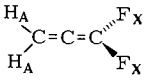
3.8. Magnetic Equivalence

The condition for the magnetic equivalence of the A and of the X or B nuclei in the AA'XX' or AA'BB' system is $J = J'$ and hence $L = 0$; one then obtains A_2X_2 or A_2B_2 spin systems.

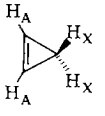
A_2X_2 systems, whose half-spectrum consists of a 1 : 2 : 1 triplet, are expected for symmetry reasons for difluoromethane *(25)*[46], 1,1-difluoroallene *(26)*, and cyclopropene *(27)*[47]. A transition AA'XX'→A_2X_2 is observed for 3,3-dimethylbutylmagnesium chloride *(28)*[48].



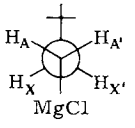
(25)



(26)



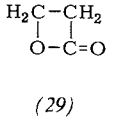
(27)



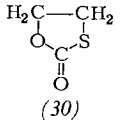
(28)

In this case, the fast inversion of the carbanion carbon at 32 °C leads to magnetic equivalence. In the calculation of the temperature-dependent line shape, the subspectral analysis was again found to be valuable. Under the condition that the parameter N remains constant, so that the line pairs a,k and b,l are unaffected by the dynamic process, it was possible to simulate the experimental spectra by the use of a simpler process ab→a_2 for the symmetrical and antisymmetrical quartets.

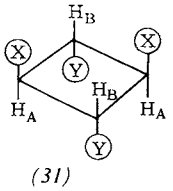
The theoretical A_2B_2 system has a half-spectrum of seven lines, and its line frequencies and intensities depend only on the ratio $J/\delta\nu$[2]. It is interesting to note that there does not at present seem to be any molecule for which this type of spectrum is obtained for protons. Earlier examples, such as propiolactone *(29)* or ethylene monothiocarbonate *(30)*, turned out to be deceptively simple AA'BB' systems[49, 50].



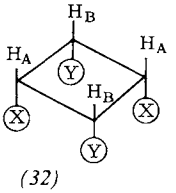
(29)



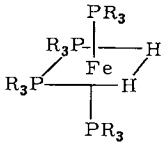
(30)



(31)



(32)



(33)

True A_2B_2 spectra should be expected on grounds of molecular symmetry (C_{2v}) for cyclobutanes of the type *(31)* or *(32)*, provided that the substituents do not induce excessively large shift differences, since an A_2X_2 spectrum would otherwise result. For the ^{31}P-NMR spectrum of the complex *(33)*, the molecular symmetry again leads to an A_2B_2 spectrum, which is indeed observed on decoupling of the protons[51].

Our own investigations cited in this review have been carried out in collaboration with Dr. W.-E. Bleck, Dr. D. Cremer, Dr. M. Görlitz, Dr. H.-H. Hinrichs, Dr. H. Klose, and Dr. R. Wenzl, to whom I am grateful for their enthusiastic cooperation. Thanks are also due to the Deutsche Forschungsgemeinschaft, to the Fonds der Chemischen Industrie, and to the Landesamt für Forschung of the State of Nordrhein-Westfalen for their support of our work.

4. Appendix

Ethylene and the A_2 System

The HMO treatment of the π system in ethylene starts with the approximation

$$\psi = c_1\phi_1 + c_2 > \phi_2 \qquad (A1)$$

as a linear combination of the orthonormalized $2p_z$ carbon atomic orbitals ϕ_1 and ϕ_2. According to a postulate of quantum mechanics, the energy of the system can be represented in such a case by the expression

$$E = \langle\psi|\mathscr{H}|\psi\rangle / \langle\psi|\psi\rangle \qquad (A2)$$

where $\mathscr{H}$ is the Hamiltonian operator, which has not been defined as yet, and where the Dirac notation is used for the integrals. The variation method[3, 52], with the abbreviations

$$\begin{aligned} \langle\phi_1|\mathscr{H}|\phi_1\rangle &\equiv H_{11} \quad \text{Coulomb integral} \\ \langle\phi_2|\mathscr{H}|\phi_2\rangle &\equiv H_{22} \\ \langle\phi_1|\mathscr{H}|\phi_2\rangle &\equiv H_{12} \quad \text{resonance integral} \\ \langle\phi_2|\mathscr{H}|\phi_1\rangle &\equiv H_{21} \end{aligned}$$

and the important approximation $\langle\phi_1|\phi_2\rangle = \langle\phi_2|\phi_1\rangle = 0$, *i. e.* neglect of the overlap integral, then gives the secular determinant

$$\begin{vmatrix} H_{11}-E & H_{12} \\ H_{21} & H_{22}-E \end{vmatrix} = 0 \qquad (A3)$$

whose solution, taking into account the identity $H_{12} = H_{21}$, leads to the eigenvalues E_1 and E_2 of the π system.

For the description of a spin system[53] of two nuclei (1) and (2) having the spin quantum number $I = {}^1/_2$, we use as the basis functions the products φ of the orthonormalized spin functions α and β, which are characterized by their total spin m_T as the sum of the magnetic quantum numbers m(i) of the individual nuclei i[54]:

$$\begin{aligned} \varphi_1 &= \alpha(1)\,\alpha(2) && m_T = +1 \\ \varphi_2 &= \alpha(1)\,\beta(2) \\ \varphi_3 &= \beta(1)\,\alpha(2) && m_T = 0 \\ \varphi_4 &= \beta(1)\,\beta(2) && m_T = -1 \end{aligned}$$

In the case of an A_2 system, both nuclei have the same Larmor frequency ν_A and are therefore indistinguishable. Thus for the case where an interaction exists between the nuclei, the states with total spin $m_T = 0$ cannot be satisfactorily characterized either by the product function φ_2 or by φ_3, both of which, unlike φ_1 and φ_4, presuppose the possibility of differentiation. We choose instead the linear combination

$$\psi = c_2'\varphi_2 + c_3'\varphi_3 \qquad (A4)$$

which expresses the fact that the two states "mix" with each other. With eq. (A2), the variation method then gives the determinant

$$\begin{vmatrix} H_{22}-E & H_{23} \\ H_{32} & H_{33}-E \end{vmatrix} = 0 \qquad (A5)$$

where

$$\langle\varphi_2|\mathscr{H}|\varphi_2\rangle \equiv H_{22}$$
$$\langle\varphi_3|\mathscr{H}|\varphi_3\rangle \equiv H_{33}$$
$$\langle\varphi_2|\mathscr{H}|\varphi_3\rangle \equiv H_{23}$$
$$\langle\varphi_3|\mathscr{H}|\varphi_2\rangle \equiv H_{32}$$

The solutions of the determinant (A5), taking into account the identity $H_{23} = H_{32}$, are the eigenvalues E_2 and E_3 of the A_2 system. It should be pointed out that neglect of the integrals $<\varphi_2|\varphi_3>$ and $<\varphi_3|\varphi_2>$, unlike neglect of the overlap integrals in the Hückel model, presents no problem here, since the spin functions naturally do not overlap, as there is no "bond" between the nuclear moments.

Definite results are obtained both for the eigenvalues E_1 and E_2 of the π system in ethylene and for the energies E_2 and E_3 of the A_2 system only if concrete values are inserted for the integrals H_{11}, H_{12}, *etc.* The HMO model avoids the difficulty of calculating these integrals by parametrization. The diagonal elements H_{kk} of the Hückel determinant are approximated by the Coulomb integral α, *i.e.* by the energy of an electron in an isolated $2p_z$ atomic orbital. The offdiagonal elements H_{kl} between adjacent centers k and l are given the adjustable value β of the resonance integral.

In NMR spectroscopy, the corresponding integrals are also not given explicitly. The phenomenological Hamiltonian operator (in Hz units)[2, 54]

$$\mathscr{H} = \sum_i \nu_i \, I_z(i) + \sum_{i<j} J_{ij} \, I(i) \, I(j) \qquad (A6)$$

on application to the spin functions, in this case gives expressions that contain the coupling constants J_{ij} in addition to the resonance frequencies ν_i. Neither of these parameters is an absolute energy quantity, since the resonance frequencies can be referred to any desired standard and the coupling constants are merely proportionality factors for the energy of the spin-spin interaction. The calculated energies are therefore relative; however, they are perfectly adequate for use in spectroscopy, where only energy differences are of interest.

For the application of the operator (A6) to the product functions φ_2 and φ_3, it is necessary to take into account the rules for the application of the nuclear spin operator $\boldsymbol{I}$ and its components $\boldsymbol{I}_x$, $\boldsymbol{I}_y$, and $\boldsymbol{I}_z$[55], as given in Table 3.

Table 3. Properties of the nuclear spin operators $\boldsymbol{I}_x$, $\boldsymbol{I}_y$, and $\boldsymbol{I}_z$.

$\boldsymbol{I}_x\alpha = \frac{1}{2}\beta$	$\boldsymbol{I}_y\alpha = i\frac{1}{2}\beta$	$\boldsymbol{I}_z\alpha = \frac{1}{2}\alpha$
$\boldsymbol{I}_x\beta = \frac{1}{2}\alpha$	$\boldsymbol{I}_y\beta = -i\frac{1}{2}\alpha$	$\boldsymbol{I}_z\beta = -\frac{1}{2}\beta$

On the basis of these relations, it is very easy to give the diagonal and offdiagonal elements of a determinant of the type (A5) in general form[56]. For the diagonal elements, we obtain

$$H_{kk} = \sum \nu_i \, m(i) + \frac{1}{4} \sum_{i<j} \sum J_{ij} \, T_{ij} \qquad (A7)$$

with $T_{ij} = +1$ if the nuclei i and j have parallel spins in the corresponding basis function φ_k, and $T_{ij} = -1$ if the nuclei i and j have antiparallel spins in the corresponding basis function φ_k.

The offdiagonal elements are given by

$$H_{kl} = \frac{1}{2} J_{ij} \, U_{ij} \quad \text{for} \quad i \neq j \qquad (A8)$$

where $U = 1$ if φ_k and φ_l differ only in the exchange of the spin functions of the pair of nuclei i,j (*e.g.* $\alpha\beta\alpha\beta$ and $\alpha\beta\beta\alpha$), and $U = 0$ in all other cases (*e.g.* $\alpha\beta\alpha\beta$ and $\beta\alpha\beta\alpha$).

According to this reasoning, the determinants (A3) and (A5) take the following form:

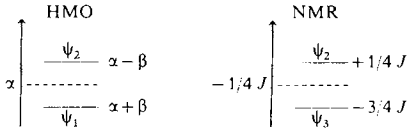
Hückel determinant

$$\begin{vmatrix} \alpha-E & \beta \\ \beta & \alpha-E \end{vmatrix} = 0 \qquad (A9)$$

NMR determinant

$$\begin{vmatrix} -1/4\,J-E & 1/2\,J \\ 1/2\,J & -1/4\,J-E \end{vmatrix} = 0 \qquad (A10)$$

Their solution leads to eigenvalue schemes in which the eigenstates are stabilized and destabilized in relation to the energy α or $-{}^1/_4 J$ by the amount β or ${}^1/_2 J$, respectively:



For the coefficients c_1 and c_2 on the one hand and c'_2 and c'_3 on the other of the linear combinations (A1) and (A4), which now have to be calculated, the determinants (A9) and (A10) yield the following equations on the basis of the variation method:

HMO	NMR
$c_1(\alpha-E)+c_2\beta=0$	$c'_2(-1/4\,J-E)+c'_3\,1/2\,J=0$
$c_1\beta+c_2(\alpha-E)=0$	$c'_2\,1/2\,J+c'_3(-1/4\,J-E)=0$

By insertion of the eigenvalues and using the relation $\sum_i c_i^2 = 1$, which is a consequence of the orthogonality of the basis functions ϕ_k or φ_k, one obtains $c_1 = c_2 = 1/\sqrt{2}$ or $c'_2 = -c'_3 = 1/\sqrt{2}$ for the more stable state, and $c_1 = -c_2 = 1/\sqrt{2}$ or $c'_2 = c'_3 = 1/\sqrt{2}$ for the state with the higher energy. The correct eigenfunctions are therefore:

HMO		NMR	
$\psi_1 = 1/\sqrt{2}\,(\phi_1+\phi_2)$	(A11)	$\psi_3 = 1/\sqrt{2}\,(\alpha\beta-\beta\alpha)$	(A13)
$\psi_2 = 1/\sqrt{2}\,(\phi_1-\phi_2)$	(A12)	$\psi_2 = 1/\sqrt{2}\,(\alpha\beta+\beta\alpha)$	(A14)

The eigenvalue scheme of the A_2 system is complete only when we also include the wave functions and eigenvalues of the states φ_1 and φ_4. The product functions $\alpha\alpha$ and $\beta\beta$ here are already eigenfunctions of the Hamiltonian operator $\mathscr{H}$; the eigenvalues E_1 and E_4 are calculated directly with the aid of the operator (A6) from the Schrödinger equation

$$\mathscr{H}\psi = E\psi \qquad (A15)$$

and are found to be $\nu_A + {}^1/_4\,J$ and $-\nu_A + {}^1/_4\,J$. In addition to the transition energies, which are found from the differences of the eigenvalues, the relative transition probabilities or intensities I of the individual lines are also of interest in NMR spectroscopy. They are calculated[2, 54] from

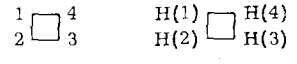
$$I = \langle\psi_k|\sum I_x(i)|\psi_l\rangle^2 \qquad \text{(A 16)}$$

as the square of the transition moment M. The complete result for the A_2 system is:

	eigenvalues	eigenfunctions	transitions	energies	intensities
(1)	$\nu_A + 1/4\,J$	s_{+1} $\alpha\alpha$	(2)→(1)	ν_A	1
(2)	$+1/4\,J$	s_0 $1/\sqrt{2}(\alpha\beta+\beta\alpha)$	(3)→(1)	$\nu_A + J$	0
(3)	$-3/4\,J$	a_0 $1/\sqrt{2}(\alpha\beta-\beta\alpha)$	(4)→(2)	ν_A	1
(4)	$-\nu_A + 1/4\,J$	s_{-1} $\beta\beta$	(4)→(3)	$\nu_A - J$	0

Thus transitions involving the eigenstate (3) are forbidden. This result can also be deduced from the symmetry behavior of the wave functions ψ_2 and ψ_3. ψ_3, as the only eigenfunction, is antisymmetric with respect to an interchange of the two nuclei. However, transitions between eigenstates with different symmetries are forbidden[2, 54]. The spectrum of the A_2 system thus consists of a single line at ν_A, *i.e.* the coupling between magnetically equivalent nuclei does not appear in the spectrum.

This brief comparison of the mathematical operations applied in the HMO theory and in calculation of NMR spectra shows clearly that the HMO formalism can be used without essential changes for the calculation of the eigenvalues and eigenfunctions for nuclei having the spin ${}^1/_2$. This similarity is not surprising in the end, since one is concerned with an eigenvalue problem in both cases[57]. For magentically equivalent nuclei, such as are present *e.g.* in a methyl group, the analogy is perceived even so far that, as in the A_2 system, the results for the corresponding π system, *i.e.* the cyclopropenylium ion can be taken over directly in this case. Differentiation is necessary for an A_4 group, owing to the different form of the Hamiltonian operator. Whereas in cyclobutadiene $\beta_{13} = \beta_{24} = 0$, it is also necessary in nuclear magnetic resonance to consider coupling *via* four bonds ($J_{1,3}$, $J_{2,4}$). Thus all the nondiagonal elements H_{kl} of



the secular determinant are different from zero in this case, and are not necessarily equal to one another. Finally, because of differences in the resonance frequencies, the diagonal elements H_{kk} also assume different values. However, there is no difficulty in simulating such a calculation with the aid of an HMO program, though this is undoubtedly only of didactic value.

Received: March 8, 1971 [A 896 IE]
German version: Angew. Chem. *84*, 907 (1972)
Translated by Express Translation Service, London

[1] *B. Dischler*, Angew. Chem. *78*, 653 (1966); Angew. Chem. internat. Edit. *5*, 623 (1966).
[2] a) *P. L. Corio*: Structure of High-Resolution NMR-Spectra. Academic Press, New York 1966, p. 143; b) *R. J. Abraham*: Analysis of High Resolution NMR Spectra. Elsevier Publ. Co., Amsterdam 1971; c) *R. A. Hoffman, S. Forsén*, and *B. Gestblom*: Analysis of NMR Spectra, in *P. Diehl, E. Fluck*, and *R. Kosfeld*: NMR-Basic Principles and Progress, Springer Verlag, Heidelberg 1971.
[3] *E. Heilbronner* and *H. Bock*: Das HMO-Modell und seine Anwendung, Vol. 1–3. Verlag Chemie, Weinheim 1968—1970.
[4] Cf. Ref. [3], Vol. 1, p. 72.
[5] Cf. Ref. [3], Vol. 1, p. 105.
[6] *P. Diehl, R. K. Harris*, and *R. G. Jones*: Subspectral Analysis, in *J. W. Emsley, J. Feeney*, and *L. H. Sutcliffe*: Progress in Nuclear Magnetic Resonance Spectroscopy, Vol. 3. Pergamon Press, Oxford 1967.
[7] *B. Dischler* and *W. Maier*, Z. Naturforsch. *16a*, 318 (1961).
[8] *B. Dischler* and *G. Englert*, Z. Naturforsch. *16a*, 1180 (1961).
[9] *B. Dischler*, Z. Naturforsch. *20a*, 888 (1965).
[10] *B. D. Nageswara-Rao* and *P. Venkateswarlu*, Proc. Indian Acad. Sci. *54 A*, 1 (1961).
[11] *T. K. Lim, A. Taurins*, and *M. A. Whitehead*, Can. J. Chem. *44*, 1211 (1966).
[12] *D. Canet* and *P. Granger*, J. Chim. Phys. Physicochim. Biol. *65*, 1606 (1968).
[13] *D. M. Grant, R. C. Hirst*, and *H. S. Gutowsky*, J. Chem. Phys. *38*, 470 (1963).
[14] *R. E. Mayo* and *J. H. Goldstein*, Spectrochim. Acta *23A*, 55 (1967).
[15] *E. W. Garbisch, Jr.*, J. Chem. Educ. *45*, 480 (1968).
[16] *W. Regel* and *W. v. Philipsborn*, Helv. Chim. Acta *52*, 1354 (1969).
[17] *W. Brügel*, Z. Elektrochem. Ber. Bunsenges. Phys. Chem. *66*, 159 (1962).
[18] *R. Wenzl*, Dissertation, Universität Köln 1969.
[19] *R. J. Abraham* and *H. J. Bernstein*, Can. J. Chem. *37*, 2095 (1959).
[20] *H. Günther* and *H.-H. Hinrichs*, Liebigs Ann. Chem. *706*, 1 (1967).
[21] *M. Görlitz*, Dissertation, Universität Köln 1969.
[22] *H. M. Hutton* and *T. Schaefer*, Can. J. Chem. *41*, 2429 (1963).
[23] *T. Sono, T. Morikawa, A. Oku*, and *R. Oda*, Tetrahedron Lett. *1964*, 791.
[24] *D. J. Patel, M. E. H. Howden*, and *J. D. Roberts*, J. Amer. Chem. Soc. *85*, 3218 (1963).
[25] *L. Cavalli*, Org. Magn. Res. *2*, 233 (1970).
[26] *E. Lustig* and *R. M. Moriarty*, J. Amer. Chem. Soc. *87*, 3252 (1965); *E. Lustig, E. P. Ragelis, N. Duy*, and *J. A. Ferretti*, J. Amer. Chem. Soc. *89*, 3953 (1967).
[27] *S. Forsén, B. Gestblom, R. A. Hoffman*, and *S. Rodmar*, J. Mol. Spectrosc. *21*, 372 (1966).
[28] *R. J. Abraham*, J. Chem. Soc. *256*, 1965.
[29] *J. G. Pritchard* and *P. C. Lauterbur*, J. Amer. Chem. Soc. *83*, 2105 (1961).
[30] *W. B. Smith* and *B. A. Shoulders*, J. Phys. Chem. *69*, 579 (1965).
[31] *N. Sheppard* and *J. J. Turner*, Proc. Roy. Soc. London *A252*, 506 (1959).
[32] *E. W. Garbisch, Jr.* and *M. G. Griffith*, J. Amer. Chem. Soc. *90*, 6543 (1968).
[33] *H. Günther, H. Klose, D. Cremer, F. Dürrholz*, and *E. Vogel*, unpublished.
[34] *R. J. Abraham* and *K. G. R. Pachler*, Mol. Phys. *7*, 165 (1963).
[35] *R. C. Hirst* and *D. M. Grant*, J. Chem. Phys. *40*, 1909 (1964).
[36] *R. J. Abraham, L. Cavalli*, and *K. G. R. Pachler*, Mol. Phys. *11*, 471 (1966); *W. C. Lin*, J. Chem. Phys. *52*, 2805 (1970).
[37] *R. J. Abraham* and *H. J. Bernstein*, Can. J. Chem. *39*, 216 (1961).
[38] *R. R. Ernst* and *W. A. Anderson*, Rev. Sci. Instrum. *37*, 93 (1966).
[39] *W. Bremser, H. D. W. Hill*, and *R. Freeman*, Messtechnik *79*, 14 (1971); cf. also *E. Breitmaier, G. Jung*, and *W. Voelter*, Angew. Chem. *83*, 659 (1971); Angew. Chem. internat. Edit. *10*, 673 (1971).
[40] *R. Freeman* and *H. D. W. Hill*, J. Chem. Phys. *54*, 301 (1971).
[41] *W.-E. Bleck*, Dissertation, Universität Köln 1969.
[42] *H. Günther, R. Wenzl*, and *W. Grimme*, J. Amer. Chem. Soc. *91*, 3808 (1969).
[43] *R. Freeman* and *W. A. Anderson*, J. Chem. Phys. *37*, 2053 (1963).
[44] *R. A. Hoffman* and *S. Forsén* in *J. W. Emsley, J. Feeney*, and *L. H. Sutcliffe*: Progress in Nuclear Magnetic Resonance Spectroscopy, Vol. 1. Pergamon Press, Oxford 1966; cf. also *W. v. Philipsborn*, Angew. Chem. *83*, 470 (1971); Angew. Chem. internat. Edit. *10*, 472 (1971).
[45] *K. Kuhlmann* and *J. D. Baldeschwieler*, J. Amer. Chem. Soc. *85*, 1012 (1963).
[46] Cf. Ref. [53a], p. 92.
[47] *J. B. Lambert, A. P. Jovanovich*, and *W. L. Oliver, Jr.*, J. Phys. Chem. *74*, 2221 (1970).
[48] *G. M. Whitesides, M. Witanowsky*, and *J. D. Roberts*, J. Amer. Chem. Soc. *87*, 2854 (1965).
[49] *R. J. Abraham*, J. Chem. Soc. *B* 1968, 173.
[50] Cf. Ref. [2a], p. 241.
[51] *P. Meakin, E. L. Muetterties, F. N. Tebbe*, and *J. P. Jesson*, J. Amer. Chem. Soc. *93*, 4701 (1971).
[52] *C. A. Coulson*: Valence. Oxford University Press 1961, p. 57.
[53] Excellent introductions to the quantum mechanics of the analysis of high-resolution NMR spectra can be found in:

a) *E. D. Becker:* High-Resolution NMR. Academic Press, New York 1969, Chapter 7; b) *E. O. Bishop* in *F. Mooney:* Annual Review of NMR Spectroscopy. Academic Press, London 1968; c) *E. W. Garbisch, Jr.*, J. Chem. Educ. *45*, 311 (1968).
[54] *J. A. Pople, W. G. Schneider*, and *H. J. Bernstein:* High-Resolution Nuclear Magnetic Resonance. McGraw Hill, New York 1969, p. 103ff.
[55] *W. Pauli*, Z. Physik *43*, 601 (1927).
[56] *H. M. McConnell, A. D. McLean*, and *C. A. Reilly*, J. Chem. Phys. *23*, 1152 (1955).
[57] *R. Zurmühl:* Matrizen. Springer-Verlag, Berlin 1964, Chapter 4.
[58] *J. B. Lambert*, Accounts Chem. Res. *4*, 87 (1971).

Structure and Stereochemistry of the Transition States and Intermediates of Heterolytic Aromatic Substitutions[**]

By Paul Rys, Peter Skrabal, and Heinrich Zollinger[*]

Dedicated to the memory of Sir Christopher Ingold (1893–1970)

In the following progress report we discuss some current problems concerning the structure of the transition states and intermediates of heterolytic aromatic substitutions. This prompts us to present a critical analysis of the methods by which the existence of one or more intermediates may be clearly established. Energy relationships can provide information about the structure of the intermediate as long as the kinetics of the reaction are not disguised by diffusion. Investigations of the stereochemistry of the intermediates, which at present are not readily amenable to experiment, indicate that these intermediates, in contrast to the Wheland concept of symmetric σ-complexes, can participate in conformational equilibria.

1. Introduction

The classical investigations of *pre*-equilibria in electrophilic aromatic substitutions by *Ingold* and co-workers[1] have made available exact information concerning the nature of the species participating in the substitution. Stimulated by *Dewar*'s postulate[2] and fundamental studies by *Mulliken*[3], we speak today of π-[4] and σ-complexes as *intermediates* in heterolytic aromatic substitutions. However, further progress in understanding the mechanism of such reactions requires an exact determination of the structure of these intermediates. That the detection of one or the other type of complex cannot always be regarded unreservedly as unambiguous proof of its intermediacy, has only been recognized in the last few years.

We shall discuss these aspects for reactions of the S_E2 type for electrophilic, and of the addition-elimination type for nucleophilic substitutions.

2. Methods for Detecting Reaction Intermediates

Huisgen[5] has recently summarized available methods for the detection of intermediates. Therefore, we shall briefly consider only those methods which additionally allow the unambigous detection of *several* (consecutive) intermediates.

2.1. Detection of Quasi-Stationary Intermediates

Identification of a non-accumulating intermediate is based on *Bodenstein*'s early (1913) treatment in which the intermediate Z exists in a small, quasi-stationary concentration during the entire course of the reaction (steady-state kinetics: $d[Z]/dt \approx 0$)[6].

For *electrophilic* aromatic substitutions of this type, in which a proton leaves in the second step with the help of a base B [reaction (1)], this treatment leads to the kinetic relationship (2).

$$E^{\oplus} + Ar{-}H \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \overset{H}{\underset{E}{Ar^{\oplus}}} \xrightarrow[k_2]{+B} Ar{-}E + HB^{\oplus} \qquad (1)$$

$$\frac{d[Ar{-}E]}{dt} = [E^{\oplus}][Ar{-}H]\frac{k_1 k_2[B]}{k_{-1}+k_2[B]} \qquad (2)$$

The presence of a quasi-stationary intermediate is established if the observed rate constants show a non-linear dependence upon the base concentration [B] ($k_2[B] \approx k_{-1}$). If one finds a linear dependence on base concentration ($k_2[B] \ll k_{-1}$) then a concerted intermediate-free reaction path cannot be excluded on the basis of the formal kinetics.

These criteria also hold for those *nucleophilic* aromatic substitutions which give rise to a quasi-stationary inter-

[*] Prof. P. Rys, Dr. P. Skrabal, and Prof. H. Zollinger
Dept. of Industrial and Engineering Chemistry of the Swiss Federal Institute of Technology (ETH)
Universitätsstrasse 6, CH-8006 Zürich (Switzerland)

[**] Expanded version of lectures given at Farbenfabriken Bayer AG in Leverkusen (January 14, 1971) and in the Società Chimica Italiana in Milan (March 3, 1971).

mediate. Their addition-elimination mechanism, as well as the existence of the intermediate, could be demonstrated for reactions of nitro-activated aryl halides with amines[7].

Rate-limiting proton extractions lead to a *kinetic hydrogen isotope effect* (k_H/k_D). This was found for the case of azo coupling reactions in 1955[8]. It is often incorrectly assumed that the isotope effect itself proves the existence of a quasi-stationary intermediate, and differentiates between a two-step and a concerted one-step mechanism. However, such proof can only come from a decrease in the numerical value of the isotope effect with increasing base concentration.

2.2. Identification of Intermediates in Reactions Involving Accumulating Adducts

In contrast to quasi-stationary intermediates, accumulating adducts can easily be detected and characterized by instrumental analysis.

If the spectrum (*e.g.* UV, NMR) of a reaction mixture is not the simple sum of the spectra of the individual reaction components, then adduct formation must have occurred. This is not necessarily a true reactive *intermediate* Z [eq. (3)], but can also be a *side-product* N [eq. (4)]. The two possibilities cannot be distinguished by kinetics if the main or side equilibrium is quickly established[9], a fact which is frequently overlooked in the study of reaction mechanisms.

$$C + D \underset{k_{-1}}{\overset{\text{fast } k_1}{\rightleftharpoons}} Z \xrightarrow[k_2]{\text{slow}} P + Q \qquad (3)$$

$$\begin{array}{l} C + D \xrightarrow[k_1]{\text{slow}} P + Q \\ \text{fast}\ \big\downarrow k_N \quad \big\uparrow k_{-N} \\ \quad N \end{array} \qquad (4)$$

In order to differentiate between (3) and (4) we shall now discuss an approximation method, which we call the "Method of Small Analogous Steps (Methode der kleinen Analogieschritte)": If the concentration of an adduct increases during a reaction, an attempt is made to progressively lower its concentration by slight changes in the reaction conditions or small changes in the structure of one of the reactants. Only if the Bodenstein equation (2) becomes valid (*i.e.* the intermediate becomes quasi-stationary) can the adduct be conclusively shown to be a reaction *intermediate*.

This method was used, for example, in studying the electrophilic substitution of 2-naphthol-6,8-disulfonic acid[10,11]. In those cases in which it does not succeed, other criteria must be employed[5]. Thus *Orvik* and *Bunnett*[12] were able to identify an accumulating adduct as an intermediate in the nucleophilic aromatic substitution of 2,4-dinitro-1-naphthyl ethyl ether. *Rys, Schmitz,* and *Zollinger*[13] found that during hydrolysis of cyanuric chloride an adduct accumulates that is involved in a side-equilibrium with a reactive intermediate. The side-equilibrium appears plausible since, as an acid-base equilibrium, it follows the Brønsted law of general acid-base catalysis, giving $\alpha + \beta = 1$ for the sum of the Brønsted coefficients. These observations support the previous mechanism postulated for the hydrolysis and alcoholysis of chlorotriazine reactive dyes[14].

2.3. Two and More Consecutive Intermediates

The same criteria as discussed in Sections 2.1 and 2.2 also hold for demonstrating the presence of two or more consecutive intermediates.

The presence of only quasi-stationary intermediates must result in a non-linear variation of the observed rate constants with the concentration of those reactants involved in the decomposition of the intermediates. The halogenation of polymethylbenzenes may be cited as an example[15].

On the other hand, if an accumulating intermediate is present in the reaction series, and the observed rate constant for its formation can be evaluated by the Bodenstein treatment (cf. Section 2.1), then the accumulating species must be preceded in the series by at least *one* quasi-stationary intermediate. This is the case, for example, in nucleophilic aromatic substitutions[12].

Proof of the existence of consecutive intermediates is of fundamental importance for the question of whether or not the sequence postulated[2] for aromatic substitutions actually occurs: reactants → first π-complex → σ-complex → second π-complex → products. Contrary to our previous view[10], the appearance of π-complexes under one set of conditions and σ-complexes when the reaction conditions are slightly altered[16] may be taken only as an indication, and not as proof, of a sequence of these two complexes in one and the same reaction. *Melander*[17] has already pointed out that intermediates may be by-passed, depending upon the reaction conditions[*].

3. Structural Information from Free Energy Relationships

H. C. Brown[19] has observed that the reaction rates of numerous electrophilic substitutions of benzene derivatives show linear free energy relationships (5) with the rate of solvolysis of substituted cumyl 2'-chlorides in water/acetone mixtures[20].

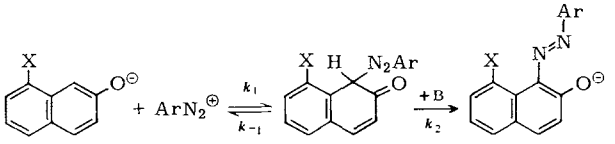
$$\log(k_x/k_0) = \rho\sigma_x^+ \qquad (5)$$

The substituent constants determined from the solvolysis kinetics are designated σ_X^+, while the reaction constants are designated ρ; by definition, $\rho = 1$ for solvolysis. *H. C. Brown* postulated that those electrophilic substitutions of benzene derivatives which are amenable to treatment by equation (5) go through a σ-complex-type, rate-limiting transition state.

An interesting extention of the Brown hypothesis is provided by the results of the azo coupling of 8-substituted 2-

[*] Currently under discussion is the question of whether or not the σ-(Meisenheimer-)complex formed during nucleophilic aromatic substitutions results from a radical anion as an *initial* (first) *intermediate* or if a parallel mechanism leads to one or more radical-type intermediates [18].

naphthol derivatives [reaction (6)][21]. These reactions are generally base catalyzed and proceed through a quasi-stationary intermediate. Therefore they follow the Bodenstein equation (2) in their kinetics. Position 8 of these 2-naphthol derivatives turns out to be a pseudo-*m*-position with respect to the reacting carbon atom, since $\log k_1$ is proportional to the m-σ_X^+ constants of the substituent X.



(6)

Remarkably, k_1—and thus also k_{-1}, from the principle of microscopic reversibility—is independent of the volume of the substituent X. However, since the steric effect of X is reflected in the ratio k_2/k_{-1}, it follows that the volume of the substituent X can only influence the second step (k_2). We will return to the conclusions derived from this observation in Section 4.

Since the rate of pyrolysis of substituted 1-phenylethyl acetates in the gas phase (300—400 °C)[22], the electrophilic substitution by diazonium ions in water[21], and the protonation equilibrium of benzene derivatives in hydrofluoric acid[23], as well as the solvolysis of cumyl derivatives in water/acetone mixtures, can be well correlated with the σ_X^+ values, these reactions are apparently all influenced by substituents in a similar manner.

Recently, *Olah*[24, 25] put forward a new postulate which extends *H. C. Brown*'s hypothesis. It says: Electrophilic substitutions of benzene derivatives have an "early" rate-limiting transition state on the potential energy surface of the reaction if the relative rates of reaction are proportional to the π-complex equilibrium constants of the respective benzene derivatives. The transition state in these cases has a structure similar to that of a π-complex. The relative rate constants of substitutions with "late" rate-determining transition states give a linear free energy relationship with the corresponding σ-complex equilibrium constants; the transition state therefore has a structure similar to that of a σ-complex.

On the one hand, *Olah* substantiates his hypothesis by citing the isomer ratios of reaction products from the Friedel-Crafts benzylation of toluene with ring-substituted benzyl chlorides[25]: The stronger the electron withdrawal of the substituents on the benzyl chlorides, the more electrophilic the carbonium ion pair formed with the catalyst, and the "earlier" the transition state along the reaction coordinate.

On the other hand, *Olah* compares the relative reactivities of methylated benzene derivatives for a series of electrophilic substitutions with the equilibrium constants of their σ- and π-complexes with hydrogen halides (cf. Table 1).

Table 1. Relative rates of electrophilic reactions of polymethylbenzenes and relative stabilities of their σ- and π-complexes (according to *Olah* [24]).

Compound	Relative rate of bromination [a]	Relative σ-complex stabilities [b]	Nitration product ratios [c]	Relative π-complex stabilities [d]
Benzene	1	1	1.00	1.00
Toluene	605	790	1.67	1.51
1,2-Xylene	5300	7900	1.75	1.81
1,3-Xylene	514000	1000000	1.65	2.06
1,4-Xylene	2500	3200	1.96	1.65
1,2,3-Trimethylbenzene	1670000	2000000		2.40
1,2,4-Trimethylbenzene	1520000	2000000		2.23
1,3,5-Trimethylbenzene	189000000	630000000	2.71	2.60
1,2,3,4-Tetramethylbenzene	11000000	20000000		2.68
1,2,3,5-Tetramethylbenzene	420000000	2000000000		2.74
1,2,4,5-Tetramethylbenzene	2830000	10000000		2.86
Pentamethylbenzene	810000000	2000000000		

[a] With Br_2/85% CH_3COOH [26].
[b] With HF/BF_3 [23].
[c] With $NO_2^{\oplus}BF_4^{\ominus}$/sulfolane [27].
[d] With HCl [28].

A very good correlation exists between the relative rates of bromination and the equilibrium constants for the addition of hydrogen fluoride, which represents[23] the formation of a σ-complex (benzenenium ion[29]). Moreover, according to *Olah*, the small substituent effect of the methyl groups on the rate of nitration of benzene derivatives with nitryl salts is further reflected in the π-complex equilibrium constants.

However, our interpretation of the data in Table 1 shows that only a part of *Olah*'s postulate can be confirmed: The relative rates of bromination and the nitration product ratios are plotted *versus* the σ- and π-basicity constants in Figures 1 and 2 respectively. One notices in Figure 1 the outstanding correlation of bromination rate with the σ-basicity constants[26]. However, only moderate correlation (Fig. 2) is found for the nitration product ratios from the competing reactions and the π-complex stabilities. We even see from Figure 3 that the nitration data are, "visually", essentially no more poorly correlated with σ-basicities! The product ratios from mixed-acid nitrations[30] give an even poorer correlation with π-complex stabilities than any of the nitrations with nitryl salt (Fig. 4).

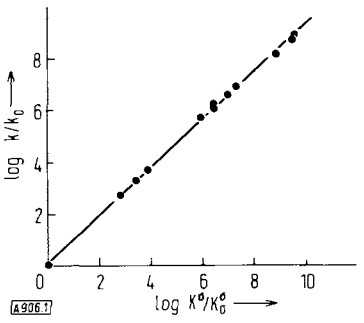


Fig. 1. Relative rate constants for the bromination of polymethylbenzenes [26] as a function of the relative σ-complex stabilities [23] (see Table 1). Correlation data: $r = 0.9988$, $a = 0.9398$, $b = 0.0804$.

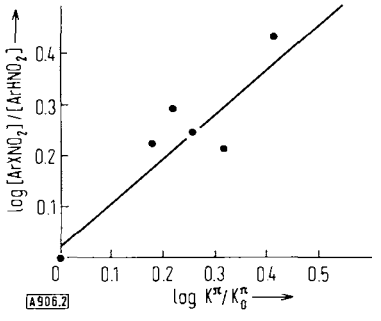


Fig. 2. Nitration product ratios of polymethylbenzenes ($NO_2^{\oplus}BF_4^{\ominus}$/sulfolane) [27] as a function of the relative π-complex stabilities [28] (see Table 1). Correlation data: $r = 0.9121$, $a = 0.9146$, $b = 0.0239$.

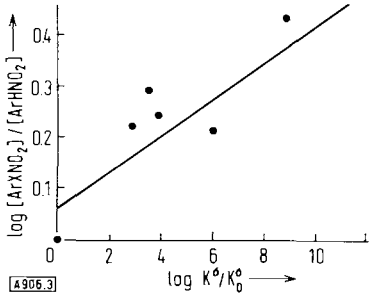


Fig. 3. Nitration product ratios of polymethylbenzenes ($NO_2^{\oplus}BF_4^{\ominus}$/sulfolane) [27] as a function of the relative σ-complex stabilities [23] (see Table 1). Correlation data: $r = 0.8820$, $a = 0.0415$, $b = 0.0610$.

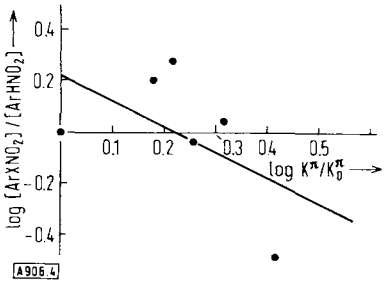


Fig. 4. Nitration product ratios of polymethylbenzenes (mixed acid/sulfolane) [30] as a function of the relative π-complex stabilities [28]. Correlation data: $r = -0.5493$, $a = -1.0284$, $b = 0.2326$.

The calculation of correlation coefficients shows this more clearly: Table 2 contains the results of a regression analysis of 18 electrophilic aromatic substitution reactions *versus* the σ^+ values of *Brown*[19]. With the exception of the nitrations and the destannylations the correlation coefficient lies between $r = -0.9988$ and -0.9807; the average is $\bar{r} = -0.9878$[31]. However, as Table 3 shows, the data from competitive nitrations also correlate poorly with the equilibrium constants of 15 different π-complexes[32] with polymethylbenzenes.

The good correlation coefficients obtained for the reactions in Table 2 leads us to believe that the transition states possess a *σ-complex-type structure*. In place of the solvolysis rate constants of cumyl chloride derivatives, the protonation equilibrium constants of polymethylbenzenes in HF (from *Mackor et al.*[23]) could just as well be used as a reference reaction for the bromination of polymethylbenzenes: The structures of the resulting benzenenium ions are supported by their NMR spectra[23].

The slope of the regression line (constant *a*, Table 2) is a measure of the "closeness" of the transition state to the σ-complex on the potential energy surface of a (three-dimensional) energy diagram: The smaller (more negative) the value of *a*, the more product-like (σ-complex-like) the transition state, in the sense of the Hammond postulate[49]. Bromination in aqueous acetic acid ($a = -13.14$) therefore proceeds through a transition state that lies energetically quite near the σ-complex. In contrast, the transition state for alkylation (Friedel-Crafts reactions) is *energetically* near the reactants since *a* is large (slightly negative); the transition state therefore lies "early" on the reaction coordinate. We conclude from the good correlation ($r = -0.9823$) obtained from the large number of points ($n = 11$) that the transition state is *structurally* similar to the *σ-complex*.

In contrast to this, *Olah*[24] would conclude—from the fact that toluene reacts only 6.0 times (ethylation) more quickly than benzene—that the transition state is "early" with a *π-complex-type* structure. However, in view of the good linear correlation with σ-complex stabilities, we cannot concur. Yet we agree in principle with the correlation between *positional* selectivity (*ortho/para* ratio) and "early"/"late" transition states which *Olah et al.* emphasize in their most recent papers[49a]. However, the criterion of positional selectivity has to be applied very carefully: *Myhre*[49b] demonstrated recently that *ortho* (but not *meta* or *para*) substitution products can be formed not only by the S_E2 mechanism (1), but also by a 1,2-rearrangement of a primary *ipso*-addition product[49c].

How can we understand the lack of correlation between *substrate* selectivity and nucleophilicity in fast electrophilic substitutions, *e.g.* nitrations? We would like to emphasize that the ratio of two (or more) products from competition reactions can only be calculated directly by the usual methods[50] (*i.e.* from the respective rate constants of the actual reaction steps) if the kinetics are not "disguised" by diffusion processes. *Wei*[51] has previously shown how often erroneous conclusions are drawn in this respect.

In general, two situations leading to diffusion effects can be differentiated: If the effective rate of a reaction is determined by the velocity of mixing of the reaction solutions, we speak, in agreement with *Ridd*[52, 53], of *mixing-con-*

Table 2. Correlation between relative rates of substitution and σ^+-constants from benzene derivatives.

Reaction, reagent, solvent	Correlation results [a]				Ref.
	n	*r*	*a*	*b*	
1. Non-base-catalyzed deprotonation substitutions					
Bromination, Br_2, $HOAc/H_2O$	16	−0.9807	−13.14	0.343	[19]
Chlorination, Cl_2, CH_3NO_2	3	−0.9988	−13.02	0.020	[33]
Chlorination, Cl_2, CH_3CN	3	−0.9953	−12.66	0.039	[33]
Polymethylbenzene bromination, Br_2, $HOAc/CH_3NO_2$	13	−0.9886	− 8.931	0.088	[19]
Chlorination, Cl_2, $HOAc/H_2O$	18	−0.9900	− 8.774	0.604	[19]
Detritiation, H_2SO_4, CF_3COOH/H_2O	15	−0.9834	− 8.617	0.395	[19]
Acetylation, CH_3COCl, $AlCl_3$, $C_2H_4Cl_2$	16	−0.9876	− 8.591	0.249	[19]
Nitration, CH_3COONO_2, Ac_2O	19	−0.9751	− 6.719	0.034	[19]
Nitration, HNO_3/H_2SO_4	9	−0.9561	− 6.419	−0.073	[34]
Chlorination, HOCl, $HClO_4/H_2O$	2	—	− 6.154	—	[33]
Bromination, HOBr, Dioxane/H_2O	9	−0.9969	− 6.127	0.031	[19]
Ethylation, C_2H_5Br, $GaBr_3$	11	−0.9823	− 2.417	−0.034	[19]
2. Base-catalyzed deprotonation substitutions [b]					
Sulfonation, $H_3SO_4^{\oplus}$	2	—	− 9.3	—	[35]
Sulfonation, $H_2S_2O_7$	2	—	− 6.1	—	[35]
Mercuration, $Hg(OAc)_2$, HOAc	17	−0.9957	− 3.977	0.169	[19]
3. Substitutions with other leaving groups					
Bromodesilylation, Br_2, HOAc	15	−0.9838	− 6.113	−0.127	[19]
Protodeboronation, H_2SO_4/H_2O	9	−0.9883	− 4.926	0.238	[19]
Protodesilylation, $HClO_4$, CH_3OH/H_2O and H_2SO_4, $HOAc/H_2O$	17	−0.9908	− 4.724	−0.266	[19]
Protodegermanylation, H_2SO_4, $HOAc/H_2O$ and $HClO_4$, CH_3OH/H_2O	25	−0.9936	− 4.052	−0.120	[19]
Iododestannylation, I_2, CH_3OH/H_2O	14	−0.9199	− 3.299	−0.163	[36a]
Protodestannylation, $HClO_4$, CH_3OH/H_2O	14	−0.9751	− 2.935	−0.181	[36b]

[a] n = number of measured relative rates; all data with the exception of cationic substituents such as $N(CH_3)_3^{\oplus}$ were evaluated; r = correlation coefficient; a,b = slope and intercept of the regression line $Y = aX + b$. Apart from the polymethylbenzene bromination, all reactions involve monosubstituted benzene derivatives.

[b] Base catalyzed reactions are listed separately since, according to equation (2), the measured rate constant in this case is not identical with the rate constant for the formation of the σ-complex, but is rather a complex function of k_1, k_{-1}, and k_2, as well as the base concentration and type.

Table 3. Correlation [a] of the nitration product ratios with relative π-complex stabilities of benzene derivatives.

Electron acceptor (solvent)		$NO_2^{\oplus}BF_4^{\ominus}$/sulfolane [27]			Mixed acid/sulfolane [30]			Ref.
	n	*r*	*a*	*b*	*r*	*a*	*b*	
Picric acid ($CHCl_3$)	6	0.9060	1.7462	0.0207	−0.4233	0.1823	−1.5231	[37]
HBr (*n*-heptane)	4	0.9602	1.0658	−0.0071	0.6460	0.1782	1.1970	[38]
HCl (*n*-heptane)	4	0.9435	1.0628	−0.0166	0.6614	0.1770	1.2436	[38]
HCl (toluene) [b]	6	0.9121	0.9146	0.0239	−0.5493	−1.0284	0.2326	[28]
CCl_4 (cyclohexane)	4	0.9675	0.8051	0.0462	−0.6694	0.1795	−0.9586	[39]
Fluoranil (CCl_4)	4	0.9675	0.7979	0.0444	−0.5534	0.2003	−0.8525	[40]
Br_2 (CCl_4)	5	0.8755	0.6502	0.0470	0.1090	0.0695	0.0943	[41]
Fluoranil ($CHCl_3$)	4	0.9722	0.6442	0.0371	−0.5430	0.2022	−0.6693	[40]
SO_3 (CCl_4)	6	0.8830	0.5154	0.0304	−0.4633	0.1958	−0.5048	[42]
Pyromellitic dianhydride (CCl_4)	5	0.8702	0.4705	0.0470	0.0329	0.0845	0.0207	[43]
ICl (CCl_4)	6	0.9502	0.4671	0.0519	−0.5704	0.2005	−0.5235	[44, 45]
I_2 (CCl_4)	6	0.8614	0.4536	0.1099	−0.7474	0.1978	−0.7374	[45]
Tetracyanoethylene (CH_2Cl_2)	6	0.9599	0.4263	0.0354	−0.5830	0.2216	−0.4834	[46]
Chloranil (cyclohexane)	4	0.9672	0.3967	−0.0018	−0.6118	0.1734	−0.4189	[47]
$Ag^{\oplus}$ (H_2O/CH_3OH)	6	−0.4434	−0.7016	0.2481	0.6600	−0.0415	1.9495	[48]

[a] See footnote [a] in Table 2.

[b] For values with $NO_2^{\oplus}BF_4^{\ominus}$/sulfolane see Fig. 2, with mixed acid/sulfolane see Fig. 4.

trolled reactions[*]. The observed reaction rate can also be influenced by the rate of formation of the encounter (collision) complex; we then call the reaction *encounter-controlled.*

In mixing-controlled reactions we are concerned with *macro*scopic, and in encounter-controlled, *micro*scopic diffusion effects. Both can largely disguise the observed kinetics of a reaction and thereby also the selectivity of competitive reactions. It is of value, on this account, to clearly distinguish the effects of diffusion on the different selectivities: While the positional selectivity is dependent mainly upon the probability of successful reaction in the encounter complex, and therefore not directly on diffusion effects, the substrate selectivity for diffusion-controlled reactions *is* disguised by such effects. This appears to be

[*] The terms mixing or encounter *controlled* (generally: diffusion *controlled*) could be misleading in that only those reactions for which no reaction sites are present *along* the diffusion path are controlled exclusively by diffusion (*i. e.* have activation energies of 2.5 — 8.4 kJ/mol, [= 0.6—2 kcal/mol]). The measured reaction rate is then only proportional to the diffusion coefficients and independent of the reaction rate constants. A completely different situation arises however if *new* reaction sites are formed along the diffusion path. In the steady state the measured maximum rate is proportional to the root of the product of the diffusion coefficient and the rate constants of the chemical reaction. The measured activation energy will then be $(E_{aD} + E_{aR})/2$, where E_{aD} is the activation energy of diffusion (2.5—8.4 kJ/mol) and E_{aR} that of the chemical reaction (60—100 kJ/mol). It would be more reasonable to speak of diffusion-*disguised* reactions.

the case in electrophilic aromatic substitutions in polar aprotic solvents using preformed electrophilic reagents (especially nitryl salts). This occurs as well with nitrations of highly reactive aromatic compounds using the conventional nitration reagents (mixed acids): In a series of independent papers, it has been shown that such substitutions are so rapid that diffusion effects play a decisive role.

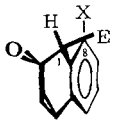
Although *Olah* and *Overchuk*[54] showed that the experiments of *Tolgyesi*[55] could not be taken as a definite proof of mixing effects, it was left to *Moodie, Schofield et al.*[56] to demonstrate that the reaction rate did not increase with increasing numbers of methyl groups for the nitration of methylated benzenes in sulfuric acid, as was initially expected. Rather, the reaction rates more often reach a limiting value, which is the rate of formation of the encounter complex between the nitryl ion and benzene derivatives. According to *Olah*'s postulate the rate limiting transition state should admittedly occur very "early" (*i. e. a* is slightly negative); however, current methods do not permit firm conclusions about the structure of these transition states. It is not surprising, therefore, that the correlation coefficient *r* of nitration with HNO_3 in H_2SO_4 (Table 2) is considerably lower than those of all other reactions. Furthermore, *Ridd et al.*[52, 53] were able to show that the product ratio for the nitration of bibenzyl *apparently* indicates that the second nitration (in the still unsubstituted phenyl ring) occurs faster than the introduction of the first nitro group.

A completely analogous result occurs with the nitration of durene—a result known since 1870[57]—where dinitrodurene is obtained almost exclusively (in nearly the 50% yield expected from theory) under conventional conditions, even at stoichiometric 1:1 reactant ratios. As we have recently been able to show in our laboratory[58], the ratio of mono- to dinitrodurene is dependent upon the mixing conditions as well as the concentration of starting material (at a stoichiometric ratio of 1:1). It could further be shown that the yield of mononitrodurene could be increased from a few percent to 83% by the introduction of small amounts of water. The theoretical examination of these results by *Rys*[59] clearly shows that we are dealing with a mixing-controlled process and that with two competing substrates the product ratio can only be of limited use in calculating the ratio of the actual rate constants.

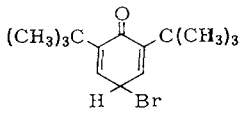
4. Instrumental Analysis of Accumulating Adducts in Electrophilic and Nucleophilic Substitution Reactions

How can we understand the observations concerning reaction (6) (Section 3)? As opposed to k_1 and k_{-1} the reaction rate constant k_2, leading from the σ-complex to products, must depend upon the size of the substituent X in position 8[21] under the following conditions:

1. C-1—H and C-1—E bonds are *asymmetric* with respect to the plane of the benzene ring *(1)*. The electrophilic substituent E occurs in a pseudo-axial and the departing proton in a pseudo-equatorial position. The "swinging" of E into the plane of the original naphthalene nucleus occurs—synchronously with proton removal—only after the departing proton is attacked by the base in the rearomatization process. The steric effect of the substituent X is manifested only during this "swinging" of E into the nuclear plane.



(1)



(2)

2. A qualitatively similar picture also arises if the bonds in the 1-position are *symmetrically* disposed. The steric hindrance of the 2nd step is due to the "swinging" of the phenylazo residue from a *less* hindered position in the σ-complex into a sterically strained, planar aromatic system in the final product.

The asymmetric arrangement of substituents about the sp^3 C atom in the σ-complex[60] obtained from 2-naphthol-1-sulfonic acid and diazonium ions and in 4-bromo-2,6-di(*tert*-butyl)cyclohexa-2,5-dienone*(2)*[61] has been discussed elsewhere[*]. *Simon, Zollinger et al.* have proposed that the proton on the tetragonal C-1 atom of the σ-complex formed during the bromination of 2-naphthol-6,8-disulfonic acid adopts a pseudo-equatorial position[10]. Under similar conditions, iodination leads only to the π-complex[10].

Our explanation for these two extreme cases is a gradual change in the steric interactions of the electrophiles with the substituent X in the substrate. On the one hand, reaction (6) giving a σ-complex has a rate constant k_1 which is independent of the volume of the substituent X. Only k_2 for the rearomatization is influenced by steric effects. On the other hand, the formation of the π-complex from 2-naphthol-6,8-disulfonic acid and iodine is the extreme case of a reaction type in which, as a consequence of the larger steric interaction, even the k_1 of the side attack of the electrophile is affected. In that case the steric hindrance to electrophilic attack is so large that only the π-complex is formed. Although only *slight*, the differences between structures 1 and 2 appear to be of fundamental importance in connection with investigations of reaction mechanisms and especially of accumulating intermediates.

Our proposal of an asymmetric σ-complex is contrary to *Wheland*'s concept of symmetrical σ-complexes[62]. The two fundamentally different arguments for the asymmetric cyclohexadienone-type σ-complex were a) the *non-planarity* of the cyclohexadienone part of the molecule and b) the *steric interactions* of the substituents. The non-planarity would necessarily be associated with an asymmetric disposition of substituents about the sp^3-hybridized C atom. Steric effects, however, could also cause the asymmetry in an otherwise *planar* intermediate.

We discuss below some examples of what is currently known about the structure of intermediates from heterolytic aromatic substitutions and what conclusions can be drawn from the known structures of model compounds.

[*] The question remains whether, after attack of the diazonium ion, the azo group in the σ-complex possesses the *cis* or *trans* configuration.

Cyclohexane is more planar than one would assume from Dreiding models. Its flattening is associated with an opening of the C—C—C angle from 109° 28′ to about 112°[63]. The introduction of just one double bond leads to a further, considerable flattening in cyclohexene. Hence, the substituents on atoms C-3 and C-6 are designated as *pseudo*-axial and -equatorial[64]. The six-membered ring in cyclohexadienones is formed from five trigonal and only one sp^3-hybridized C atom. How great is the tendency, therefore, of such molecules to be planar and thereby symmetrical with respect to the bonds to the sp^3 C atom?

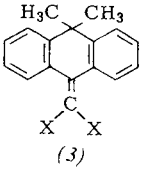
Dreiding models show that in 2,4-cyclohexadienone-type σ-complexes, the oxygen atom of the carbonyl group and the pseudo-equatorial substituent on C-6 occur in eclipsed positions. In order to bring two substituents in a saturated hydrocarbon into an eclipsed position about 12 kJ/mol (2.8 kcal/mol) is required. The opening of a C—C—C angle of about 5° requires only 2 kJ/mol and the energy barrier for twisting of a single bond attached to a C=O bond amounts to about 3.5 kJ/mol[65]. These numbers indicate that the conformations suggested by models are only approximately correct and that the real relationships in molecules can be considerably different.

The various possibilities for reactions of substituted 2,4- and 2,5-cyclohexadienones, and derivatives containing these chromophores, have been systematically studied[66]. However, very little is known about their conformations.

As research tools, NMR spectroscopy and X-ray structure analysis have much to offer. The latter naturally provides the most exact information concerning the spatial structure of molecules. Surprisingly, there appear to be no X-ray structures available for cyclohexadienone derivatives, although *p*-dienones form the chromophore of numerous natural products[*][**].

Systematic investigations of the PMR spectra of substituted cyclohexadienone derivatives do exist[68]: they show that, at room temperature, the dienones are at least statistically planar, since large activation energies for conformational changes can be ruled out. In order to differentiate between statistical and real planarity, it is necessary to examine the temperature dependence of the NMR spectra. Even if these investigations were to show that two separate conformations cannot be detected at low temperatures, it still would not prove that the molecules are planar. It might be possible that the activation energies of these conformational isomerizations are too small to permit freezing of the equilibria. However, if this were the case, then such equilibria should not be attributed any importance in reaction mechanistic considerations.

If there is a large steric interaction between substituents in cyclohexadienone derivatives, then the activation energy for conformational isomerization can be increased to such an extent that two conformers can be detected. In the PMR spectra of 9,10-dihydro-9,9-dimethyl-10-methyleneanthracene and derivatives *(3)* either one or two signals were found for both methyl groups in the position 9, depending upon temperature and substituent X[69].

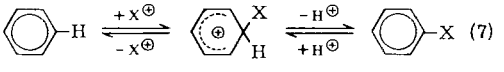


(3)

As a consequence of this observation, one can speak of a pseudo-axial and pseudo-equatorial methyl group. The authors therefore conclude that *(3)*, like 9,10-dihydroanthracene whose X-ray structure analysis is available[70], exists in the boat conformation. At room temperature, 10,10-dimethyl- and 10,10-diethylanthracenes appear to have equivalent substituents[71]. Likewise, a singlet was found for the methyl groups of 2-formyl-4,4-dimethyl-2,5-cyclohexadienone in the PMR spectrum[72]. In such work, low-temperature experiments should provide further help[73].

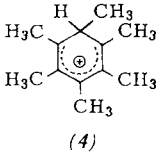
If one finds coupling of the nuclei of a substituent on an sp^3-hybridized C atom with nuclei of the ring, then it is, in principle, possible to deduce the conformation of the sp^3-hybridized C atom from the size of the coupling constants by the theory of spin-spin interactions. Under the constraint that the Karplus relation[74] cannot be precisely applied to dienone systems, a dihedral angle of 44° was calculated for *(2)*[61]. However, as long as these conclusions are not supported by results from known model compounds, they may not be considered as a structural proof. This is due to the large substituent effect on the coupling constants. Progress in this direction was made by *Colpa*, *McLean*, and *Mackor*[75, 76] who calculated the coupling constants in benzenenium ions.

Benzenenium ions (in general, arenenium ions)[29] can be considered as σ-complexes formed during electrophilic aromatic substitutions[77].

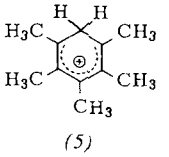


(7)

The PMR spectrum of hexamethylbenzenenium ion *(4)* shows a coupling of 2.0 Hz for the acidic protons with the *p*-methyl group. The analogous coupling constant of the CH_2-protons in pentamethylbenzenenium ion *(5)* amounts to 3.5 Hz[77].



(4)



(5)

Steric interaction between the $CHCH_3$-methyl group and both *o*-methyl groups in *(4)* is responsible for an asym-

[*] X-ray structures and HMO calculations of cyclohexadienone derivatives are in progress by Prof. *M. Simonetta*, University of Milan, at our suggestion. Recently, the X-ray analysis of 10-bromoanthrone which corresponds to the σ-complex of the bromination of 9-anthrole, was completed: 10-bromoanthrone has a boatlike middle ring, *i.e.* it is not planar [67]. Recent CNDO/2 calculations by *M. Simonetta* suggest that a pseudo-axial position of the attacking arylazo group in the σ-complex, concerning the azo coupling to 2-naphthol is probable.

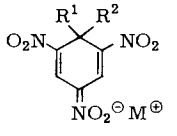
[**] Note added in proof, Sept. 11, 1972: A recently published X-ray analysis of spiro[5,5]undeca-1,4-diene-3-one shows that the cyclohexadienone ring is planar (*H. Koyama* and *T. Irie*, J. Chem. Soc. Perkin II *1972*, 351).

metric conformation. The angle between the C—H bond and the plane of the rings is lowered from *ca.* 54° in *(5)* to *ca.* 35°, whereby the smaller coupling constant in *(4)* results[77].

In the range of −20 to +70°C, the PMR spectra of the 9-H$^{\oplus}$- and 10-H$^{\oplus}$-9-ethyl-10-methylanthracenenium ions, as well as those of the 10,10-dimethyl- and 10,10-diethyl-9-hydroxyanthracenenium ions, are independent of temperature[71]. From data in the literature[69, 70], we would consider the boat conformation, with a very small isomerization energy, as most probable. Isolable arenenium salts are probably too unstable for X-ray structure analysis[78].

Whereas there are no X-ray structure analyses for the above-mentioned σ-complexes of electrophilic aromatic substitutions, three such studies have been performed on the anionic σ-complexes of nucleophilic aromatic substitutions[79]. *Simonetta et al.*[80] and *Tanaka et al.*[81] have determined the crystal structures of *(6)* and *(7)*, respectively, while *Palenik* and *Messmer* have elucidated that of *(8)*[82].

Not only the picryl ether adducts of *(6)* and *(7)*, but also the 4-methoxy-5,7-dinitrobenzofurazan adduct *(8)*, possess



(6), $R^1 = R^2 = OC_2H_5$
(7), $R^1 = R^2 = OCH_3$



(8)

planar ring systems. The planar arrangement of five sp^2- and one sp^3-hybridized ring C atoms leads to an opening of the C—C—C angles of the trigonal C atoms from 120° up to as much as 127°. As expected, the planarity of these σ-complexes is associated with a symmetrical disposition of the substituents $R^1 = R^2$ about the tetragonal C atom. Only with this symmetrical arrangement are the steric interactions reduced to a minimum. The most interesting question can only be answered, however, by future structural analyses: What is the structure of Meisenheimer complexes substituted at the tetragonal C atom by $R^1 \neq R^2$?

The PMR spectra of Meisenheimer complexes in which R^1 differs from R^2 and in which R^1 is H have not, to our knowledge, been subjected to quantitative conformational analyses[83].

Both π- and *molecular*-complexes as adducts must be considered separately. Their existence as intermediates in heterolytic aromatic substitutions is experimentally uncertain, almost without exception[4, 10, 11, 36a]. We here refer the reader to the excellent summary by *Banthorpe*[4].

5. Prospects

The currently available X-ray structure analyses of Meisenheimer complexes confirm that as long as they carry two identical substituents on the tetragonal C atom these σ-complexes possess a planar ring and a symmetrical arrangement of the substituents. Future work will show which conformations are the most favorable for unequally substituted compounds.

Little is known so far about the conformations of cationic σ-complexes and cyclohexadienone-type intermediates. X-ray structures must not, however, be uncritically assumed for the molecular state in solution since intermolecular forces in crystals are able to influence conformations. It will be of great value, therefore, to use NMR spectroscopy along with kinetic experiments in order to obtain *kinetically* relevant information concerning the conformations of intermediates. The previously available results from NMR studies on arenenium ions and cyclohexadienone derivatives, however, allow the conclusion that it is safe to assume asymmetrical conformations for intermediates with large steric interactions. From refined MO calculations one should be able to obtain further information concerning the relative energies of planar and non-planar structures of σ-complex-type intermediates[67].

Helgstrand, as well as *Jakubetz* and *Schuster*[84], has ascertained by CNDO/2 methods that the π-complex of a proton with benzene ($C_6H_6 \ldots H^+$) is unsymmetrical and about 84 kJ/mol more stable than the σ-complex. Since these calculations only apply to the gas phase and neither solvation nor gegenion interactions are accounted for, they can hardly be considered valid for reaction in solution.

Apart from the above-mentioned structural (particularly conformational) problems, the question should also be studied whether several consecutive intermediates appear *at all* in heterolytic aromatic substitutions of the type discussed here, and if so when. The importance of mixing and encounter control—as apparent from the work of *Ridd*[52], *Schofield*[56, 85], and ourselves[58, 59]—must be considered in the interpretation of relative reactivities.

We would like to thank Professors G. A. Olah (Case Western Reserve University, Cleveland), J. H. Ridd (University College, London), and M. Simonetta (Università di Milano) for stimulating discussions and for making available unpublished work, Dipl.-Ing. Chem. F. Pfister (ETH) for the collection and evaluation of the data in Tables 2 and 3, as well as the Schweizerischer Nationalfonds zur Förderung der Wissenschaften for financial support of the research results included herein (Project No. 2.245.69).

Received: September 23, 1971 [A 906 IE]
German version: Angew. Chem. *84*, 921 (1972)
Translated by Dr. *Stefan Unger*, Zürich

[1] The archetypal study in this area remains the investigation of nitrating reagents by *C. K. Ingold, E. D. Hughes, et al.*, J. Chem. Soc. *1938*, 929; *1950*, 2400–2552.

[2] *M. J. S. Dewar*, Nature *156*, 784 (1945); The Electronic Theory of Organic Chemistry. Clarendon Press, Oxford 1949.

[3] *R. S. Mulliken*, J. Amer. Chem. Soc. *74*, 811 (1952); J. Phys. Chem. *56*, 801 (1952).

[4] For a distinction between π- and molecular complexes, see *D. V. Banthorpe*, Chem. Rev. *70*, 295 (1970).

[5] *R. Huisgen*, Angew. Chem. *82*, 783 (1970); Angew. Chem. internat. Edit. *9*, 751 (1970).

[6] *M. Bodenstein*, Z. Phys. Chem. *85*, 329 (1913).

[7] *J. F. Bunnett* and *J. J. Randall*, J. Amer. Chem. Soc. *80*, 6020 (1958); *J. F. Bunnett* and *R. H. Garst*, *ibid.* *87*, 3875, 3879 (1965).

[8] *H. Zollinger*, Helv. Chim. Acta *38*, 1597, 1617, 1623 (1955).

[9] *P. B. D. de la Mare* and *J. H. Ridd:* Aromatic Substitution. Butterworth, London 1959, p. 43.

[10] *M. Christen, W. Koch, W. Simon*, and *H. Zollinger*, Helv. Chim. Acta *45*, 2077 (1962).

[11] *S. Koller* and *H. Zollinger*, Helv. Chim. Acta *53*, 78 (1970).

[12] *J. A. Orvik* and *J. F. Bunnett*, J. Amer. Chem. Soc. *92*, 2417 (1970). in Organic Chemistry. Holden-Day, San Francisco 1964, pp. 153—156; see also *B. Z. Senkowski* and *G. S. Panson*, J. Org. Chem. *26*, 943 (1961).

[13] *P. Rys, A. Schmitz*, and *H. Zollinger*, Helv. Chim. Acta *54*, 163 (1971).

[14] *P. Rys* and *H. Zollinger*, Helv. Chim. Acta *49*, 761 (1966); *P. Rys*, Textilveredlung *2*, 95 (1967).

[15] Summary: *L. J. Andrews* and *R. M. Keefer:* Molecular Complexes

[16] *R. Nakane, A. Natsubori, O. Kurihara*, and *T. Oyama*, J. Amer. Chem. Soc. *87*, 3597 (1965); *88*, 3011 (1966); *91*, 4528 (1969); J. Org. Chem. *33*, 275 (1968); *34*, 949 (1969); J. Phys. Chem. *70*, 1146 (1966).

[17] *L. Melander*, Ark. Kemi *17*, 291 (1961).

[18] *S. M. Shein, L. V. Bryukhovetskaya, A. D. Khmelinskaya, V. F. Starichenko*, and *T. M. Ivanova*, Reakts. Sposobnost Org. Soedin *6*, 1087 (1969); Chem. Abstr. *73*, 24629 (1970); *N. M. Katkova, V. S. Vainer, V. V. Brovko, S. M. Shein*, and *Y. N. Molin*, Kinet. Katal. *11*, 64 (English translation, p. 49) (1970); *J. K. Kim* and *J. F. Bunnett*, J. Amer. Chem. Soc. *92*, 7463, 7464 (1970); *J. R. Hazen*, unpublished.

[19] Summary: *L. M. Stock* and *H. C. Brown*, Adv. Phys. Org. Chem. *1*, 35 (1963).

[20] Further correlations essentially analogous to equation (5) are summarized by *R. O. C. Norman* and *R. Taylor:* Electrophilic Substitution in Benzenoid Compounds. Elsevier, Amsterdam 1965, Ch. 11.

[21] *F. Snyckers* and *H. Zollinger*, Helv. Chim. Acta *53*, 1294 (1970).

[22] *R. Taylor*, J. Chem. Soc. *B 1971*, 255, and earlier papers.

[23] *E. L. Mackor, A. Hofstra*, and *J. H. van der Waals*, Trans. Faraday Soc. *54*, 66, 187 (1958).

[24] *G. A. Olah*, Accounts Chem. Res. *4*, 240 (1971).

[25] *G. A. Olah, M. Tashiro*, and *S. Kobayashi*, J. Amer. Chem. Soc. *92*, 6369 (1970).

[26] Compare also *H. C. Brown* and *L. M. Stock*, J. Amer. Chem. Soc. *79*, 1421, 5175 (1957).

[27] *G. A. Olah, S. J. Kuhn*, and *S. H. Flood*, J. Amer. Chem. Soc. *83*, 4571 (1961).

[28] After *L. J. Andrews* and *R. M. Keefer* [15], p. 93.

[29] According to a proposal of *G. A. Olah*, J. Amer. Chem. Soc. *94*, 808 (1972); Angew. Chem., in press; Angew. Chem. internat. Edit., in press; we use the systematic term "benzenenium ion" (generally: "arenenium ion") for the σ-complex $C_6H_7^{\oplus}$ because of the coordinatively trivalent cationic carbon.

[30] *G. A. Olah, S. J. Kuhn, S. H. Flood*, and *J. C. Evans*, J. Amer. Chem. Soc. *84*, 3687 (1962).

[31] Table 2 also contains, for comparison, three reactions for which the reaction rates of only two benzene derivatives have been determined. These were not considered in the calculation of $\bar{r}$.

[32] Since, in contrast to σ-complexes, there are very different types of π- and molecular-complexes [4], we have compared the nitration product ratios in Table 3 with 15 different π-complex stabilities.

[33] *L. M. Stock* and *A. Himoe*, J. Amer. Chem. Soc. *83*, 4605 (1961); *L. J. Andrews* and *R. M. Keefer, ibid. 81*, 1063 (1959); *P. B. D. de la Mare et al.*, J. Chem. Soc. *1958*, 2756.

[34] *R. G. Coombes, D. H. G. Crout, J. G. Hoggett, R. B. Moodie*, and *K. Schofield*, J. Chem. Soc. *B 1970*, 347.

[35] *C. W. F. Kort*, Dissertation, Amsterdam University 1970; *C. W. F. Kort* and *H. Cerfontain*, Rec. Trav. Chim. Pays-Bas *86*, 865 (1967); *87*, 24 (1968); *88*, 860, 1298 (1969).

[36] a) *R. W. Bott, C. Eaborn*, and *J. A. Waters*, J. Chem. Soc. *1963*, 681; cf. also *R. W. Bott, C. Eaborn*, and *P. M. Greasley, ibid. 1964*, 4804; b) *C. Eaborn* and *J. A. Waters, ibid. 1961*, 542.

[37] *H. D. Anderson* and *D. L. Hammick*, J. Chem. Soc. *1950*, 1089.

[38] *H. C. Brown* and *J. J. Melchiore*, J. Amer. Chem. Soc. *87*, 5269 (1965).

[39] *D. R. Rosseinsky* and *H. Kellawi*, J. Chem. Soc. *A 1969*, 1207.

[40] *N. M. D. Brown, R. Foster*, and *C. A. Fyfe*, J. Chem. Soc. *B 1967*, 406.

[41] *R. M. Keefer* and *L. J. Andrews*, J. Amer. Chem. Soc. *72*, 4677 (1950).

[42] *L. J. Andrews* and *R. M. Keefer*, J. Amer. Chem. Soc. *73*, 4169 (1951).

[43] *L. L. Ferstandig, W. G. Toland*, and *D. Heaton*, J. Amer. Chem. Soc. *83*, 1151 (1961).

[44] *N. Ogimachi, L. J. Andrews*, and *R. M. Keefer*, J. Amer. Chem. Soc. *77*, 4202 (1955).

[45] *L. J. Andrews* and *R. M. Keefer*, J. Amer. Chem. Soc. *74*, 4500 (1952).

[46] *R. E. Merrifield* and *W. D. Phillips*, J. Amer. Chem. Soc. *80*, 2778 (1958).

[47] *R. Foster, D. Ll. Hammick*, and *B. N. Parsons*, J. Chem. Soc. *1956*, 555.

[48] *N. Ogimachi, L. J. Andrews*, and *R. M. Keefer*, J. Amer. Chem. Soc. *78*, 2210 (1956).

[49] *G. S. Hammond*, J. Amer. Chem. Soc. *77*, 334 (1955). The so-called Hammond postulate was already proposed earlier by other authors in a somewhat different form: *M. G. Evans* and *M. Polanyi*, Trans. Faraday Soc. *32*, 1340 (1936), and *R. P. Bell*, Proc. Roy. Soc. *A 154*, 414 (1936). *M. J. S. Dewar:* The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969, p. 284, therefore called it the BEP postulate.

[49a] *G. A. Olah et al.*, J. Amer. Chem. Soc., in press.

[49b] *P. C. Myhre*, J. Amer. Chem. Soc., in press.

[49c] For a discussion and definition of *ipso*-addition products see *C. L. Perrin*, J. Org. Chem. *36*, 420 (1971), and *P. B. Fischer* and *H. Zollinger*, Helv. Chim. Acta, *55*, 2139, 2146 (1972).

[50] *A. A. Frost* and *R. G. Pearson:* Kinetics and Mechanism. John Wiley, New York 1961; *Z. G. Szabo* in *C. H. Bamford* and *C. F. H. Tipper:* Comprehensive Chemical Kinetics. Elsevier, Amsterdam 1969, Vol. 2, p. 1.

[51] *J. Wei*, J. Catalysis *3*, 299 (1964).

[52] *P. F. Christy, J. H. Ridd*, and *N. D. Stears*, J. Chem. Soc. *B 1970*, 797.

[53] *J. H. Ridd*, Accounts Chem. Res. *4*, 248 (1971).

[54] *G. A. Olah* and *N. A. Overchuk*, Can. J. Chem. *43*, 3279 (1965).

[55] *W. S. Tolgyesi*, Can. J. Chem. *43*, 343 (1965).

[56] *R. G. Coombes, R. B. Moodie*, and *K. Schofield*, J. Chem. Soc. *B 1968*, 800; *J. G. Hoggett, R. B. Moodie*, and *K. Schofield, ibid. B 1969*, 1; Chem. Commun. *1969*, 605; [85], Section 2.5.

[57] *R. Fittig* and *P. Jannasch*, Z. für Chemie *1870*, 162. For further older literature, see [55].

[58] *S. B. Hanna, E. Hunziker, T. Saito*, and *H. Zollinger*, Helv. Chim. Acta *52*, 1537 (1969); *E. Hunziker, J. R. Penton*, and *H. Zollinger, ibid. 54*, 2043 (1971).

[59] *P. Rys*, Inaugural Thesis, ETH Zürich 1970.

[60] *A. P. Jaecklin, P. Skrabal*, and *H. Zollinger*, Helv. Chim. Acta *54*, 2870 (1971).

[61] *W. Koch* and *H. Zollinger*, Helv. Chim. Acta *48*, 554 (1965).

[62] *G. W. Wheland*, J. Amer. Chem. Soc. *64*, 900 (1942).

[63] *M. Davis* and *O. Hassel*, Acta Chem. Scand. *17*, 1181 (1963).

[64] *E. L. Eliel:* Stereochemistry of Carbon Compounds. McGraw-Hill, New York 1962.

[65] *J. Dale*, Angew. Chem. *78*, 1070 (1966); Angew. Chem. internat. Edit. *5*, 1000 (1966).

[66] See, *e. g., B. Miller* in *B. S. Thyagarajan:* Mechanisms of Molecular Migrations. Interscience, New York 1968, Vol. I, p. 247.

[67] *T. Beringhelli d'Alfonso, R. Destro*, and *M. Simonetta*, unpublished.

[68] *W. Regel* and *W. von Philipsborn*, Helv. Chim. Acta *51*, 867 (1968); *52*, 1354 (1969).

[69] *D. Y. Curtin, C. G. Carlson*, and *C. G. McCarty*, Can. J. Chem. *42*, 565 (1964).

[70] *W. G. Ferrier* and *J. Iball*, Chem. Ind. (London) *1954*, 1296.

[71] *D. M. Brouwer* and *J. A. van Doorn*, Rec. Trav. Chim. Pays-Bas *89*, 88 (1970).

[72] *H. V. Secor, M. Bourlas*, and *J. F. De Bardeleben*, Experientia *27*, 18 (1971).

[73] *G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly*, and *G. D. Mateescu*, J. Amer. Chem. Soc. *94*, 2034 (1972), have found no splitting of the CH_2 singlets down to −125 °C in the NMR spectrum of benzenenium and other arenenium ions.

[74] *M. Karplus*, J. Chem. Phys. *30*, 11 (1959).

[75] *J. P. Colpa, C. MacLean*, and *E. L. Mackor*, Tetrahedron *19*, Suppl. 2, 65 (1963).

[76] See also *A. W. Brinkmann, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers*, and *A. L. Ternay, Jr.*, J. Amer. Chem. Soc. *92*, 5912 (1970).

[77] *D. M. Brouwer, E. L. Mackor*, and *C. MacLean* in *G. A. Olah* and *P. von R. Schleyer*: Carbonium Ions. Wiley, New York 1970, Vol. 2, p. 837.

[78] *G. A. Olah* and *M. W. Meyer* in *G. A. Olah*: Friedel-Crafts and Related Reactions. Interscience, New York 1963, Vol. 1, p. 731.

[79] See also the summaries by *M. R. Crampton*, Advan. Phys. Org. Chem. *7*, 211 (1969); *T. N. Hall* and *C. F. Poranski* in *H. Feuer*: The Chemistry of the Nitro and Nitroso Groups. Interscience, New York 1970, Part 2, p. 329; *M. J. Strauss*, Chem. Rev. *70*, 667 (1970).

[80] *R. Destro, C. M. Gramaccioli*, and *M. Simonetta*, Acta Cryst. *24 B*, 1369 (1968).

[81] *H. Ueda, N. Sakabe, J. Tanaka*, and *A. Furusaki*, Bull. Chem. Soc. Jap. *41*, 2866 (1968).

[82] *G. G. Messmer* and *G. J. Palenik*, Chem. Commun. *1969*, 470.

[83] Compare the qualitative interpretation of *C. A. Fyfe*, Can. J. Chem. *46*, 3047 (1968).

[84] *E. Helgstrand*, Acta Chem. Scand. *24*, 3687 (1970); *W. Jakubetz* and *W. Schuster*, Tetrahedron *27*, 101 (1971); Angew. Chem. *83*, 499 (1971); Angew. Chem. internat. Edit. *10*, 497 (1971).

[85] *J. G. Hoggett, R. B. Moodie, J. R. Penton*, and *K. Schofield*: Nitration and Aromatic Reactivity. Cambridge University Press, Cambridge 1971, p. 117.

Transcription of Genetic Information and Its Regulation by Protein Factors

By Wolfgang Rüger[*]

During transcription, genetic information is transferred from DNA to mRNA, the process being catalyzed by DNA-dependent RNA polymerase. Transcription comprises binding of the RNA polymerase to DNA, initiation, elongation, and termination. The interplay of the positive and negative control elements of these processes is illustrated for bacteria and bacteriophages.

1. Introduction

The genetic information of all life forms except RNA viruses is stored in DNA. This information, which determines the amino acid sequences of cellular or viral proteins, is not transmitted directly from the DNA to the protein-synthesizing ribosomes; instead, the base sequence of one of the two DNA strands, the reading or the codogenic strand, is transferred section by section and without errors to an intermediary molecule, messenger RNA (mRNA). mRNA is thus also a carrier of information. In each individual information section, only one of the two DNA strands carries the information which is therefore read off asymmetrically. Two groups of "translators", the transfer ribonucleic acids (tRNAs) and the aminoacyl-tRNA synthetases, then assign certain amino acids to certain mRNA base sequences on the ribosomes. The first step of information transfer (DNA→mRNA) is known as transcription since the genetic code is retained, while the second step (mRNA→protein) is termed translation.

The enzyme catalyzing the synthesis of all RNAs on the DNA is DNA-dependent RNA polymerase. The transcription of a genome is regulated by an interaction of this polymerase with positive and negative control elements, which are often proteins. Positive control elements permit transcription, while negative elements prevent it. Regulation ensures that only a fraction of all the possible transcription products is present in the cell at any one time, depending on the environmental conditions.

The following steps can be distinguished in the course of the transcription:

1. Binding of RNA polymerase to DNA.

2. Initiation: A series of events ultimately leading to formation of the first phosphodiester linkage.

3. Elongation: The elongation of the RNA chain by attachment of new nucleotides to the growing polynucleotide, whose sequence is complementary to the base sequence of the reading strand, as stipulated by the model of *Watson* and *Crick*. At the same time, the enzyme must move along the DNA strand, and the last nucleotide incorporated must be transposed from the hypothetical substrate site to the hypothetical product site of the enzyme (translocation), to allow the binding of new substrate molecules (Fig. 1).

4. Termination: The cesessation of RNA synthesis after transcription of a definite section of genetic information. This last step includes: (a) the recognition of a "termination signal" for the transcription of a genome section; (b) the release of the synthesized polynucleotide from the transcription complex comprising DNA, enzyme, triphosphates, and RNA; and (c) the separation of RNA polymerase from DNA.

RNA polymerase has been isolated from many organisms, but the *E. coli* enzyme has been the most extensively purified and studied[1-3].

[*] Priv.-Doz. Dr. W. Rüger
Lehrstuhl für Biologie der Mikroorganismen, Universität Bochum
4630 Bochum-Querenburg, Postfach 2148 (Germany)

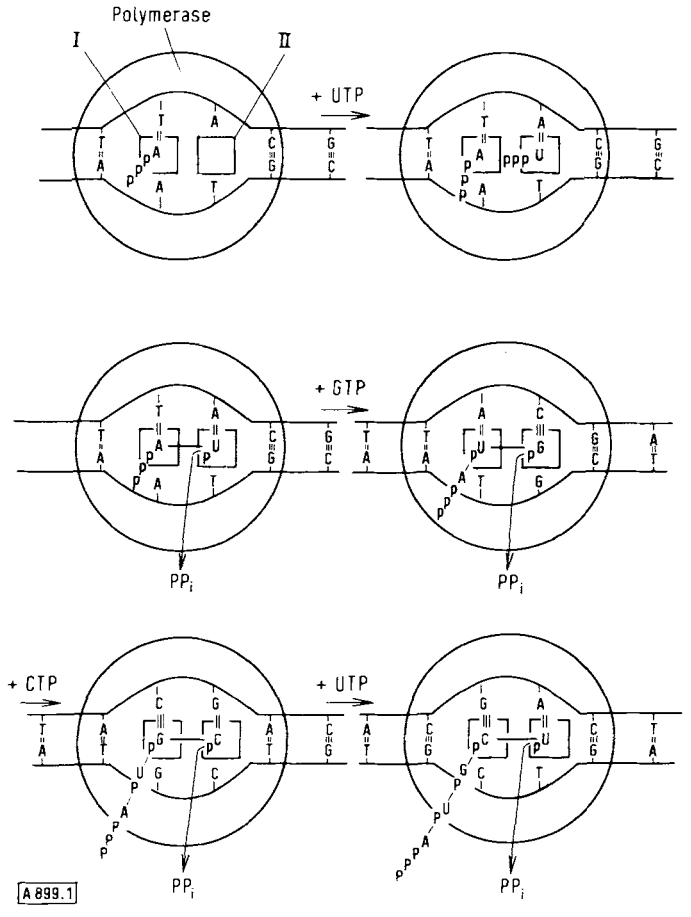


Fig. 1. Synthesis of RNA by the DNA-dependent RNA polymerase on a double-stranded DNA template.
Top: Reading strand. I = product binding site. II = substrate binding site; A = adenine, T = thymine, G = guanine, C = cytosine, U = uracil, p = phosphate residue, pp_i = inorganic diphosphate.

2. DNA-Dependent RNA Polymerase

E. coli RNA polymerase consists of several subunits. In the presence of sodium dodecyl sulfate or urea these subunits can be separated electrophoretically in polyacrylamide gels, even without prior reductive cleavage of disulfide bridges. The enzyme is made up of one β′ (MW 165000), one β (MW 155000), and two α subunits (MW 40000)[4, 5], and in this arrangement it is known as core enzyme. A further subunit is the σ factor[6], a polypeptide (MW 95000) which is firmly associated with core enzyme, but is removed during transcription and can then associate with another core enzyme molecule[7]. This form of the polymerase ($\beta'\beta 2\alpha)\sigma$, is known as "holoenzyme". A small polypeptide chain ω (MW 9000) is also found, but it has not yet been established whether this protein is an enzyme component (possibly with a regulating action) or an impurity that cannot be removed during enzyme isolation.

The subunits can be separated preparatively by ultracentrifugation in sucrose gradients, in the presence of 3 mol/l of LiCl, or by electrophoresis on cellulose acetate blocks. They can reassociate to form the active enzyme. This technique[8, 9] made it possible to investigate the subunits separately and to gain information regarding their function.

The α-free complex ββ′ is very strongly bound to phosphate groups[4] and to DNA[8]. If holoenzyme is ultracentrifuged with an excess of DNA, only little protein remains in the supernatant. Since it contains only the polypeptides α and β, it probably comprises enzyme molecules without the β′ subunit and hence cannot be bound by the DNA. This observation, the comparatively high isoelectric point of the β′ subunit (between pH 8 and 9), and the reaction of the β′ enzyme with heparin, which can competitively displace the DNA from a DNA-enzyme complex, make the β′subunit the most likely candidate for binding the enzyme to DNA[10].

If the subunits of wild type polymerase are reassociated with subunits of mutant polymerases resistant to the antibiotics rifampicin[11] or streptolydigin[12], the resistance of the holoenzyme is altered only by replacement of the β subunit[9]. Since rifampicin inhibits initiation of RNA synthesis[13] and streptolydigin inhibits translocation[11, 14], it was concluded that the β subunit is involved both in initiation and in translocation. The β subunit also binds the α and σ polypeptides[10].

Nothing is known as yet about the function of the α subunit. It is likely that a certain steric arrangement is essential for optimum functioning of polymerase polypeptide chains. The two small α chains may be required for this arrangement.

The σ factor is involved in steps leading to the initiation of RNA synthesis. Its possible functions will be discussed later.

The ω-polypeptide chains have not yet been further characterized.

The RNA polymerases of other bacteria investigated have similar structures[15–17]. Though the enzyme was first found in rat liver nuclei[18], the RNA polymerases isolated from higher organisms have not yet been so well characterized because these enzymes are difficult to separate from the nucleoprotein of the cells and are rather unstable. The polymerases of higher organisms also consist of several subunits, but these differ from those of the bacterial enzymes in number and molecular weight distribution[19–21].

3. Transcription

3.1. Binding of RNA Polymerase to DNA

Binding of RNA polymerase to DNA is observed *in vitro* less than 15 s after addition of the polymerase to DNA[22]. It depends on ionic strength and pH, but does not require any bivalent cations (Mg^{2+}) or nucleoside triphosphates, and occurs even at 0 °C. At low ionic strengths ($\mu \leq 0.05$), the reaction is nonspecific and reversible. The DNA can be densely packed with polymerase molecules[22, 24], but bound enzyme may exchange with new enzyme molecules or else combine with freshly added DNA[25]. These reactions are observed both for single-stranded and double-stranded DNA. If the ionic strength is increased (μ between 0.1 and 0.2), the polymerase binds to double-stranded DNA at only a few points, probably indicating specific

binding[23]. Above 20 °C and in the presence of σ factor the enzyme-DNA complex no longer dissociates[10, 26], and was found to be resistant to the action of heparin and rifampicin[10, 27], even in the absence of nucleoside triphosphates.

Since free polymerase is immediately inactivated by heparin and rifampicin, the resistance of the complex suggests that the polymerase, once bound under these conditions, does not leave the DNA until initiation and synthesis of the RNA chain is complete. The binding sites must be located close to, or must be identical with, the start signals (promoters) for the transcription[28].

It has not yet been established whether the nonspecific binding of the polymerase to the DNA, observed *in vitro*, is only an artefact of the experiments, or whether it is a necessary intermediate reaction in the search for specific binding sites and in the formation of the stable initiation complex. Knowledge of the base sequence of these binding sites would contribute greatly to an understanding of transcription, and particularly of initiation.

Does the RNA polymerase recognize a sequence of bases, or are the promoters sites on the DNA with a particular secondary structure? The characteristic groups of the four bases, *i.e.* the N—1 and the C—6 positions in the case of the adenine-thymine pair and also the C—2 position in that of the guanine-cytosine pair, are not readily accessible to the enzyme, since either they lie inside the double helix (N—1) or the substituents are involved in hydrogen bonding[29]. Moreover, the stacking free energy of the bases[30] keeps the purine-pyrimidine assembly tightly closed. In addition, in the DNA of phage T4, α- or β-glucosyl residues attached to the 5-hydroxymethylcytosine protect the bases from the surroundings[31]. Therefore it is inconceivable that the enzyme can recognize promoter sites determined only by a characteristic base sequence without opening of the helix structure.

In double-stranded DNA, however, sequences of ten or more pyrimidines on one DNA strand face complementary purines on the other[32, 33]. Such regions have a secondary structure different from those with the average base composition[34]. If the RNA polymerase could recognize these regions as promoters[35], or if such regions were recognized by the polymerase as "pointers" to nearby promoters, a second problem would be simultaneously solved, *i.e.* the selection of the codogenic strand. The pyrimidine-rich strand is in fact the reading strand *in vitro*[36, 37].

Other suggestions have been made concerning the structure of promoter regions[38, 39]. However, this question can be answered unequivocally only if the promoter regions can be isolated and sequenced. Relevant experiments are currently being conducted in various laboratories[40].

3.2. Initiation of Transcription

The term "initiation" covers all reaction steps between binding of the polymerase near or in the promoter region and condensation of the first two ribonucleotide 5′-triphosphates to form a dinucleotide. An mRNA molecule synthesized by the RNA polymerase always starts with a purine. The 5′-triphosphate group of the first nucleotide is retained. The second nucleotide of an mRNA chain usually is a pyrimidine[42]. The reactions leading to the initiation remain to be fully clarified, but some idea of the course of events can be derived from the following observations.

Native T4-DNA is transcribed only by holoenzyme: the σ factor therefore is essential for RNA synthesis on this double-stranded DNA[6]. Since single-stranded DNA or a polymer of alternating adenyl and thymidyl residues[43, 44], or even double-stranded DNA with single-strand breaks[45], is readily transcribed by core enzyme, the enzyme in this configuration evidently requires single-stranded or partly single-stranded structures to avoid the reaction influenced by the σ factor in the initiation of transcription on double-stranded DNA.

For what reaction, therefore, is the σ factor responsible? In studies of diphosphate exchange[157], another reaction

$$\mathrm{pA + pppU \xrightarrow[\text{polymerization}]{} pApU + pp_i}$$
$$\mathrm{pApU + {}^{32}pp_i \xrightarrow[\text{phosphorolysis}]{} pA + {}^{32}pppU}$$

catalyzed by polymerase, it was shown that σ acts at some time before the completion of the first phosphodiester linkage[46], and thus has nothing to do with the actual synthesis of the polynucleotide chain. Hybridization experiments showed that only very specific DNA regions are transcribed in presence of σ factor[47, 48]. Therefore it is concluded that σ influences the selection of the promoters for the transcription of these specific DNA regions. Since σ is a fairly negatively charged polypeptide[5] which by itself has not much affinity for DNA it is unlikely that this polypeptide directly participates in the binding of the enzyme to DNA. Rather it is assumed to allosterically reduce the affinity of the core enzyme for all DNA regions except for the promoter[49], possibly by triggering a conformational change of the β′ polypeptide. Thus, σ would indirectly enable the enzyme to attach to promoter regions preferentially.

Initiation of RNA synthesis on a double-stranded DNA *in vitro* includes a temperature-sensitive process, which proceeds rapidly at 37 °C but slowly at 20 °C[50]. Since on the one hand binding of polymerase to DNA occurs in seconds and is not hindered by low temperatures, and on the other no temperature-induced retardation of the start of synthesis has been observed when the polymerase transcribes single-stranded DNA, the temperature-sensitive process can be interpreted as the local opening of the DNA double helix. This interpretation is supported by the observation that RNA synthesis is also retarded at 37 °C if the salt concentration is increased, since it is well known that the melting point of double-stranded DNA rises with increasing salt concentration. Local opening of the promoter region hence would be the reaction which is not necessary on single-stranded DNA, enabling also core enzyme to transcribe this template.

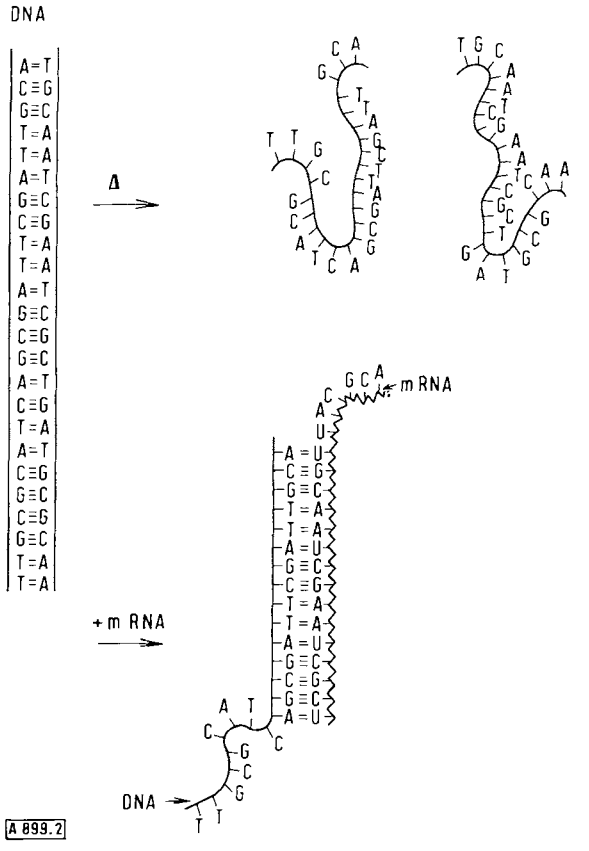


Fig. 2. The hybridization technique [41] is the most important method for identification of transcription products. Its principle is as follows. When double-stranded DNA is heated, the hydrogen bonds between the pairs of nucleotides are broken. The double-stranded molecule dissociates into two single strands. If this thermally denatured DNA is allowed to cool slowly, double-stranded DNA molecules are reformed. The re-aggregation of the single DNA strands can be prevented by fixation, *e.g.* on nitrocellulose membrane filters (DNA filters). If these DNA filters are incubated together with radioactively labeled mRNA, DNA-RNA hybrid molecules are formed provided that the mRNA was transcribed from the DNA species fixed on the filters. The extent of hybrid formation can be estimated from the radioactivity found on the filter. The hybrid molecule is stable. The reaction is extremely sensitive, and exhibits a high degree of specificity.

Thus there may be at least two reaction steps catalyzed by the σ factor in the course of initiation of mRNA synthesis: The effect of this factor on the selection of the promoters has been proved. This point is important to the regulation of transcription as will be shown later. It still remains unclear whether the factor functions in the opening of the promoter region. Possibly the heparin and rifampicin resistance of the enzyme bound to specific DNA regions, as mentioned in the preceding section, and the local opening of the promoter region are merely different aspects of the same reaction. Though it can be shown that the DNA double helix is opened in the course of transcription[51], it has not yet been possible to measure this process directly on a DNA-enzyme complex without nucleoside triphosphates; the disturbance of the DNA structure by the opening of the promoter may be insufficient without active transcription.

During or shortly after initiation, σ is released from the holoenzyme and can then initiate the synthesis of a new RNA chain together with another molecule of core enzyme[7]. This also appears to be the case *in vivo*, since no σ factor is found on careful isolation of a DNA and RNA polymerase complex in the process of transcription[52]. The factor is no longer required for polynucleotide elongation[53].

How is the σ factor released from the initiation complex? It is known that a short RNA chain, possibly of less than six nucleotides, must first be synthesized[54]. To explain this, it has been suggested that σ is attached to the enzyme close to the product binding site. During initiation, this site is brought into the proximity of the promoter region. If an RNA chain is now synthesized and incorporated into the transcription complex, the steric arrangement of the enzyme may consequently be changed, either purely mechanically or as a result of a new charge distribution, in such a way that σ is liberated.

The sequence of events leading from free polymerase and DNA, *via* the binding of the two components, to initiation is shown schematically in Figure 3[10].

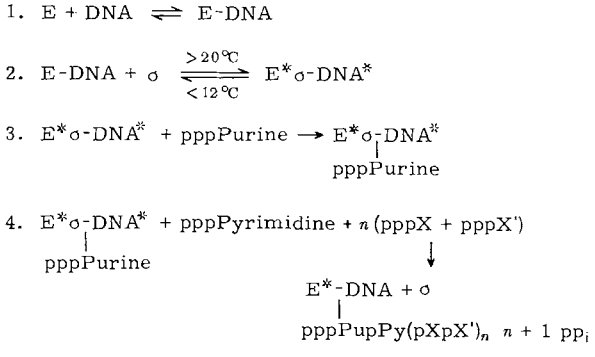


Fig. 3. Step 1: Primary binding, reversible; step 2: activated complex, reversible depending on temperature; step 3: initiation complex; step 4: initiation. Pu = purine, Py = pyrimidine, X, X' = any nucleobases, p = phosphate residue, pp_i = inorganic diphosphate, E = enzyme.

3.3. Elongation

As mentioned above, binding of polymerase to DNA is largely reversible. During or shortly after initiation, however, the transcription complex composed of DNA, enzyme, and nascent RNA becomes stable[55]. The completion of a single nucleotide linkage is sufficient to prevent the dissociation of the complex, even at salt concentrations which do not permit binding of free polymerase to DNA[56]. The finding that the addition of the two possible starting nucleotide 5'-triphosphates ATP and GTP is sufficient to bring about this stabilization in controversial[57]. With only a few exceptions[58], stabilization of the transcription complex prevents the liberation of incomplete RNA chains. This is essential for smooth and, with regard to the energy balance of the cells, economical transmission of the information *in vivo*.

In contrast, the transcription complex containing single-stranded DNA, cannot be stabilized, even at low salt concentrations. RNA synthesized *in vitro* on single-stranded DNA has a low molecular weight; the sedimentation constant is as low as 5S[59]. New RNA chains are continuously initiated[42], showing that transcription on single-stranded DNA probably does not correspond to the situation *in vivo*.

The rate of synthesis of mRNA chains on double-stranded DNA *in vitro* depends on the ionic strength, the substrate concentration, and the nature of the DNA. Average increases of 3—17 nucleotides per second and per RNA chain were found for T4-DNA at low ionic strengths ($\mu < 0.1$)[55, 60]. At higher ionic strengths ($\mu \approx 0.2$), 20—36 nucleotides are incorporated per second[60, 61]. This is close to the synthesis rate of 28 nucleotides per second found *in vivo*[62]. The higher ionic strengths in the *in vitro* experiments roughly correspond to the physiological conditions of growing cells[63]. Differences between the synthesis rates at lower and at higher ionic strengths are due to product inhibition[64, 65] in a manner yet to be clarified[66].

It has been considered in this connection whether the transcription rate might be influenced *in vivo* by the occupation of the nascent RNA with ribosomes and by a protein synthesis proceeding simultaneously with transcription[67]. Since the mRNA in the protein synthesis is translated in the 5′→3′ direction, coinciding with the direction of transcription[68], the ribosomes could occupy the mRNA even before completion of synthesis. The mRNA would thus be largely protected against enzymatic degradation by ribonuclease, and product inhibition would possibly also be prevented. However, a translation coupled with the transcription has not yet been proved to influence the rate of mRNA synthesis.

3.4. Termination

If the transcription complex is stabilized by active RNA synthesis, the question arises as to how RNA and enzyme are released after a section of information has been transcribed.

At higher ionic strengths, RNA synthesis stops by itself after a certain time. The transcription complex dissociates, polymerase and product are liberated, and the polymerase is again available for initiation[69]. It is not known whether these events require the recognition of certain DNA base sequences. Though the transcription products occurring under these conditions are larger (MW 2.2×10^6) than the corresponding mRNA formed *in vivo* (MW $0.2—1.1 \times 10^6$), the base at the 3′ end of the RNA product in most cases is uridine[66, 70]. Naturally occurring 5S and 23S RNA also end with a uridine nucleotide. Polyribonucleotide chains synthesized under these conditions carry genetic information, and can be used as mRNA for cell-free protein synthesis of, *e.g.*, active lysozyme[71, 72]. On the other hand, active lysozyme cannot be synthesized on mRNA transcribed under the same conditions from single-stranded DNA. This therefore contains the information only incompletely or not at all.

These results show that physiologically active RNA is synthesized *in vitro* on transcription at high ionic strengths and on double-stranded DNA. Consequently, the termination of transcription cannot be random under these conditions.

Another form of termination brought about by a protein factor was reported recently. This termination factor ϱ is isolated as a tetramer. Its polypeptide chains have a molecular weight of about 50000. mRNA synthesized *in vitro* in the presence of ϱ has a molecular weight similar to that of the corresponding mRNA formed *in vivo*[73].

The ϱ factor terminates mRNA synthesis at definite points even at high salt concentrations ($\mu \approx 0.2$)[74]. It is bound by RNA[75] and also by DNA[76, 77]. Since mRNA synthesized *in vitro* at high salt concentrations is not broken down into mRNA molecules of lower molecular weight by pure preparations of ϱ factor, it is unlikely that ϱ terminates the elongation of an mRNA chain by enzymatic cleavage at a termination signal coded on the mRNA. Its mode of action is therefore most simply explained as recognition of a specific DNA sequence as a termination signal. By binding to these positions, it could prevent the progress of the polymerase along the DNA molecule, and so terminate transcription. On the basis of other findings, however, more complicated hypotheses have also been developed[78]. For instance, it has been proposed that ϱ changes the conformation of a ternary complex comprising DNA, enzyme, and RNA, which could lead to the termination of transcription. Up to now it is unclear whether ϱ releases only the RNA from the transcription complex, or whether the polymerase is also released by ϱ action and consequently can initiate transcription of new RNA chains.

4. Regulation of Transcription in Bacteria

4.1. Reversible Regulation Processes

The bacterial cell can rapidly adapt its metabolism to suit the existing environmental conditions. For example, if the supply of available carbon sources changes, the cell synthesizes enzymes present only in small quantities or not at all which enable it to utilize the new energy sources. It will be shown below that such processes can be regulated at the level of transcription.

In 1961, *Jacob* und *Monod*[79] formulated a theory stating that the transcription of a group of structural genes forming a transcriptional unit (operon) is controlled by specific

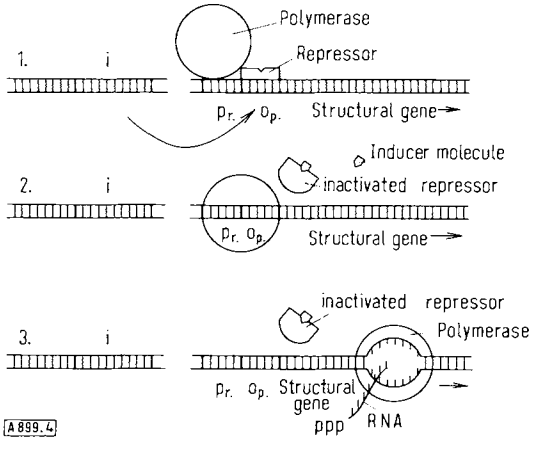


Fig. 4. Model for the transcription of a repressible operon. Left: "i" gene coding for the repressor. Pr. = promoter, Op. = operator. Step 1: repression; step 2: induction; step 3: transcription.

molecules, known as repressors. The repressors, which are readily diffusible products of the regulator genes, react with the operator, a DNA region of the operon, and thus block the transcription of the structural genes. The operator is situated proximally to the structural genes (Fig. 4). To induce the transcription of an operon blocked by the repressor, the corresponding repressor must be inactivated. This is achieved by specific metabolites, the inducers. These react with the repressors, which thus lose their affinity for the operator region, and the operon can be transcribed. This theory was developed to explain the regulation of the lactose *(lac)* operon and has proved entirely correct in genetic and biochemical experiments[80].

Experiments have shown that the promoter region is closely coupled with the operator[81, 82]. It has been possible to isolate three genetically defined repressors[83–85] which are all proteins capable of firm binding to the corresponding operator region of the DNA[86, 87].

The λ repressor, which represses the lytic development of λ bacteriophage *in vivo* and for which no low molecular weight inducer is known at present, was found also to prevent *in vitro* transcription of certain gene sections on the phage genome[88]. It binds strongly to DNA which is not chemically modified in the process. If the same DNA is first transcribed in presence of repressor and then deproteinated by phenol treatment and transcribed again without repressor, different RNA products are found. In the first case, the two operons which are under the control of the repressor in question are not transcribed; in the second case, these two operons are transcribed. If DNA with a mutation in the operator region is transcribed, the effect of the repressor on transcription is reduced; the repressor is totally inactive if the operator region in question has been genetically exchanged for that of a related phage (λimm^{434}).

Similar results were obtained with the isolated *lac* repressor. The transcription of the *lac* operon is subject not only to negative control by the repressor but also to positive control by another regulatory protein, the CRP factor [abbreviation for *c*yclic 3′:5′-adenosine monophosphate (cAMP) *r*eceptor *p*rotein][89]. In presence of cAMP, the CRP factor is attached to DNA. Both cAMP and CRP factor are necessary for the binding of RNA polymerase to *lac* promoter[90] and for asymmetric transcription[91] of the *lac* region. If *lac* repressor is added to this transcription system, the *lac* operon is not transcribed. However, if the *lac* repressor in this system is inactivated by addition of the inducer IPTG (abbreviation for *iso*propyl *thio*galactoside), *lac*-mRNA is synthesized.

The binding constants between the *lac* and the λ repressors and their operators are 2×10^{-11} and 7.3×10^{-12} mol/l respectively[92, 93], the binding constants between polymerase and promoter in both cases being 1×10^{-9} mol/l[94]. Though these values were determined at different temperatures and salt concentrations, and therefore are not strictly comparable, they nevertheless show that the polymerase can displace the repressor from its complex with DNA only when present in a 1000-fold excess. The experiments described above show that the binding of the repressor to the operator prevents transcription of an operon. The repressor therefore is a protein with a regulatory effect on transcription.

Another example of a protein factor auxiliary to transcription is ψ_r[*]. Though polymerase effectively transcribes the DNA of most phages, little RNA is synthesized *in vitro* on *E. coli* DNA. In rapidly growing *E. coli* cells, the content of ribosomal RNA (rRNA) increases up to 40% of the total cellular RNA[95, 96], though only 0.2—0.4% of the total *E. coli* genome codes for rRNA[95, 97]. This disparity suggested that some special mechanism exists for the transcription of these genes. Since rRNA is not synthesized in measurable quantities *in vitro*, there may be an "effector" that causes the preferential transcription of the rRNA genes.

A protein factor ψ_r that stimulates the synthesis of rRNA *in vitro* together with the holoenzyme has in fact been isolated from cell extracts of *E. coli*[98]. In presence of ψ_r, 30% of all RNA synthesized was ribosomal RNA. However, it has yet to be proved that ψ_r stimulates only the synthesis of rRNA, and thus controls the transcription of a specific class of genes. The activity of the ψ_r factor is inhibited by guanosine 5′-diphosphate 3′-diphosphate (ppGpp)[99], which accumulates in the cells under certain restrictive growth conditions[100] and which also negatively influences transcription by *E. coli* polymerase[101].

Both negative control by the repressor and positive control by protein factors such as ψ_r enable the cell to react rapidly and reversibly at the level of transcription to changes in its environment. These two systems are no exceptions. Several inducible catabolic enzyme systems that are regulated in a similar way to the *lac* operon have now been reported and genetically defined, and further protein factors that also have a stimulating effect on RNA synthesis, such as the M factor[102], have also been found and partly characterized; however, these will not be discussed further here.

4.2. Irreversible Regulation Processes

Not only reversible changes in metabolism, but also changes that are irreversible to the cell are regulated at the level of transcription. An example is the sporulation of *Bac. subtilis*.

RNA molecules different from those found in the vegetative phase occur in the sporulation phase of this organism[103]. The sporulating cells lack several enzymes found in the vegetative cells, and *vice versa*[104, 105].

The following genetic observations suggested that there must be a connection between RNA polymerase and sporulation.

1. Rifampicin-resistant mutants of *Bac. subtilis* are frequently found to include some which, in a single mutation

[*] During the printing of this paper some controversy arose concerning the ψ_r factor. Attempts to repeat the experiments were unsuccessful. Careful analysis of the RNA transcribed in presence of this factor yielded no evidence for preferential transcription of rRNA [158]. The function of ψ_r therefore remains to be clarified.

step, acquire rifampicin resistance and simultaneously lose the ability to form normal spores[106].

2. If cells of *Bac. subtilis* in the early sporulation phase are infected with the virulent phage φe, the sporulating cells, unlike the vegetative cells, can no longer transcribe the phage genes. The phage genome is incorporated into the spore. Transcription of phage DNA and multiplication begin only on germination of the spore. However, some sporulation-negative mutants can multiply the phage also at a time when proteins characteristic of the sporulation phase are present[107].

According to its electrophoretic behavior, the RNA polymerase isolated from vegetative cells of *Bac. subtilis* is similar to the RNA polymerase of *E. coli*. Therefore the corresponding designations were used for its subunits. Like the *E. coli* RNA polymerase, it is composed of a β′ and a β subunit (MW 155000 and 120000 respectively), two identical α units (MW 45000), and a σ factor (MW 57000)[108–110]. φe DNA is transcribed *in vitro* by the holoenzyme from vegetative cells, but not by core enzyme. On the other hand, transcription of φe DNA cannot be achieved with polymerase from sporulating cells, even when σ factor isolated from vegetative cells is added[111].

Comparison of the two *Bac. subtilis* enzymes revealed that the β subunit has a lower molecular weight in the polymerase from sporulating cells[108]. It remains to be clarified whether the change in molecular weight is due to modification, *e.g.* proteolytic cleavage, or whether a new β-polypeptide is synthesized in the early sporulation phase subsequently replacing the β unit from the enzyme of the vegetative form. Since σ factor of this enzyme is necessary for transcription of φe DNA, the change in the β subunit could prevent further synthesis of "vegetative mRNA".

In the case of *E. coli* polymerase the β subunit is responsible for the rifampicin resistance and the binding of σ. Application of these findings to RNA polymerases from vegetative and from sporulating cells of *Bac. subtilis* affords an explanation of the differences in transcription behavior. The enzyme of sporulating cells with the modified β-polypeptide might not be able to bind the "vegetative σ factor", which specifically initiates the "vegetative operons". The relationship pointed out between rifampicin resistance and sporulation could then be explained by assuming that the β subunit rendered resistant to rifampicin by mutation can no longer be exchanged for or converted into a sporulation-specific subunit. Experiments are being carried out to establish whether the change in the β subunit is sufficient by itself to change the initiation specificity of the polymerase from sporulating cells, or whether a new σ factor that forms a sporulation-specific holoenzyme with the modified core enzyme also occurs.

5. Regulation of Transcription in Bacteriophage Development

5.1. Phage T 4

T4 is one of the largest and most complex bacteriophages. Its DNA is double-stranded, and its molecular weight is *ca.* 1.1×10^8. It carries about 70 genes, the functions of a number of which are known[112, 113].

If *E. coli* bacteria are infected with T4, the multiplication of the phage proceeds in an ordered sequence of syntheses until the host bacteria lyse and the T4 progeny are liberated. This multiplication cycle takes about 20 minutes. Immediately upon infection synthesis of "early" proteins is started. They are responsible for "switching off" mRNA and protein synthesis of the host bacterium and for phage-specific DNA synthesis[114–116]. About 5 minutes after infection replication of phage DNA begins. At this stage mainly coat proteins, *i.e.* "late" proteins[117], are found. At the same time, synthesis of early proteins levels off, and can no longer be detected approximately 10 minutes after infection[118].

As in the case of the proteins, a distinction is made between early mRNA before, and late mRNA after the start of DNA replication. 98% of the early mRNA is read from the "l strand" of the DNA, while 80% of the late mRNA is copied from the "r strand"[119] [*]. Both the early and the late mRNA can be divided into at least two subclasses, *i.e.* the pre-early and the early mRNA[**] on the one hand, and the quasi-late and the late mRNA on the other[120].

How do the four classes of mRNA differ? The synthesis of the pre-early mRNA even occurs when the bacteria are infected in the presence of chloramphenicol, *i.e.* independently of phage-specific protein synthesis[121]. The appearance of the early mRNA two minutes after infection and of the two other classes of mRNA, on the other hand, depends on the phage-specific protein synthesis. Quasi-late mRNA is a class that appears in small quantities shortly before the start of DNA replication. Late mRNA is synthesized only when DNA replication has already started[122] and when the gene product of phage gene 55 is present[123]. The gene product of gene 33 stimulates the synthesis of late mRNA[124].

The sequential appearance of clearly distinguishable classes of mRNA parallel to the appearance of different classes of proteins suggested that the multiplication of T4 is regulated mainly at the level of transcription. How is this regulation effected? In presence of σ, *E. coli* polymerase synthesizes only pre-early mRNA[125]. This explains why this mRNA is synthesized even without phage-specific protein synthesis. Immediately after infection, the *E. coli* enzyme with *E. coli* σ factor transcribes a series of genes. The σ factor acts here as a positive control element, which allows the RNA polymerase to transcribe selectively a certain part of the T4 genome.

How are the other parts of the phage genome transcribed? Throughout phage development, the RNA polymerase remains sensitive to rifampicin[126]. Therefore it is assumed that at least that part of the polymerase which is responsible for the rifampicin phenotype of the enzyme participates in transcription of all types of T4-mRNA. In contrast,

[*] The l strand by definition is the strand transcribed counterclockwise relative to the circular genetic map of T4; the r strand is transcribed clockwise.

[**] Two nomenclatures are commonly used in the literature for the classes of T4 – mRNA. The simpler nomenclature has been chosen here, though some authors cited prefer the other.

transcription of the mRNAs which appear later depends on phage-specific protein synthesis, thus leading to the conclusion that at least one of the components responsible for transcription of this group of mRNAs must be coded for on the phage genome. Corresponding to the σ factor, selectively controlling the transcription of the pre-early mRNA, there could exist phage-coded protein factors altering the initiation specificity of polymerase for the synthesis of other classes of mRNA.

Such a protein factor σ^{T4} has in fact been isolated from T4-infected cells[127]. It stimulates core enzyme to transcribe the DNA of T4 and of two closely related phages, a mRNA class occurring *in vivo* between 1.75 and 2.5 min after infection[128].

What causes the core enzyme to exchange factor σ for σ^{T4}? Conceivably, σ factors no longer "wanted" for further transcription are inactivated, either by interaction with an "anti-σ" activity[129] or by structural modification. Some time after infection, the σ protein can no longer be found[130]. Moreover, a modification of the core enzyme could also lead to a decrease in its affinity for σ in favor of σ^{T4}. In fact soon after infection a change is observed in the electrophoretic behavior of the α chain[131], which depends on the phage-specific protein synthesis[132]. Roughly half of the α chains are affected within two minutes after infection, and the change is complete after four minutes. The change, however, is not due to a *de novo* synthesis and mutual exchange of the two α chains but rather to a modification of the α-polypeptide of the host polymerase. This includes the covalent bonding of a 5'-adenylate residue, presumably 5'-adenosine monophosphate[133].

In the course of the infection cycle changes can be observed also in the other enzyme subunits. Distinct differences are found in the fingerprints of the peptides obtained on trypsin digestion of the polymerase subunits from uninfected and from T4-infected cells. It can be deduced from these differences that the enzyme subunits are modified in the course of the infection cycle by the addition of newly sythesized peptide material[10]. In the β' unit, this modification occurs between 10 and 15 minutes after infection. It depends on the synthesis of late mRNA[134] and is therefore undoubtedly effected by a late protein.

However, the appearance of a phage-specific factor and the modification of the host enzyme are not the only model that could explain the regulation of the synthesis of early mRNA.

The genes for the early mRNA are interspersed between the genes for the pre-early mRNA[135]. Since both classes of mRNA are copied from the same DNA strand[119], the transition from synthesis of pre-early to early mRNA can be explained as follows[135]. Both classes of mRNA are coded for on the same transcription unit. The synthesis of the "pre-early" mRNA is initiated by the host polymerase. The ρ factor then terminates the transcription of this mRNA at certain points. It has been suggested that the pre-early mRNA also carries the information for the synthesis of an antitermination factor[136]. This inactivates ρ. Polymerization beginning transfer at this time in the infection cycle would still start at the pre-early promoters but because of inactivation of ρ would now also synthesize early mRNA. This "reading through" is observed *in vitro* if the ρ factor is absent from the transcription system[135] and also occurs *in vivo*, since early mRNA is found on long mRNA molecules that were initiated immediately after infection, *i.e.* at a time when pre-early promoters were recognized exclusively[137]. Transcription could terminate by itself without further termination factors, as is observed *in vitro* at high salt concentrations. The two models for the regulation of synthesis of early mRNA are not mutually exclusive, and experimental observations indicate that both views are correct.

There may be still other classes of early mRNA, which cannot be resolved by methods used so far. For example mRNAs could exist that are transcribed only together with pre-early mRNA after the termination factor has been inactivated, as could mRNAs that have their own promoters and are initiated in presence of modified core enzyme and σ^{T4}. The transcription of the first class would reach an optimum during a short period after infection, until the core enzyme is modified and σ is no longer functioning; the other class would then be transcribed for a longer time, until it is relieved by the appearance of the quasi-late and late mRNAs.

Late mRNA is generally synthesized only if the replication of DNA takes place at the same time, *i.e.* transcription of late mRNA does not occur from the parental DNA, and the DNA must in some way be "competent" for the transcription of the late mRNA. What constitutes this competence? On the basis of several experimental findings[138], it is assumed that single-strand breaks in the DNA are necessary in order to allow transcription of the late mRNA. It is known that such breaks occur in DNA that has just been replicated[139]. It is also conceivable that an endonuclease cleaves the DNA at specific points. Since the late mRNA is mainly transcribed from the "r strand" of the DNA, the single-strand breaks would have to be asymmetrically distributed on the two DNA strands.

Late mRNA is synthesized only in presence of gene 55 product[140]. What is the function of this product in the synthesis of the late mRNA?

1. It could be a protein factor that enables a further modified core enzyme to recognize certain single-strand breaks in the DNA and to initiate synthesis of late mRNA. A new protein factor appearing 18 minutes after infection of *E. coli* bacteria with T4 has recently been identified[134]. Together with core enzyme, it stimulates "r strand"-specific transcription. No connection has so far been found between this factor and gene 55 product. Work is in progress on further characterization of this factor.

2. Gene 55 product could react directly with DNA. By binding to DNA regions with single-strand breaks, initiation points could be provided for synthesis of late mRNA. This view is in agreement with the observation that modification of core enzyme leads to an increased affinity for single-stranded DNA[141]. It is unlikely that gene 55 product itself causes single-strand breaks in DNA and so makes it competent for the transcription of late mRNA[138].

3. It has not yet been ruled out that gene 55 product is a new polymerase coded on the phage genome, with entirely new initiation properties specially for synthesis of late mRNA.

As mentioned earlier, polymerase remains sensitive to rifampicin throughout the infection cycle, and it was therefore concluded that at least one subunit is involved in the synthesis of all T4-mRNA. However, it is conceivable that the host polymerase must remain active throughout the infection cycle and continuously transcribe some DNA regions specific for early mRNA in order to maintain the synthesis of the late mRNA classes by the phage-specific polymerase[142]. It will be shown in the next section that synthesis of a new polymerase is in fact used for regulation of phage development.

5.2. Phages T7 and T3

The *E. coli* phages T7 and T3 number among the smaller T phages. They are closely related and their DNA is double-stranded. The molecular weight of T7-DNA is about 2.5×10^7[143]. In the case of T7, 19 essential genes have so far been genetically localized[144, 145]. The products of a series of these genes are known[146].

On T7 infection, the host DNA is broken down[144]; six to seven minutes after infection at 30 °C only phage-specific mRNA is found. The "switch-off" of host RNA synthesis is probably controlled by an early phage-specific protein[37]. In contrast to transcription of T4-DNA, all T7-mRNA is transcribed from the "r strand" *in vivo* and transcription of late mRNA is independent of the DNA replication. Late and early mRNAs are distinguished according to whether phage-specific protein synthesis is necessary for their transcription[147, 148].

On the basis of an average molecular weight of 50000 per polypeptide, it may be estimated that the phage genome can carry the information for at most 26 genes. In view of this small number, it was thought feasible to identify each of the T7 proteins individually, and hence, since the genome is also well characterized genetically, to obtain an insight into the regulation of the development of this phage. Both the phage-specific proteins and their mRNAs were resolved into separate bands by radioactive labeling, polyacrylamide electrophoresis, and subsequent autoradiography. On attempting to assign individual protein or mRNA bands to each of the T7 genes by infection with phage mutants that cannot synthesize a gene product under very specific growth conditions (conditionally lethal mutants) it was found that gene no. 1 exerts a special regulatory role in transcription of the phage genome. When *E. coli* bacteria were infected under restrictive growth conditions with phages having such a mutation in gene no. 1, only three of twelve known T7-mRNA bands[147] and only three of 25 known protein bands were found[148]. Upon infection with phage mutants exhibiting a mutation in any other gene, at most one band was absent in each case.

On the basis of a number of other experimental observations and the knowledge of the role of σ in the *E. coli*-T4 system, it was assumed at first that gene 1 product was a new σ factor that changes the initiation specificity of the host polymerase in favor of the promoters for transcription of late mRNA[149]. In the attempt to isolate this T7-specific protein component complexed with the host enzyme, it was found that the T7 component itself was a new polymerase[142]. Unlike the *E. coli* enzyme, it consists of only one polypeptide chain having a molecular weight of 107000. It transcribes T7-DNA asymmetrically and is responsible for the transcription of late mRNA. A polymerase having a similar molecular weight (110000) was also isolated from T3-infected cells[150, 151]. Both the T3 and T7 polymerase exhibit high DNA specificity. Apart from T3-DNA, T7 polymerase transcribes only T7-DNA, while T3 enzyme transcribes only T3-DNA, and no T7-DNA. Neither of these polymerases is inhibited either by rifampicin or by streptolydigin. Higher salt concentrations, which stimulate the transcription by *E. coli* polymerase, inhibit T3 and T7 polymerases.

Following the discovery of T7 and T3 polymerases, a new model can be developed for the positive control of transcription of these phage genomes.

A small quantity of the infecting DNA is first transcribed by the *E. coli* polymerase. In the case of T3-DNA, three types of mRNA molecules are found *in vitro* at high salt concentrations and in presence of the termination factor ρ[74]; these RNAs are all copied from the "r strand". The resulting transcription products correspond to early *in vivo* T7 or T3 mRNA. The translation of these messengers results in the synthesis of three early proteins, *i.e.* the polymerase and two others whose function is not yet known. The newly synthesized T7 polymerase recognizes the promoters for transcription of the remaining DNA regions, and then takes over the synthesis of the late mRNA. In this system, therefore, there must be at least two types of promoters[152]. In this connection, it is necessary to point out the following:

1. The "r strands" of T7 and T3 contain pyrimidine-rich (cytosine-rich) regions[153]; no such regions are found in the "l strand".

2. The *E. coli* polymerase, in addition to a series of DNA molecules of other organisms, also transcribes the small d(A—T) copolymer very satisfactorily, whereas dGdC is hardly transcribed at all[1]. Apart from their own DNAs, the T7 and T3 polymerase transcribe only dGdC, but not the d(A—T) copolymer[142, 150].

Ten minutes after infection of *E. coli* cells with T7, synthesis of gene 1 protein stops[148]. The phage thus evidently also carries the information for a protein that exerts a negative control on transcription. It is not yet known how this control is exerted. One of several possibilities would be the modification of one or more subunits of *E. coli* polymerase by one of the late proteins.

6. Closing Remarks

Out of a number of systems that are particularly suitable for the study of regulation, a few have been selected to illustrate the possibilities for the regulation of transcription of certain sections of the genetic information. By no means all of the existing data on this topic have been presented. Thus two other extensively studied systems have been

omitted. These are the regulation of phage λ transcription (this has already been reviewed[38, 154]) and the regulation of transcription of the *Bac. subtilis* phage SPO1, which seems at present to be as complicated as that of T4, but has not yet been as thoroughly investigated[155, 156].

It was shown that in both uninfected and infected bacterial cells, there are several possibilities for switching the transcription of certain groups of genes on or off. "Switching on" can take place:

1. by the change in the initiation specificity of the enzyme caused by modification of the subunits and/or by synthesis of new protein factors such as σ and ψ_r;

2. by the synthesis of an antitermination factor, which enables the polymerase to transcribe new gene groups beyond certain "stop signals"; and

3. by the synthesis of a new polymerase with a different initiation specificity.

These three possibilities are not mutually exclusive, but may operate together, since several classes of mRNA occur in some cases.

The "switching off" of the transcription of gene groups can occur:

1. by modification of enzyme subunits, as a result of which certain promoters are no longer recognized; and

2. by the synthesis of repressors that can be bound to DNA in the neighborhood of individual promoters and can thus prevent transcription of the corresponding gene section.

The proteins taking part in the regulation of transcription can be inhibited in some cases by low molecular weight substances, such as the ψ_r factor by ppGpp or the *lac* repressor by lactose. This enables the cell to react rapidly and reversibly to changes in environmental conditions.

Though the regulation even of simple systems is not yet fully understood, the existing data show that the cell functions can be very effectively regulated at the level of transcription by a balanced cooperation of positive and negative control elements.

This article covers the literature published up to June 1971. I am grateful to Prof. Dr. U. Winkler for encouragement and continued interest in this work, as well as to all those who have assisted in the preparation of the manuscript. I also thank Mrs. A. Hörling for typing the manuscript and Mrs. B. Benninghoven for preparing the drawings. This work was supported by the Deutsche Forschungsgemeinschaft.

Received: July 19, 1971 [A 899 IE]
German version: Angew. Chem. *84*, 961 (1972)
Translated by Express Translation Service, London

[1] *M. Chamberlin* and *P. Berg*, Proc. Nat. Acad. Sci. USA *48*, 81 (1962).
[2] *W. Zillig, F. Fuchs*, and *R. Millette* in *G. L. Cantoni* and *D. R. Davies*: Procedures in Nucleic Acid Research. Harper and Row, New York 1967.
[3] *R. R. Burgess*, J. Biol. Chem. *244*, 6160 (1969).
[4] *R. R. Burgess*, J. Biol. Chem. *244*, 6168 (1969).
[5] *W. Zillig, E. Fuchs, P. Palm, D. Rabussay*, and *K. Zechel*: 1st Lepetit Colloquium on Biology and Medicine. North Holland Publ. Co., Amsterdam 1969, p. 151.
[6] *R. R. Burgess, A. A. Travers, J. J. Dunn*, and *E. K. F. Bautz*, Nature *221*, 43 (1969).
[7] *A. A. Travers* and *R. R. Burgess*, Nature *222*, 537 (1969).
[8] *V. S. Sethi, W. Zillig*, and *H. Bauer*, FEBS Lett. *8*, 236 (1970).
[9] *A. Heil* and *W. Zillig*, FEBS Lett. *11*, 165 (1970).
[10] *W. Zillig, K. Zechel, D. Rabussay, M. Schachner, V. S. Sethi, P. Palm, A. Heil*, and *W. Seifert*, Cold Spring Harbor Symp. Quant. Biol. *35*, 47 (1970).
[11] *G. Hartmann, K. O. Honikel, F. Knüsel*, and *J. Nüesch*, Biochim. Biophys. Acta *145*, 843 (1967).
[12] *C. Siddhikol, J. W. Erbstoeszer*, and *B. Weisblum*, J. Bacteriol. *99*, 151 (1969).
[13] *H. Lill, U. Lill, A. Sippel*, and *G. Hartmann*: 1st Lepetit Colloquium on Biology and Medicine. North Holland Publ. Co., Amsterdam 1969, p. 55.
[14] *G. Cassani, R. R. Burgess, H. M. Goodman*, and *L. Gold*, Nature New Biol. *230*, 197 (1971).
[15] *J. S. Krakow, K. Daley*, and *M. Karstadt*, Proc. Nat. Acad. Sci. USA *62*, 432 (1969).
[16] *J. Avila, J. M. Hermoso, E. Viñuela*, and *M. Salas*, Nature *226*, 1244 (1970).
[17] *R. Losick, R. G. Shorenstein*, and *A. L. Sonenshein*, Nature *227*, 910 (1970).
[18] *S. B. Weiss* and *L. Gladstone*, J. Amer. Chem. Soc. *81*, 4418 (1959).
[19] *S. P. Blatti, C. J. Ingles, T. J. Lindell, P. W. Morris, R. F. Weaver, F. Weinberg*, and *W. J. Rutter*, Cold Spring Harbor Symp. Quant. Biol. *35*, 649 (1970).
[20] *B. Sugden* and *J. Sambrook*, Cold Spring Harbor Symp. Quant. Biol. *35*, 663 (1970).
[21] *P. Chambon, F. Gissinger, J. L. Mandel Jr., C. Kedinger, M. Gniazdowski*, and *M. Meihlac*, Cold Spring Harbor Symp. Quant. Biol. *35*, 693 (1970).
[22] *J. P. Richardson*, Progr. Nucl. Acid Res. *9*, 75 (1969).
[23] *D. Pettijohn* and *T. Kamiya*, J. Mol. Biol. *29*, 275 (1967).
[24] *J. P. Richardson*, J. Mol. Biol. *21*, 83 (1966).
[25] *M. Sternberger* and *A. Stevens*, Biochem. Biophys. Res. Commun *24*, 937 (1966).
[26] *D. C. Hinkle* and *M. Chamberlin*, Cold Spring Harbor Symp. Quant. Biol. *35*, 65 (1970).
[27] *A. Sippel* and *G. Hartmann*, Eur. J. Biochem. *16*, 152 (1970).
[28] *K. Ippen, J. H. Miller, J. Scaife* and *J. Beckwith*, Nature *217*, 825 (1968).
[29] *M. Yarus*, Annu. Rev. Biochem. *38*, 841 (1969).
[30] *D. M. Crothers* and *B. H. Zimm*, J. Mol. Biol. *9*, 1 (1964).
[31] *J. R. Lehman* and *E. A. Pratt*, J. Biol. Chem. *235*, 3254 (1960).
[32] *J. H. Spencer* and *E. Chargaff*, Biochim. Biophys. Acta *68*, 18 (1963).
[33] *W. E Mushinsky* and *J. H. Spencer*, J. Mol. Biol. *52*, 91 (1970).
[34] *R. Langridge*, J. Cell. Physiol. *74*, Suppl. 1, 1 (1969).
[35] *W. Szybalski, H. Kubinski* and *P. Sheldrick*, Cold Spring Harbor Symp. Quant. Biol. *31*, 123 (1966).
[36] *K. Taylor, Z. Hradecna* and *W. Szybalski*, Proc. Nat. Acad. Sci. USA *57*, 1618 (1967).
[37] *W. C. Summers* and *W. Szybalski*, Virology *34*, 9 (1968).
[38] *W. Szybalski, K. Bøvre, M. Fiandt, A. Guha, Z. Hradecna, S. Kumar, H. A. Lozeron, Sr. V. M. Maher, H. J. J. Nijkamp, W. C. Summers*, and *K. Taylor*, J. Cell. Physiol. *74*, Suppl. 1, 33 (1969).
[39] *A. Gierer*, Nature *212*, 1480 (1966).
[40] *W. Rüger*, Biochim. Biophys. Acta *238*, 202 (1971).
[41] *B. J. McCarthy* and *R. B. Church*, Annu. Rev. Biochem. *39*, 131 (1970).
[42] *U. Maitra, Y. Nakata*, and *J. Hurwitz*, J. Biol. Chem. *242*, 4908 (1967).
[43] *R. B. Inman* and *R. L. Baldwin*, J. Mol. Biol. *5*, 172 (1962).
[44] *D. Berg, K. Barrett*, and *M. J. Chamberlin* in: Methods in Enzymology. Academic Press, New York 1971, Vol. *21 D*.
[45] *V. Vogt*, Nature *223*, 854 (1969).
[46] *J. J. Dunn* and *E. K. F. Bautz*, Biochem. Biophys. Res. Commun. *36*, 925 (1969).
[47] *E. K. F. Bautz, F. A. Bautz*, and *J. J. Dunn*, Nature *223*, 1022 (1969).
[48] *M. Sugiura, T. Okamoto*, and *M. Takanami*, Nature *225*, 598 (1970).
[49] *K. Mueller*, Mol. Gen. Genet. *3*, 273 (1971).
[50] *G. Walter, W. Zillig, P. Palm*, and *E. Fuchs*, Eur. J. Biochem. *3*, 194 (1967).
[51] *Yu. N. Kasaganov, M. I. Zarudnaja, Yu. S. Lazurkin, M. D. Frank-Kamenetskii, R. Sh. Beabealashvilli*, and *U. L. P. Savochkina*, Nature New Biol. *231*, 212 (1971).
[52] *D. E. Pettijohn, O. G. Stenington*, and *C. R. Kossman*, Nature *228*, 235 (1970).
[53] *J. L. Darlix, A. Sentenac, A. Ruet*, and *P. Fromageot*, Eur. J. Biochem. *11*, 43 (1969).
[54] *J. S. Krakow* and *K. von der Helm*, Cold Spring Harbor Symp. Quant. Biol. *35*, 73 (1970).
[55] *H. Bremer* and *M. W. Konrad*, Proc. Nat. Acad. Sci. USA *51*, 801 (1964).
[56] *A. G. So* and *K. M. Downey*, Biochemistry *9*, 4788 (1970).

[57] *D. D. Anthony, E. Zeszotek*, and *D. A. Goldthwait*, Proc. Nat. Acad. Sci. USA *56*, 1026 (1966).
[58] *K. Mueller* and *H. Bremer*, J. Mol. Biol. *43*, 89 (1969).
[59] *H. Bremer, M. Konrad*, and *R. Bruner*, J. Mol. Biol. *16*, 104 (1966).
[60] *J. P. Richardson*, J. Mol. Biol. *49*, 235 (1970).
[61] *H. Bremer*, Cold Spring Harbor Symp. Quant. Biol. *35*, 109 (1970).
[62] *H. Bremer* and *D. Yuan*, J. Mol. Biol. *34*, 527 (1968).
[63] *M. Lubin* and *H. L. Ennis*, Biochim. Biophys. Acta *80*, 614 (1964).
[64] *J. S. Krakow*, J. Biol. Chem. *241*, 1830 (1966).
[65] *E. Fuchs, R. L. Millette, W. Zillig*, and *G. Walter*, Eur. J. Biochem. *3*, 183 (1967).
[66] *R. L. Millette* and *C. D. Trotter*, Proc. Nat. Acad. Sci. USA *66*, 701 (1970).
[67] *E. P. Geiduschek* and *R. Haselkorn*, Annu. Rev. Biochem. *38*, 661 (1969).
[68] *G. Streisinger, Y. Okada, J. Emrich, J. Newton, A. Tsugita, E. Terzaghi*, and *M. Inouye*, Cold Spring Harbor Symp. Quant. Biol. *31*, 77 (1966).
[69] *J. P. Richardson*, Nature *225*, 1109 (1970).
[70] *U. Maitra*, Biochem. Biophys. Res. Commun. *41*, 1255 (1970).
[71] *R. L. Millette, C. D. Trotter, P. Herrlich*, and *M. Schweiger*, Cold Spring Harbor Symp. Quant. Biol. *35*, 135 (1970).
[72] *U. Maitra, A. H. Lockwood, J. S. Dubnoff*, and *A. Guha*, Cold Springer Harbor Symp. Quant. Biol. *35*, 143 (1970).
[73] *J. W. Roberts*, Nature *224*, 1168 (1969).
[74] *J. J. Dunn* and *E. K. F. Bautz*, personal communication.
[75] *J. P. Richardson*, Cold Spring Harbor Symp. Quant. Biol. *35*, 127 (1970).
[76] *J. L. Darlix, A. Sentenac*, and *P. Fromageot*, FEBS Lett. *13*, 165 (1971).
[77] *J. S. Beckmann, V. Daniel, Y. Tichauer*, and *U. Z. Littauer*, Biochem. Biophys. Res. Commun. *43*, 806 (1971).
[78] *A. R. Goldberg*, Cold Spring Harbor Symp. Quant. Biol. *35*, 157 (1970).
[79] *F. Jacob* and *J. Monod*, J. Mol. Biol. *3*, 318 (1961).
[80] *B. Müller-Hill*, Angew. Chem. *83*, 195 (1971); Angew. Chem. internat. Edit. *10*, 160 (1971).
[81] *F. Jacob* and *J. Monod*, CR. Acad. Sci. *258*, 3125 (1964).
[82] *J. Scaife* and *J. R. Beckwith*, Cold Spring Harbor Symp. Quant. Biol. *31*, 403 (1966).
[83] *W. Gilbert* and *B. Müller-Hill*, Proc. Nat. Acad. Sci. USA *56*, 1891 (1966).
[84] *M. Ptashne*, Proc. Nat. Acad. Sci. USA *57*, 306 (1967).
[85] *U. Pirrotta* and *M. Ptashne*, Nature *222*, 541 (1969).
[86] *M. Ptashne*, Nature *214*, 232 (1967).
[87] *W. Gilbert* and *B. Müller-Hill*, Proc. Nat. Acad. Sci. USA *58*, 2415 (1967).
[88] *R. A. Steinberg* and *M. Ptashne*, Nature New Biol. *230*, 76 (1971).
[89] *G. Zubay, D. Schwartz*, and *J. Beckwith*, Proc. Nat. Acad. Sci. USA *66*, 104 (1970).
[90] *B. de Crombrugghe, B. Chen, W. Anderson, P. Nissley, M. Gottesman, J. Pastan*, and *R. Perlman*, Nature New Biol. *231*, 139 (1971).
[91] *B. de Crombrugghe, B. Chen, M. Gottesman, J. Pastan, H. E. Varmus, M. Emmer*, and *R. L. Perlman*, Nature New Biol. *230*, 37 (1971).
[92] *W. Gilbert* and *B. Müller-Hill*, Proc. Nat. Acad. Sci. USA *58*, 2415 (1967).
[93] *P. Chadwick, V. Pirrotta, R. Steinberg, N. Hopkins*, and *M. Ptashne*, Cold Spring Harbor Symp. Quant. Biol. *35*, 283 (1970).
[94] *E. K. F. Bautz* and *F. A. Bautz*, Nature *226*, 1219 (1970).
[95] *D. Kennel*, J. Mol. Biol. *34*, 85 (1968).
[96] *R. A. Lazzarini* and *R. M. Winslow*, Cold Spring Harbor Symp. Quant. Biol. *35*, 383 (1970).
[97] *S. A. Yanofsky* and *S. Spiegelman*, Proc. Nat. Acad. Sci. USA *48*, 1466 (1962).
[98] *A. A. Travers, R. I. Kamen*, and *R. F. Schleif*, Nature *228*, 748 (1970).
[99] *A. Travers, R. Kamen*, and *M. Cashel*, Cold Spring Harbor Symp. Quant. Biol. *35*, 415 (1970).
[100] *M. Cashel* and *J. Gallant*, Nature *221*, 838 (1969).
[101] *M. Cashel*, Cold Spring Harbor Symp. Quant. Biol. *35*, 407 (1970).
[102] *J. Davison, L. M. Pilarski*, and *H. Echols*, Proc. Nat. Acad. Sci. USA *63*, 168 (1969).
[103] *A. J. Aronson*, J. Mol. Biol. *11*, 576 (1965).
[104] *M. P. Deutscher* and *A. Kornberg*, J. Biol. Chem. *243*, 4653 (1968).
[105] *M. L. Bach* and *C. Cilvarg*, J. Biol. Chem. *241*, 4563 (1966).
[106] *A. L. Sonenshein* and *R. Losick*, Nature *227*, 906 (1970).
[107] *A. L. Sonenshein* and *D. H. Roscoe*, Virology *39*, 265 (1969).
[108] *R. Losick, R. G. Shorenstein*, and *A. L. Sonenshein*, Nature *227*, 910 (1970).
[109] *P. Kerjan* and *J. Szulmajster*, FEBS Lett. *5*, 288 (1969).
[110] *J. Avila, J. M. Hermoso, E. Viñuela*, and *M. Salas*, Eur. J. Biochem., in press.
[111] *R. Losick* and *A. Sonenshein*, Nature *224*, 35 (1969).
[112] *W. B. Wood, R. S. Edgar, J. King, J. Lielausis*, and *M. Henninger*, Fed. Proc. *27*, 1160 (1968).
[113] *J. Emrich*, Virology *35*, 158 (1968).
[114] *M. Adesnik* and *C. Levinthal*, J. Mol. Biol. *48*, 187 (1970).
[115] *H. L. Ennis*, Virology *40*, 727 (1970).
[116] *S. S. Cohen:* Virus Induced Enzymes. Columbia University Press, New York 1968.
[117] *J. Hosada* and *C. Levinthal*, Virology *34*, 709 (1968).
[118] *J. S. Wiberg, M. Dirksen, R. H. Epstein, S. E. Luria*, and *J. Buchanan*, Proc. Nat. Acad. Sci. USA *48*, 293 (1962).
[119] *A. Guha* and *W. Szybalski*, Virology *34*, 608 (1968).
[120] *W. Salser, A. Bolle*, and *R. Epstein*, J. Mol. Biol. *49*, 271 (1970).
[121] *R. J. Grasso* and *J. M. Buchanan*, Nature *224*, 882 (1969).
[122] *R. Bruner* and *R. E. Cape*, J. Mol. Biol. *53*, 69 (1970).
[123] *L. Snyder* and *E. P. Geiduschek*, Proc. Nat. Acad. Sci. USA *59*, 459 (1968).
[124] *A. Bolle, R. Epstein, W. Salser*, and *E. P. Geiduschek*, J. Mol. Biol. *33*, 339 (1968).
[125] *E. K. F. Bautz, F. A. Bautz*, and *J. J. Dunn*, Nature *223*, 1022 (1969).
[126] *R. Haselkorn, M. Vogel*, and *R. D. Brown*, Nature *221*, 836 (1969).
[127] *A. A. Travers*, Nature *223*, 1107 (1969).
[128] *A. A. Travers*, Nature *225*, 1009 (1970).
[129] *R. B. Khesin:* 1st Lepetit Colloquium on Biology and Medicine. North Holland Publ. Co., Amsterdam 1969, p. 167.
[130] *W. Seifert:* 1st Lepetit Colloquium on Biology and Medicine. North Holland Publ. Co., Amsterdam 1969, p. 158.
[131] *G. Walter, W. Seifert*, and *W. Zillig*, Biochem. Biophys. Res. Commun. *30*, 240 (1968).
[132] *W. Seifert, P. Qasba, G. Walter, P. Palm, M. Schachner*, and *W. Zillig*, Eur. J. Biochem. *9*, 319 (1969).
[133] *C. G. Goff* and *K. Weber*, Cold Spring Harbor Symp. Quant. Biol. *35*, 101 (1970).
[134] *A. Travers*, Cold Spring Harbor Symp. Quant. Biol. *35*, 241 (1970).
[135] *G. Milanesi, E. N. Brody*, and *E. P. Geiduschek*, Nature *221*, 1014 (1969).
[136] *D. A. Schmidt, A. J. Mazaitis, T. Kasai*, and *E. K. F. Bautz*, Nature *225*, 1012 (1970).
[137] *E. Brody, R. Sederoff, A. Bolle*, and *R. H. Epstein*, Cold Spring Harbor Symp. Quant. Biol. *35*, 203 (1970).
[138] *A. Cascino, S. Riva*, and *E. P. Geiduschek*, Cold Spring Harbor Symp. Quant. Biol. *35*, 213 (1970).
[139] *R. Okazaki, T. Okazaki, K. Sakabe, K. Sugimoto*, and *A. Sugino*, Proc. Nat. Acad. Sci. USA *59*, 598 (1968).
[140] *J. Pulitzer* and *E. P. Geiduschek*, J. Mol. Biol. *49*, 489 (1970).
[141] *A. A. Travers*, Nature *229*, 69 (1971).
[142] *M. Chamberlin, J. McGrath*, and *L. Waskell*, Nature *228*, 227 (1970).
[143] *F. C. Bancroft* and *D. Freifelder*, J. Mol. Biol. *54*, 537 (1970).
[144] *R. Hausmann* and *B. Gomez*, J. Virol. *1*, 779 (1967).
[145] *F. W. Studier*, Virology *39*, 562 (1969).
[146] *M. S. Center, F. W. Studier*, and *C. C. Richardson*, Proc. Nat. Acad. Sci. USA *65*, 242 (1970).
[147] *R. B. Siegel* and *W. C. Summers*, J. Mol. Biol. *49*, 115 (1970).
[148] *F. W. Studier* and *J. V. Maizel*, Virology *39*, 575 (1969).
[149] *W. C. Summers* and *R. B. Siegel*, Nature *223*, 1111 (1969).
[150] *J. J. Dunn, F. A. Bautz*, and *E. K. F. Bautz*, Nature New Biol. *230*, 94 (1971).
[151] *U. Maitra*, Biochem. Biophys. Res. Commun. *43*, 443 (1971).
[152] *W. C. Summers* and *R. B. Siegel*, Cold Spring Harbor Symp. Quant. Biol. *35*, 253 (1970).
[153] *W. C. Summers* and *W. Szybalski*, Biochim. Biophys. Acta *166*, 371 (1968).
[154] *A. M. Wu, S. Ghosh, M. Willard, J. Davison*, and *H. Echols* in *A. Hershey:* The Bacteriophage Lambda. Cold Spring Harbor Press, New York, in press.
[155] *E. P. Geiduschek, D. L. Wilson*, and *L. P. Gage*, J. Cell. Physiol. *74*, 81 (1969).
[156] *L. P. Gage* and *E. P. Geiduschek*, J. Mol. Biol. *57*, 279 (1971).
[157] *J. S. Krakow* and *E. Frank*, J. Biol. Chem. *244*, 5988 (1969).
[158] *W. Haseltine*, Nature *235*, 329 (1972).

Cooperative Conformational Changes in Globular Proteins

By Fritz M. Pohl[*]

In globular proteins, the complicated steric arrangement of the polypeptide chain is determined by several interdependent cooperative interactions. These macromolecules are capable of reacting to changes in the environmental conditions such as temperature and pressure or the concentration of a wide range of compounds by changing their conformation and hence their biological and chemical properties. They are thus suitable for regulation processes or information storage in solution with a wide range of time constants. Environmental effects of this kind can be followed and explained in part at the molecular level by investigation of the time-dependent reversible unfolding of a number of proteins that can be described to a good approximation by a strongly cooperative "all-or-none" transition between two states.

1. Introduction

Proteins are among the most complicated of all organic molecules, and also among the most fascinating[1]. Together with the "linear" macromolecules, the nucleic acids, which serve in particular for the storage and transfer of genetic information, the "two-dimensional" membranes, which serve also as boundaries and partitions for the separation of compartments, and water with its special properties as a solvent[2-5], they are responsible for numerous structures and processes in biology. As enzymes, the proteins have the function of accelerating chemical reactions and considerably increasing their specificity. Proteins are important molecules for regulation processes in the cell, without which it would be impossible for the many reactions to proceed in an orderly manner under changing environmental conditions[6, 7].

The large number of natural proteins is understandable from their chemical structure. A very large number of possible sequences can be produced by linking together 20 different amino acids to form polypeptide chains of 100—500 members in most cases. Weak interactions such as hydrogen bonds, "hydrophobic" bonds, van der Waals interactions, and "ionic bonds" occur between the members of the same chain and also between the chain and other small and large molecules[8-10]. These interactions influence one another and lead to the cooperative stabilization of certain steric arrangements. Cooperative effects of this type are familiar for small molecules in the form of phase transitions such as melting and evaporation.

Many biological and biochemical properties of the proteins are associated with one particular three-dimensional arrangement of functional groups, which is often referred to as the "native" form. If this arrangement or "conformation" is changed, the corresponding properties of the proteins are also changed. It is thus possible to build up molecular control and switching circuits in which changes in the environment are reflected in changes in the macromolecular conformation, often intensified by cooperativity[11], as for example in a non-linear response to changes in the concentration of small molecules.

The environmental influences can be best summarized by equation (1)[12]. In this equation, ΔG_p^0 is the change in the free energy of a protein upon a change in temperature of ΔT, in pressure of ΔP, or in the mole fraction of the i-th type of particle of ΔM_i (effects due to a change in electric field $\Delta\mathfrak{E}$ are not taken into account):

$$\Delta G_p^0 = \sum_i \mu_i \Delta M_i - S\Delta T + V\Delta P \qquad (1)$$

(μ_i are the chemical potentials, S is the entropy of the system, V is the volume). Eq. (1) can be illustrated by the impressions of the senses, such as smell and taste (ΔM_i), heat and cold (ΔT), and sound and touch perceptions (ΔP). In all these cases, a change in the conformation of certain "receptor" proteins, *i.e.* ΔG_p^0, is very probably important to the initiation of the stimulus.

In addition to an accurate determination of the native conformation itself, questions of special interest include the extent, the rate, and the reason for the conformational change of a protein on variation of the environment. Apart from general observations on the conformation of globular proteins, problems of conformational changes connected with eq. (1) are discussed here with respect to a particular example, *i.e.* the kinetics of the reversible unfolding of certain mutually "related" proteins[13].

The conformation of a protein is the steric arrangement of the polypeptide chain, which consists of 1000—10000 atoms in many cases. The conformers can be converted into one another by rotation about covalent bonds[14]. A conformational change is a change in which no chemical bonds (with the exception of hydrogen bonds) are altered and the torsion angles θ about the bonds are the essential variables. Figure 1 shows part of a peptide chain with the designations of the principal torsion angles.

Strictly speaking, this definition rules out any change in the bond lengths b and bond angles α. This is justifiable to a first approximation for the general steric arrangement of the main and side chains[15, 16]. Thus for an energy consumption of kT, the relative position of a C^α atom, for

[*] Priv.-Doz. Dr. F. M. Pohl
Max-Planck-Institut für Biophysikalische Chemie
34 Göttingen-Nikolausberg (Germany)

example, changes by ± 0.04 Å on variation of b, by ± 0.15 Å on variation of α, but by ± 1 Å on variation of θ. This naturally does not mean that such changes in b or α cannot be of particular importance, *e.g.* in enzymatic catalysis.

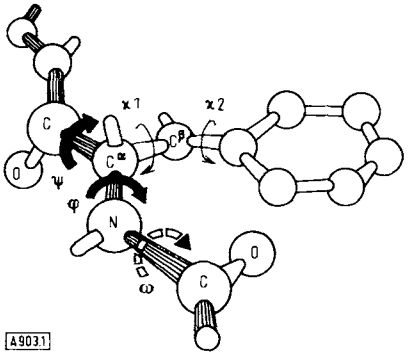


Fig. 1. Schematic representation of part of a polypeptide chain, with designation of the torsion angles about bonds of the main chain (ϕ, ψ, ω) and of the side chains of phenylalanine ($\chi 1$, $\chi 2$) [14].

This "geometric" definition, which is oriented in particular toward the requirements of the X-ray structure analysis of protein crystals, does not give any lower limit for conformational changes. In this progress report, a change will be referred to as a conformational change only if the torsion angle changes by at least 30°.

The determination of changes in certain torsion angles in solution is still rather hopeless for macromolecules, despite the progress that has been made *e.g.* for cyclic oligopeptides[17]. In many cases, an indication of conformational changes in macromolecules is the observation that reaction steps are independent of the protein concentration or that such steps are necessary for the quantitative explanation of the reaction scheme[18-20].

Reversible conformational changes may involve the rotation of a single side chain or they may involve the collapse of the entire steric structure. It is therefore often necessary to use very different methods for their measurement. (Conformational changes in which protein properties such as absorption or fluorescence of aromatic side chains are altered can fairly easily be followed *directly*.) For processes involving a large part of a protein molecule, at least a rough classification seems justifiable:

1. The change *e.g.* in the activity is due to a change from the native to a "flexible" conformation ($A \rightleftharpoons F$), the investigation of which is possible practically only in solution. Readily measurable changes *e.g.* in the hydrodynamic and thermodynamic properties occur here. An example that has been intensively studied is the glyceraldehyde-3-P dehydrogenase (GAPDH) from yeast[20-22]. However, this group also includes processes such as reversible denaturation (by extreme temperatures and pH values or by a change of solvent), which can be best compared with transitions between a solid and a liquid phase of the macromolecule.

2. The change is due to the transition from a "relaxed" to a "locked" or "strained" conformation, *i.e.* both have solid-like properties and can be investigated by X-ray analysis in the crystal. An example is the transition from the arterial form of hemoglobin into the venous form ($A \rightleftharpoons V$) on release of oxygen[23], which can be compared with transitions between two solid phases.

2. Conformation of Globular Proteins

2.1. Anatomy of Proteins

Two methods complement each other excellently in the determination of the static three-dimensional arrangement of the polypeptide chain:

1. The determination of the electron density distribution with atomic resolution by X-ray diffraction in protein crystals[24-26]. (The distribution of nuclei (mainly hydrogen) can now also be determined by neutron diffraction[27].)

2. The determination of the amino acid sequence by chemical methods[28-30].

By means of the two methods together, it is possible to construct models of globular proteins in which the nature and the steric positions of a few thousand atoms are given. The rapid progress in this field is indicated in Figure 2.

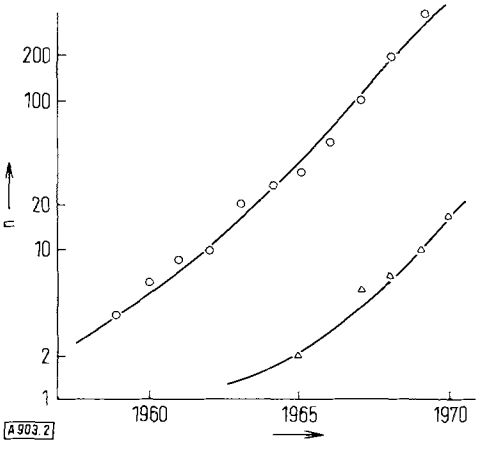


Fig. 2. Number n of globular proteins whose primary structure (—o—o—) [30] and whose three-dimensional crystal structure with an atomic resolution of better than 3.5 Å (—△—△—) have been determined in recent years [25, 26]. The rapid progress is impressively shown even by the logarithmic plot.

No simple "geometric" structural principles can be deduced from the structures obtained. Even the description of the secondary structure, *i.e.* the arrangement of small regions of the main chain, by α (helix) and β (pleated sheet) structures is only a relatively rough approximation; considerable deviations occur from the geometry observed for polyamino acids. An example of the complicated structure of two related enzymes is illustrated in Figure 3, where only the course of the peptide chain is shown[31-33]. This great similarity of the conformations, though only 39% of the amino acids are homologous, is also found in other members of this family of proteins, chymotrypsinogen A[34] and trypsin[35].

Different crystal forms of the same protein, such as α- and γ-chymotrypsin[36] or subtilisin novo and subtilisin

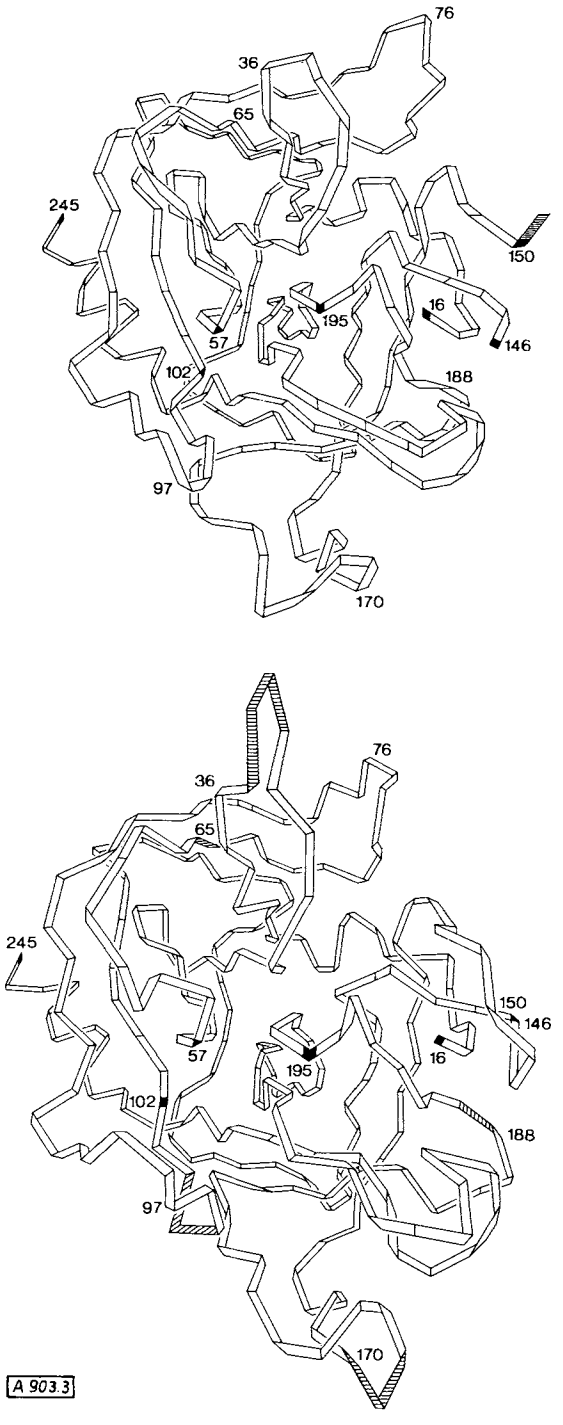


Fig. 3. Conformation of the polypeptide chain of α-chymotrypsin (top) and of elastase (bottom), two related proteins, as found from X-ray diffraction on protein crystals. The band, which is bent at each C^{α} atom, represents the main chain (after [33]). Though the two enzymes differ in a number of amino acids, a very similar steric folding is found.

BPN[37, 38] also show only minor differences in conformation. However, small differences in conformation even within the same crystal can be observed for the two proteins constituting the dimers of α-chymotrypsin or insulin[31, 39]. Great similarities, such as have already been found between myoglobin and hemoglobin, suggest that the influence of the exchange of amino acids on the conformation of proteins of various species can be predicted relatively accurately if the fundamental structure is known.

It is interesting to correlate the conformation of dissolved proteins with the conformation in the crystal. Observations so far indicate that under comparable conditions, the two conformations probably often differ only in the mobility of some side chains at the surface of the molecule.

An "energetic" structural principle is confirmed at least as a very good approximation by all X-ray structure analyses. The polar side chains are nearly all in contact with the aqueous solution, while mainly apolar or hydrophobic side chains are arranged in the interior[8, 40]. The magnitude of such interactions with water can be estimated from the solubility of amino acids in water and in organic solvents respectively[41]. The change in free energy when amino acids are transferred from ethanol into water (ΔG_t^0)[42, 43] is shown in Figure 4 as a function[71] of their volume[44].

The dangers of the simple application of these numerical values to changes in conformation lie in the fact that it is not entirely certain whether and to what extent the free energy is additive for macromolecules. Models for liquid mixtures suggest *e.g.* a higher than linear dependence on the relative volume[45]. Moreover, it has not been established how well a thermodynamic description of the interior of the protein as a liquid organic or oily phase fits the facts. The results of X-ray diffraction are more easily reconciled with a "solid" phase and very dense packing of the amino acids[49, 43]. Furthermore, the ΔG_t^0 values for the transfer

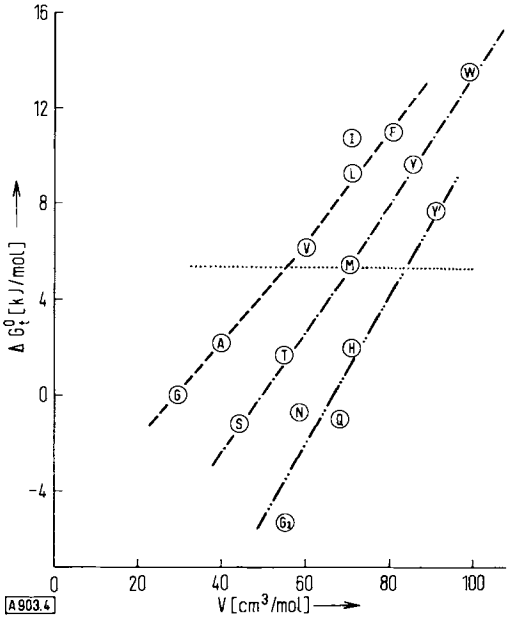


Fig. 4. Change in free energy ΔG_t^0 for the transfer of several amino acids from water into ethanol at 25 °C [42, 43], plotted as a function [71] of the molecular volume [44]. The curves connect amino acids whose side chains contain no polar atoms (– – –), one polar atom (–.–.–), or two polar atoms (–..–..–) such as nitrogen or oxygen. ΔG_t^0 was deduced from the solubility [43]; the value for glycine was taken as zero. If the solubility difference of the peptide group as found from the difference between glycine and diglycine is also taken into account, the dotted line roughly represents the zero line for the transfer of a peptide. The parts of the polypeptide chain that have side chains above this dotted line will prefer a nonaqueous environment, while the remainder will prefer contact with water. The amino acids are denoted in accordance with the one-letter code [30]: A (alanine), F (phenylalanine), G (glycine), G_2 (diglycine), H (histidine), I (isoleucine), L (leucine), M (methionine), N (asparagine), Q (glutamine), S (serine), T (threonine), V (valine), W (tryptophan), Y (tyrosine), and Y' (dihydroxytyrosine).

of peptide groups are difficult to estimate, and are indicated in Figure 4 only very approximately. However, these values and data on the influence of solvent mixtures on the thermodynamics of conformational changes may allow at least a rough estimation of the number of additional amino acids that come into contact with the solution[41,46].

This example of a "hydrophobicity scale" shows that though the behavior of small molecules is relatively well known, additional problems arise in the application of the data to proteins, and quantitative conclusions can therefore be drawn only with reservations. The same is true of stabilization by hydrogen bonds or electrostatic interactions[47,48].

In this connection, it should be pointed out that practically no systematic investigations on the packing properties of "irregular" polymers have been reported. The minimum free space required in the interior of a polypeptide is unknown. On the other hand, the rules for the tight packing of polypeptide chains are particularly important to the understanding of the conformation of globular proteins[49] since relatively large amounts of energy must be supplied to produce an "empty" volume in water.

Another difficulty in the deduction of thermodynamic stabilities of proteins from the crystal structure is that too little is known, at least with the required accuracy, about the height of the barriers to rotation about individual bonds in polypeptide chains[15]. Values for several thousand bonds have to be added together and this also presents a difficult problem. A possible simplification by consideration of the distribution of the various conformations observed in proteins themselves is discussed in Section 2.2.

2.2. Conformational Analysis

The numerous conformations that have been established experimentally (Fig. 2) allow the derivation of additional information. The most probable conformations around certain bonds can be determined by the use of all the corresponding data found for many proteins at high resolution for the construction of "empirical protein energy maps"[50]. Though peculiarities of a particular protein are lost by this averaging procedure, the underlying "conformation patterns" become very clear.

To illustrate this with an example, Figure 5 shows the distribution of the conformations of aromatic side chains found in eleven proteins for the torsion about the C^{α}—C^{β} bond, which is described by the torsion angle $\chi 1$ (Fig. 1). A logarithmic plot was chosen, from which a kind of conformation energy $E_{\chi 1}$ can be derived which, apart from a constant Q, is given by

$$E_{\chi 1} = -RT(\ln q_{\chi 1} + \ln Q) \qquad (2)$$

The relative density of experimental values $q_{\chi 1}$ from as many proteins as possible is equal to the number $n_{\chi 1}$ of conformations observed in the range of angles $\chi 1 \pm \Delta\chi 1$, divided by the total number of observed values N. Figure 5 shows the conformations of $N = 230$ aromatic side chains given for intervals of $\pm 10°$[50]. The curve shown is obtained by superposition of two harmonic functions

$$E_{\chi 1} = \frac{E_1}{2} \times \sin(\chi 1) + \frac{E_3}{2} \times \cos(3\chi 1) \qquad (3)$$

where E_3, the three-fold barrier to rotation about the C^{α}—C^{β} bond, is 8.6 kJ/mol. This is comparable with the values found by very different methods for small molecules[51]. The other contribution to the conformation energy, $E_1 = -5.4$ kJ/mol, represents the interaction between the peptide chain and the aromatic ring. The relative populations of the three conformations I, II, and III are given in Table 1. This distribution is practically the same for the side chains of phenylalanine, tyrosine, histidine, and tryptophan, and agrees well with the values found from NMR measurements on model molecules[52].

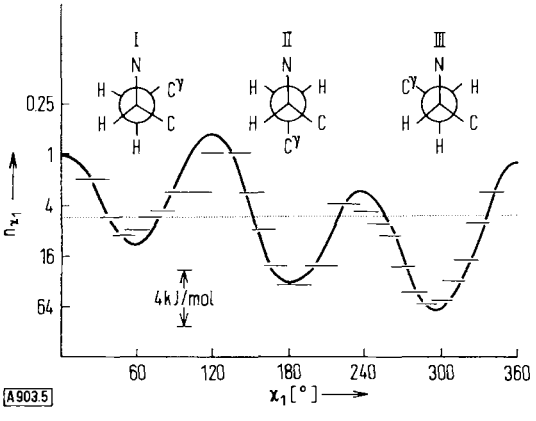


Fig. 5. Distribution of the conformations of 230 aromatic side chains as found for eleven proteins by X-ray structure analysis with a resolution of 2.8 Å or better [50]; the conformations I, II, and III, which differ in torsion about the C^{α}—C^{β} bond, are shown as Newman projections. The observed number of conformations $n_{\chi 1}$ per 20° of the torsion angle $\chi 1$ (short dashes) is shown in a logarithmic plot to facilitate comparison with the conformation energies in accordance with eq. (2). The continuous curve is the superposition of two harmonic functions in accordance with eq. (3).

An advantage of the method outlined here is that important information can be obtained relatively easily from the immense volume of data on the X-ray structure analysis of proteins. This is naturally not restricted to rotation about a single bond. When sufficient data are available, correla-

Table 1. Relative abundances of the three conformers I, II, and III (Fig. 5), which differ in rotation about the C^{α}—C^{β} bond, in the side chains of aromatic amino acids. For comparison, data found from NMR spectroscopy for the tripeptide Gly-Phe-Gly in D_2O are also given [52]. The data for the side chains (see Fig. 5) were obtained from conformations observed in the crystal structure of eleven different proteins [50].

Side chains of	Number of observations	Population		
	N	p_{I}	p_{II}	p_{III}
Histidine	53	0.09	0.36	0.55
Tryptophan	34	0.15	0.35	0.50
Tyrosine	65	0.11	0.29	0.60
Phenylalanine	78	0.09	0.37	0.54
Total:	230	0.11	0.34	0.55
Gly-Phe-Gly [52]		0.14	0.34	0.52

tions in two and more variables can be established; these should be of considerable value in the prediction of unknown conformations, and should contribute to the molecular explanation of conformational changes. Empirical distributions of this type can also be compared with calculations of the conformation energy[16, 53, 54].

3. Reversible Conformational Changes

3.1. Theoretical Considerations

An extensive literature exists on the theory of cooperative structural changes of linear polymers, such as helix-coil transitions of polypeptides; this literature deals both with the statistical mechanics and thermodynamics of such systems and with their kinetics[55-57]. The "linear Ising model", in which interactions with nearest neighbors are taken into account, has proved particularly useful.

Numerical calculations have been carried out on a simple three-dimensional Ising model for cooperative transitions of globular proteins[58]. However, a complicating factor here is that the state of an element in the three-dimensional network of the interactions not only depends on the state of the nearest neighbors in the chain or in space, but may also be influenced by the state of relatively remote parts of the macromolecule. An example is provided by the changes in the positions of a number of groups in chymotrypsinogen A as a result of the breakage of the peptide chain in positions remote from these groups on activation[59].

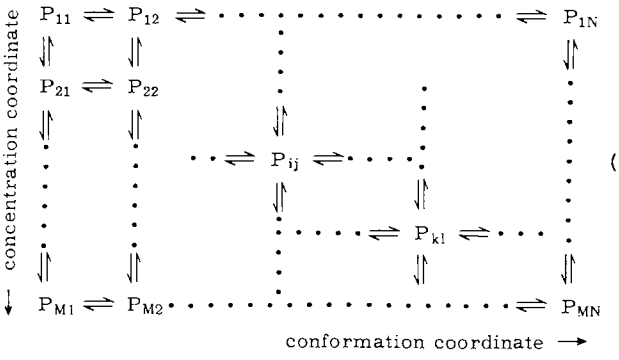
The folding of proteins can also be regarded as analogous to the nucleation and condensation phenomena in phase transitions[61-63].

However, the most serious problems are due to the fact that a large number of parameters must be known before a moderately realistic quantitative description on the molecular level is possible. Moreover, relatively few conformational changes have so far been experimentally studied so systematically as to allow a decision in favor of one of several models[60].

If one disregards "small" conformational changes, such as the reorientation of a single side chain, for which the description normally used for small molecules is adequate, a large number of elementary steps such as opening and closing of hydrogen bonds and simultaneous rotation about one or more bonds must always be expected in cooperative changes. This can be represented in a greatly simplified form by a general conformation coordinate

$$P_1 \rightleftharpoons P_2 \rightleftharpoons \ldots P_i \ldots \rightleftharpoons P_N \qquad (4)$$

where the P_i each denote a different conformation. Even if it is assumed that each of the n amino acids can exist in only two conformations, there will be $N = 2^n$ possible states; however, these will be occupied with very different weights. Since the conformational changes take place in solution and not in a vacuum, the influence of other molecules must also be taken into account[64, 65]. This is achieved with the aid of a general concentration coordinate. The two coordinates can be combined to give (5):



(5)

The states within a column differ in the number and positions of "bound" water molecules, cations, anions, *etc.* The relative concentrations of the states and their dependence on external variables are important to the description of such a system. A relaxation spectrum is generally to be

$$\phi(t) = \sum_i \beta_i \exp(-t/\tau_i) \qquad (6)$$

expected for the kinetics if a small sudden disturbance of the equilibrium occurs, *i.e.* a superposition of exponential functions with different time constants τ_i and amplitudes β_i should be observed if the various states are present in comparable concentrations[56].

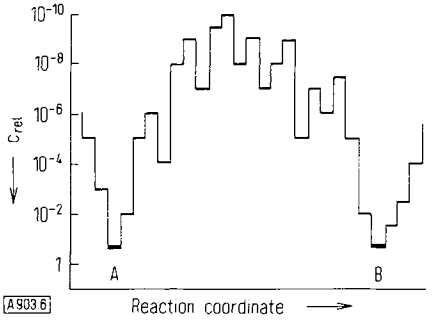


Fig. 6. Schematic representation of a concentration distribution (relative concentration C_{rel} in arbitrary units) of the distinguishable conformations of a protein as expected if *e.g.* unfolding at the melting point T_m can be described as an "all-or-none" process. The states A and B may each represent a collection of somewhat different conformations, which cannot be distinguished experimentally [79].

A significant simplification results if only two states P_{ij} and P_{kl} can be detected, as indicated schematically in Figure 6. If the concentrations of intermediate states and their variation with time can be disregarded, we have an "all-or-none" process, which is described by two overall or steady state rate constants:

$$A \underset{\bar{k}}{\overset{\vec{k}}{\rightleftharpoons}} B \qquad (7)$$

Information on the individual intermediate states is largely lost here. However, the simplification also allows a closed solution of extensive systems of kinetic differential equations, since under steady-state conditions, the change in the concentration of intermediate states as a function of time is zero; the overall rate constants $\vec{k}$ and $\bar{k}$ are then obtained by straightforward calculations.

3.2. Model Systems

Investigations have so far been carried out in solution only for relatively few cooperative conformational changes in proteins that are fully reversible, *i.e.* in which the initial state is restored after a disturbance and in which a parameter that directly characterizes the conformation of the protein is followed. Measurements are often hindered by the low concentrations, which are around $10^{-4}-10^{-6}$ mol/l in many cases. It is sometimes also difficult to distinguish clearly between changes in the conformation itself and in the bonding of small molecules.

As was mentioned earlier, the cooperative effects are particularly important. Unfortunately, there are no macromolecules with simple structures that exhibit *three-dimensional* folding similar to that shown by globular proteins, so that it is necessary at present to investigate natural proteins. To observe these cooperative effects within a molecule, there should be no aggregation between the molecules which might mask intramolecular processes. The main problem is that, in many proteins consisting of subunits[65, 66], cooperative unfolding is often not fully reversible[67]; thermodynamic and kinetic data are then only of limited validity.

The acid denaturation of some intensively studied proteins such as chymotrypsinogen, trypsin, ribonuclease, and lysozyme is at present the simplest model system for the investigation of cooperative and reversible conformational changes in globular proteins, in which many biologically interesting phenomena can also be simulated. This reaction, which is also known as transition I, can be best described as a transition from a compact to a more mobile conformation, which, however, involves only parts of the protein and apparently does not lead to a completely random coil conformation[9].

There are a series of excellent reviews on this transition, which deal in particular with the equilibrium properties[9, 68, 69]. As a typical example, Figure 7 shows the transition of chymotrypsinogen A in acidic solution as a function of temperature[70, 71]. The change in the tryptophan absorption of the protein was measured here after equilibrium had been reached at various temperatures.

When the solution is cooled, the original values are restored; the transition curve can be transversed repeatedly with no deviation from the original curve, *i.e.* the transition is fully reversible. (In the case of α-chymotrypsin, the enzymatic properties are also fully restored if the refolding takes place in acidic solution, but only partially in neutral solution[71].)

Several properties of the native form A, which exists at low temperatures, change into those of the unfolded form B within a range of about 15 °C. The transition may also be regarded as a melting process within the macromolecule[79]. The temperature in the middle of the transition is also referred to as the melting temperature T_m.

The transition can be initiated by various experimental methods; changes in the temperature, pH, or the pressure [eq. (1)][70-73] reflect "environmental changes". Spectroscopic detection of the conformational change is advantageous *e.g.* in kinetic measurements down to the nanosecond range. The most important of the methods used so far to follow the equilibrium of transition I, in addition to the measurement of UV and IR absorption, optical rotation, fluorescence, and NMR spectra[68-74], include measurements of viscosity, sedimentation behavior, specific volume[75], specific heat[76], solubility[77], and tritium exchange[78].

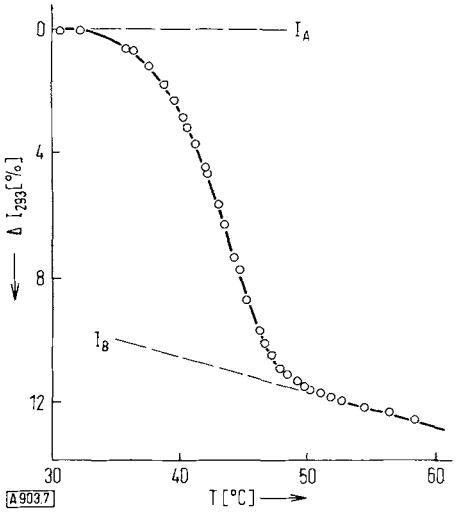


Fig. 7. Equilibrium curve of the transition I of chymotrypsinogen A at pH = 2.0 as a function of the temperature. The percentage decrease in the tryptophan absorption at 293 nm (I_{293}) was measured after equilibrium had been reached. I_A and I_B (---) are the values for forms A and B in the transition region extrapolated from the optical behavior at low and at high temperatures respectively.

One question is whether this transition can be described as an "all-or-none" process between two macroscopic conformations of the protein, *i.e.* whether half of the molecules are in the form A and the other half in the form B at the temperature T_m, or whether at T_m *e.g.* half of each individual molecule is changed, and very many different conformations are present in measurable concentrations, as is expected for the helix-coil transition of long polypeptides[80]. It is difficult to answer this question on the basis of equilibrium measurements. Important tests are[79]:

1. A two-state model may be assumed if several parameters change by the same relative amount when an external variable is changed. The methods mentioned above should therefore give the same equilibrium constant K [eq. (7)] under comparable conditions. Extremely high accuracy of measurement is often necessary for such a comparison; this criterion is satisfied *e.g.* by isosbestic points in the protein spectra in the transition region.

2. Another test is the agreement of the enthalpy found by calorimetric measurement with that calculated from the van't Hoff equation. This test has satisfactorily confirmed a two-state model in acidic solution for the three proteins investigated so far, *i.e.* chymotrypsinogen[76], ribonuclease A[81], and lysozyme[82].

3. A further test, which can also be applied to very small quantities of substance, is the examination of the kinetic behavior after a rapid perturbation of the equilibrium.

4. Kinetics of Reversible Folding

Kinetic measurements, in addition to the information on the thermodynamics of the system, also provide information on its behavior as a function of time. This is particularly important for biological phenomena, with their strong time dependence. Even intermediate states with very short lifetimes can be detected, and it may thus become easier to decide between several possible reaction mechanisms.

4.1. Methods

As a result of the development of kinetic methods, the variation of the conformation with time after a sudden or periodic disturbance of an external parameter in equation (1) can be followed over many orders of magnitude[83-85]. For very fast reactions, rapid mixing of solutions in stop-flow apparatus (ΔM_i) and relaxation methods, *e.g.* temperature jump (ΔT) and pressure jump (ΔP) methods, are particularly important, as well as ultrasonic and nuclear magnetic resonance measurements.

To follow the kinetics of the transition I (Fig. 7), one need only vary the temperature rapidly enough and follow the establishment of a new equilibrium, *e.g.* on the basis of the change in absorption. This is a relatively slow process, in the second to minute region. A very simple temperature jump method has proved to be very suitable for this purpose[70].

In this method, the solution to be investigated is placed in a thermostatically controllable microcell, which allows a fast temperature equilibration (half time $\approx$ 1s) between the thermostat liquid and the solution. The solution can be subjected to positive and negative temperature jumps of any size by the alternate passage of the liquids from two thermostats at different temperatures through the thermostat jacket of the cell with the aid of magnetic valves. The variation of the absorption, fluorescence, optical rotation, *etc.* with time is then recorded.

4.2. Kinetic Criteria for an "All-or-None" Process

For a multi-stage reaction system of type (5) which must certainly be the case for the unfolding of a protein, a relaxation spectrum in accordance with (6) will be expected for a small disturbance of the equilibrium. Such a relaxation spectrum has been observed in the denaturation of high molecular weight DNA[86, 71]. If the measurable concentration distributions before and after the disturbance correspond roughly to those indicated in Figure 5, very stringent conditions must be satisfied for the kinetics (see Fig. 8)[13, 87].

1. The establishment of the new equilibrium as a function of time after a sudden disturbance follows a simple exponential function, which gives a straight line in a semi-logarithmic plot (Fig. 8a); the relaxation time or time constant τ can be determined from the slope of this line. (Changes such as those responsible for the change in the density of the solution after a sudden temperature change or the change in the bonding of small molecules, must be considered separately.)

2. The rexalation time is independent of the parameter followed, *e.g.* absorption at various wavelengths, solubility, *etc.*

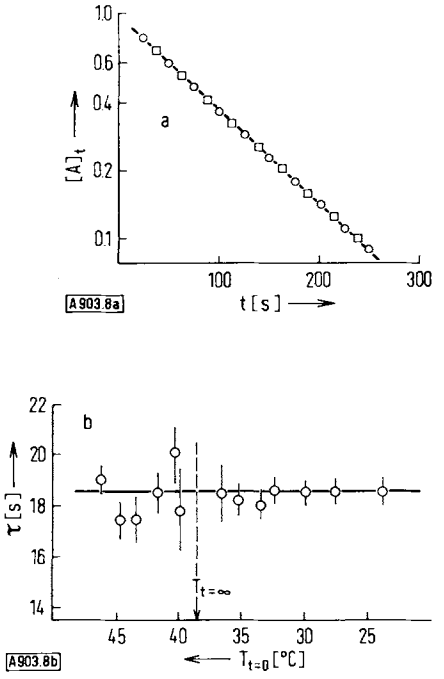


Fig. 8. "All-or-none" transition of trypsin at pH = 1.8 [87, 13]. The relaxation time τ is independent of the protein concentration ($10^{-7}-10^{-5}$ mol/l). a) Change in the optical rotation at 315 nm (— o — o —) and in the absorption at 293 nm (— □ — □ —), divided by the total change between $t=0$ and $t=\infty$, as a function of time. (Temperature jump from the transition region at 39 °C to 20.0 °C.) b) Lack of dependence of the relaxation time τ on the initial state (temperature at time zero, $T_{t=0}$) and on the magnitude of the disturbance. The final temperature is constant at 38.4 °C. The varying error limits are due to the different amplitudes of the relaxation curves.

3. The time constant τ depends only on the final state reached after the disturbance, and not on the initial state (Fig. 8b), as is to be expected from the equation[88]

$$[A]_t = ([A]_{t=0} - [A]_{t=\infty})\, e^{-t/\tau} + [A]_{t=\infty} \qquad (8)$$

which describes the change in the concentration of A as a function of time after a sudden disturbance.

If these criteria are satisfied, as in the transition I discussed here, it is justifiable to describe the conformational change in the approximation of an "all-or-none" process. (With very sensitive kinetic methods, it is also possible to detect fast preceding equilibria, though these usually account for only a few percent of the total change[70, 108].) The overall rate constants for the folding $\vec{k}$ and for the unfolding $\overleftarrow{k}$ can be determined. The equilibrium constant K can be deduced *e.g.* in accordance with eq. (9)

$$K = [A]_{t=\infty}/(1-[A]_{t=\infty}) = \vec{k}/\overleftarrow{k} \qquad (9)$$

from the relative amplitude $[A]_{t=0} - [A]_{t=\infty}$, which also contains all the thermodynamic information. Together with the definition of the relaxation time

$$\tau^{-1} = \vec{k} + \overleftarrow{k} \qquad (10)$$

two equations for the determination of the two unknowns $\vec{k}$ and $\overleftarrow{k}$ are given.

These two overall rate constants can be regarded, according to the theory of the activated state[89], as "quasi-thermodynamic quantities" the zero of the free energy of activation ($\Delta\vec{G}$ or $\Delta\overleftarrow{G}$) being taken as $RT \ln (kT/h)$ (where k is Boltzmann's constant and h is Planck's constant). For the unfolding, this leads to

$$\vec{k} = (kT/h) \times \exp(-\Delta\vec{G}/RT) = (kT/h) \times \exp(-\Delta\vec{H}/RT + \Delta\vec{S}/R) \quad (11)$$

with $\Delta\vec{H}$ as the enthalpy and $\Delta\vec{S}$ as the entropy of activation. $\Delta\vec{H}$ can be obtained from the Arrhenius equation or the first derivative of $\Delta\vec{G}$ with respect to the temperature.

$$\Delta\vec{H} = RT^2 \frac{\mathrm{d} \ln \vec{k}}{\mathrm{d}T} - RT \quad (12)$$

If $\Delta\vec{H}$ itself is temperature-dependent, it is also possible to define a specific heat of activation.

$$\Delta\vec{C} = \mathrm{d}\vec{H}/\mathrm{d}T \quad (13)$$

Similar equations are found for $\overleftarrow{k}$; the connection with the usual thermodynamic functions in the case of the equilibrium is provided by eq. (9) and the expression for the free energy ΔG^0:

$$\Delta G^0 = -RT \ln K \quad (14)$$

4.3. Temperature Dependence

The relaxation time as a function of temperature for the transition I of chymotrypsinogen A, a typical example, is shown in Figure 9[93]. (The corresponding dependence of the overall rate constants is also given.) It can be seen that below the transition temperature, the reciprocal relaxation time τ^{-1} becomes equal to the rate constant for folding $\vec{k}$; at high temperatures, τ^{-1} becomes equal to $\overleftarrow{k}$. The experimental values found some 20 years ago by *Eisenberg* and *Schwert*[77] are also plotted. Instead of the tryptophan absorption, these authors used the solubility of the protein in a precipitation buffer as the parameter. The good agreement, among other things, supports the proposed course of the transition.

A striking feature in comparison with conventional chemical reactions in this temperature and time range is the high positive activation energy for unfolding ($\Delta\vec{H}$) and the strong temperature dependence of $\Delta\overleftarrow{H}$ for folding, with negative values at high temperatures (Fig. 10). Both observations indicate that several elementary steps are necessary for this conformational change[103, 108]. A similar temperature dependence is observed in the denaturing of other heterogeneous biopolymers such as DNA and collagen[90, 91], as well as in phase transitions[63]. The transition I can thus be placed in the larger group of problems of cooperative processes involving nucleation.

An important result is that high positive, but also zero or negative, temperature coefficients are found for the kinetics

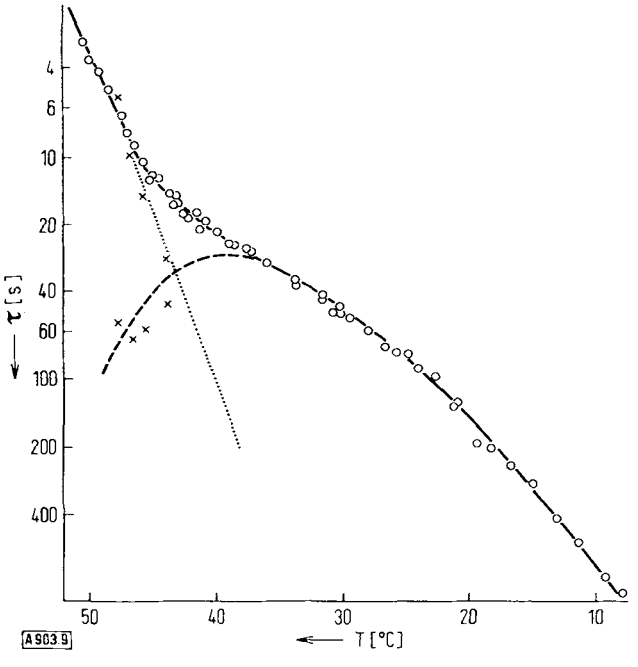


Fig. 9. Relaxation time τ (--o--o--) for the transition I of chymotrypsinogen A at pH = 2.0 as a function of the final temperature, determined by following the change in the tryptophan absorption of the protein as a function of time [70, 71]. In the transition region, the overall rate constants for unfolding $\vec{k}$ (. . . .) and folding $\overleftarrow{k}$ (– – –) are given. The values + and × were obtained by *Eisenberg* and *Schwert* [77] by following the change in the solubility of the protein as a function of time.

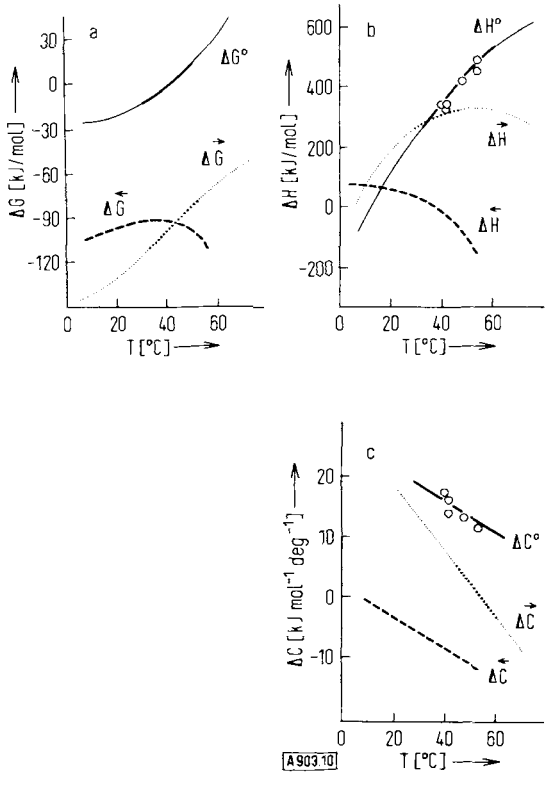


Fig. 10. Temperature dependence of the thermodynamic and kinetic parameters for the transition I from chymotrypsinogen A. a) Free energy, b) enthalpy, c) specific heat. The thin lines indicate the extrapolation of the experimental data when the change in the specific heat ΔC is described by a linear dependence on temperature. (—o—o—) denotes data from calorimetric measurements [76] and (——) the equilibrium data determined by optical measurements. The kinetic quantities for unfolding (....) and for folding (– – –) are given. (An error of ±0.1 °C in the measurement of the temperature and of 5% in the rate constants over a temperature range of 10 °C gives an uncertainty of about ±4 kJ mol^{-1} deg^{-1} for ΔC.)

in such conformational changes of proteins. The negative activation energy of $\Delta\vec{H}$ at high temperatures can be attributed to the fact that several steps are necessary for the nucleation, which for its part determines the rate of the folding. With falling temperature, instead of the formation of a nucleus, the further folding of the polypeptide chain may be rate-determining.

Another explanation is that falling temperatures lead to the formation of more and more "false" nuclei, which must be reopened before a successful nucleus is formed. Both can lead to $\Delta\vec{H} < 0$ at high temperatures. The interaction of apolar groups with water, as expressed in the form of the concentration coordinate [see (5)] and the associated contributions to the free energy, may be very important in this respect. Hydrophobic interactions of this type can be responsible for the temperature dependence of the activation energy, since these involve fast pre-equilibria, which enter into the overall rate constants.

Figure 10 shows the currently accepted temperature dependences of the thermodynamic and kinetic functions, a linear temperature dependence being assumed for the variation of the specific heat. (The accuracy of measurement is not sufficient to allow a definite decision as to whether and how ΔC depends on the temperature.) The corresponding functions for the enthalpy and the free energy are then found by integration. If the curves for $\vec{k}$ and $\overleftarrow{k}$ intersect at low temperatures, a cold transition may also be observed[92, 93].

The considerable change in the specific heat was pointed out in particular by *Brandts*[92]. Corresponding results for a series of protein reactions are summarized in Table 2.

Table 2. The change in the specific heat at constant pressure, ΔC^0, for several protein reactions.

Reaction	ΔC^0 [kJ mol^{-1} deg^{-1}]	Ref.
Chymotrypsinogen A:		
solvation	10	[76]
transition I, pH = 2.0, A → B	14	[76]
Ribonuclease A: transition I, pH = 2.8	8.2	[81]
S-protein + S-peptide → RNase S	2.9	[112]
GAPDH (yeast) → holoenzyme + NAD	2.2	[22]
α-Chymotrypsin: dimer → monomer	2.8	[113]

(Calorimetric measurements on small molecules, both apolar and polar, show that their interaction with water leads to changes in the specific heat[5].)

4.4. pH Dependence

Not only does the transition I exhibit a strong and complicated temperature dependence, but the pH dependence also reflects the cooperativity of the transition. Thus for the proteins investigated so far, the rate constant for unfolding $\vec{k}$ increases with the second to third power of the H_3O^+ activity (Fig. 11). Protons influence the native form A as "negative" effectors, since they destabilize this form with increasing concentration[93]. The rate constant for folding $\overleftarrow{k}$, on the other hand, changes only slightly; it decreases somewhat. Much more complicated molecules may act as cooperative effectors (E)[6] on proteins built up from subunits, and may *e.g.* stabilize the native form, as in the stabilization of GAPDH from yeast by NAD at high temperatures and pH values[19].

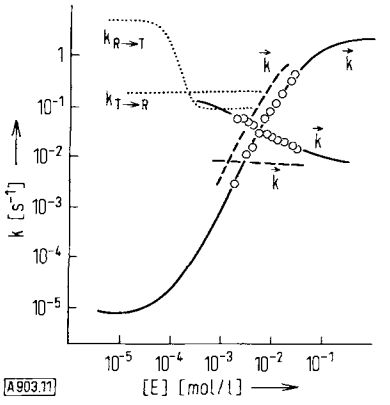


Fig. 11. Rate constants for the conformational change as a function of the effector concentration [E]. (—o—o—) $\vec{k}$ and $\overleftarrow{k}$ for chymotrypsinogen A with H_3O^+ as the effector. Additional measurements in urea solutions were used for the extrapolation [71, 95]. (----) $\vec{k}$ and $\overleftarrow{k}$ after chemical modification (removal of the negative charge) of 13 of the 16 carboxyl groups of chymotrypsinogen A [97, 71]. There are only minor changes in the pH dependence of $\vec{k}$, which is evidence for the stabilization of the form A by special "trigger groups". (....) As a comparison, the kinetics of an "allosteric transition" in an enzyme consisting of four identical subunits, *i.e.* the GAPDH from yeast with NAD as the effector molecule (after [19]).

The dependence of the overall rate constants $\overleftarrow{k}$, $\vec{k}$ of the conformational change can be described in both cases by a very similar reaction scheme. Thus for trypsin with two such peculiar binding sites we have[87]

$$\begin{array}{ccccc} 2H & + A_0 & \rightleftharpoons & B_0 & + 2H \\ K_a \downuparrows & & & \downuparrows K_b & \\ H & + A_1 & \rightleftharpoons & B_1 & + H \\ K_a \downuparrows & & & \downuparrows K_b & \\ & A_2 & \rightleftharpoons & B_2 & \end{array}$$

The concentration dependence of τ is found in a closed form in the case of simplifying and well satisfied assumptions[83]. The assumptions are:

1. The binding of the effector is fast in comparison with the conformational change (a bimolecular rate constant of about 10^{10} l mol^{-1}s^{-1} can be expected for protonation reactions[96]).

2. The change in the concentration of free effector following the disturbance of the equilibrium and the change in the conformation can be disregarded.

3. Within the forms A and B, all n binding sites have equal binding constants for the particular effector; however, the values for the two forms are different ($pK_a \neq pK_b$)[6, 87, 92].

From the values of $\vec{k}$ and $\overleftarrow{k}$, *e.g.* for the measured pH dependence in the case of chymotrypsinogen or α-chymotrypsin, it is found, on the assumption of an "all-or-none" process, that three binding sites for protons with a dissociation constant $K_a = 0.05$ mol/l considerably stabilize the native form A in the unprotonated form, by a factor of about 100—1000 per binding site. The constants K_b (pK values of 3.5—4.5) found for these binding sites in state B are

close to the values expected for carboxyl groups in water and are accordingly smaller by a factor of 100—1000.

A possible explanation for this effect of protons on the conformation is that ionic bonds are formed between certain carboxyl groups and ammonium groups, *e.g.* of lysine, which stabilize the form A[93]. Up to five such ionic bonds are present in crystalline α-chymotrypsin, two being completely shielded from the solution[113].

An experimental confirmation of such "trigger groups" is the observation that the pH dependence of the transition I is not appreciably influenced by removal of the negative charge of 13 of the 16 carboxyl groups in chymotrypsinogen A by chemical modification (Fig. 11)[97, 71]. This is to be expected if the electrostatic repulsion of the positive net charge of the protein in water contributes only slightly to the destabilization of the form A. For such a general electrostatic effect, a monotic dependence of the rate constants on the ionic strength would be expected, which is not observed (Fig. 12a). Ionic bonds of this nature explain also the very low pK value found for carboxyl groups in form A. The proximity of a positive charge causes a considerable pK shift even in small molecules[98].

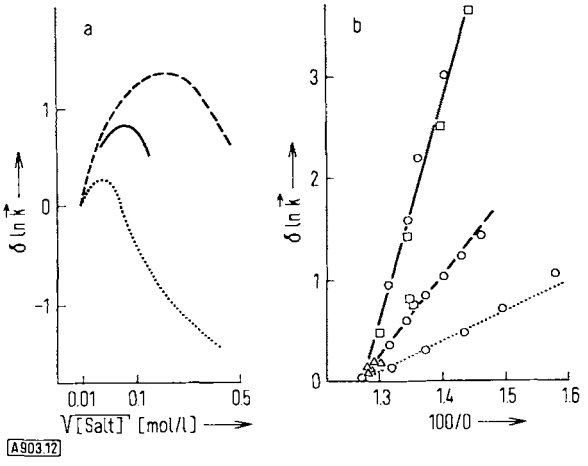


Fig. 12. Influence of monovalent ions (a) and small molecules (b) on the rate constant for unfolding $\vec{k}$ in 8×10^{-3} M HCl for (——) chymotrypsinogen A, (– – – –) trypsin, and (. . . .) ribonuclease [13, 93]. $\delta \ln \vec{k}$ represents the ratio of the rate constant in the corresponding solvent mixture to that in 8×10^{-3} M HCl. a) Change on addition of salts such as NaCl, corrected for the secondary salt effect; b) change in solvent mixtures at 30 °C, plotted against the reciprocal of the macroscopic dielectric constant D of the mixture [93]. (—□—□—) up to 15 vol.% dioxane, (—○—○—) up to 25% ethanol, and (—△—△—) up to 25% ethylene glycol.

4.5. Salt Effects

The unfolding reaction depends in a complicated manner on the salt concentration. A maximum is found for $\vec{k}$, indicating two factors with opposing effects (Fig. 12a). An explanation for the salt dependence of $\vec{k}$ is that the ionic bonds (and hence form A) are destabilized at low ionic strengths by binding of counterions, whereas at higher salt concentrations the electrostatic shielding of the net charge of the protein predominates and $\vec{k}$ decreases[93]. However, such reasoning, which is familiar and justified for small molecules, is not always permissible for proteins[94]. At very high salt concentrations, destabilization of the native form may also occur because the ions change the structure of water[99, 5].

4.6. Variation of Solvent

Slight differences in the transition I are observed when it takes place in heavy water instead of in water (see Table 3). The difference in behavior in H_2O and D_2O found for complicated biological systems[100] may be partly due to the same causes; a possible explanation is provided by small changes in the structure and thermodynamic properties of water upon deuteration[101].

The use of solvent mixtures makes it possible to vary the dielectric constant, the viscosity, *etc.* continuously. The thermodynamic properties of small molecules in these mixtures can be compared with those of the macromolecules[92].

Figure 12b shows experimental values for $\vec{k}$ in several solvent mixtures. A plot of the relative free energy of activation $\delta\vec{G}$ against the reciprocal of the dielectric constant D gives a surprisingly good linear relationship, such as one could expect for electrostatic interactions. No such simple relationships are found for the folding, however, particularly at low temperatures[87]. $\delta\vec{G}$ depends in a very similar manner on the solvent composition and the temperature as does the solubility of apolar molecules[102]. This may be regarded as evidence of the additional interactions of apolar groups with water in the form B[92, 93].

4.7. Change in Covalent Structure of Proteins

Quantitative data on the influence of chemical modifications or the exchange of amino acids on the stability of proteins are important, in particular because of their industrial and medicinal use. The recent successes in the chemical synthesis of proteins offer the possibility of systematically investigating the influence of an amino acid exchange[104]. Another, less systematic method is the comparison of families of proteins or proteins of mutants or of different species.

4.7.1. Exchange of Several Amino Acids

An example is the family of serine proteinases such as chymotrypsinogen A and B, trypsin, and elastase, where parts of the amino acid sequence agree with each other. [Their crystal structure is also very similar (Fig. 3).] The stability and the kinetics of the transition I in acidic solution are also very similar for these proteins (Fig. 13 and Table 3).

4.7.2. Chemical Modifications

Several chemical reactions allow a more or less selective, mild, and specific modification of the side chains of proteins[105]. A modification of carboxyl groups and its influence on the pH dependence has already been mentioned (Fig. 11).

Another example is the modification of the active site of α-chymotrypsin by a diisopropylphosphoryl (DIP-CT) or an anthraniloyl group (AN-CT), these groups being covalently bonded to the active center. There are differences in stability, which are mainly due to a lower unfolding rate (Table 3). With the aid of the fluorescent AN group, however, it is also possible to follow the transfer of energy from tryptophan side chains to the chromophore. This energy

transfer is very sensitive to distance[106], so that distance measurements can be carried out within the protein molecule during the unfolding or folding. Kinetic results obtained in this way agree with the behavior expected for an "all-or-none" process[71].

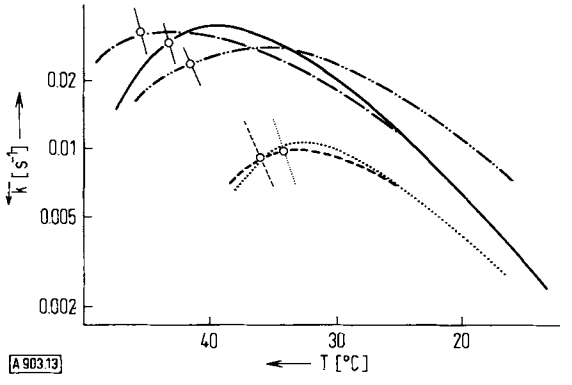


Fig. 13. Rate constant for folding ($\vec{k}$) for several members of a family of proteins at pH = 2.0 as a function of the temperature [13, 93] after a change in the covalent structure. Exchange of several amino acids: (——) chymotrypsinogen A, (—·—·—) chymotrypsinogen B, and (—··—··—) trypsin; specific breakage of the polypeptide chain of chymotrypsinogen A; once: (– – –) gives δ-chymotrypsin, twice: (.....) α-chymotrypsin. The circles show the middle of the transition (T_m), where $\vec{k}$ is equal to $\overleftarrow{k}$. The short lines indicate the dependence of the rate constant for unfolding ($\overleftarrow{k}$).

The introduction of covalently bonded "reporter groups" also offers the possibility of measuring conformational changes in systems in which other parameters are difficult to follow optically[107].

Table 3. Kinetic parameters for folding (←) and unfolding (→) in the transition I for several proteins in 0.01 M HCl at 30 °C [13].

Protein	$-\ln \overleftarrow{k}$ [s^{-1}]	$-\ln \vec{k}$ [s^{-1}]	$\Delta\vec{H}$ [kJ mol]	$\Delta\overleftarrow{H}$ [kJ mol]	$\Delta\vec{C}$ [kJ mol^{-1} deg^{-1}]
Chrymotrypsinogen A	11.1	3.90	340	70	6
δ-Chymotrypsin	6.8	4.88	230	33	12
α-Chymotrypsin	6.8	4.88	350	33	12
AN-Chymotrypsin [a]	6.8	5.10	320	25	14
DIP-Chymotrypsin [b]	7.5	5.30	330	42	10
Chymotrypsinogen B	10.8	4.05	370	80	8
Trypsin	8.4	3.77	280	50	14
Trypsin (D_2O)	8.2	3.44	190	50	14
Ribonuclease A	6.0	3.5	280	20	5

[a] AN = anthraniloyl.
[b] DIP = disopropylphoryl.

4.7.3. Cleavage of Peptide Chains

If the polypeptide chain in globular proteins is broken, their stability decreases in the cases investigated so far. In the enzymatic activation of chymotrypsinogen A to δ and α-chymotrypsin, the peptide chain is broken once and twice respectively. The first break also leads to the most important changes in the crystal structure[37]. This is also reflected in the kinetics of the transition I. The order of the reaction does not change; the reaction remains intramolecular, since the parts of the chain are still joined by disulfide bridges (Fig. 13 and Table 3).

5. Closing Remarks

With the transition I of some "simple" globular proteins as an example, the influence of "environmental changes" (pH, temperature, *etc.*) or of a change in the covalent structure of the protein on the thermodynamics and kinetics of cooperative conformational changes in proteins can be relatively easily investigated and described. This is greatly facilitated by the fact that this reversible partial unfolding can be represented to a very good approximation by an "all-or-none" process between two macroscopic states of the protein. This approximation is less satisfying in other reversible folding reactions[109, 110], so that generalizations are not possible, and are not really to be expected for such complicated systems depending on many parameters. However, reversible transitions of this type are suitable for use as models of "molecular switches".

In contrast to the cooperative transitions of linear homopolymers, for which the thermodynamics and kinetics can be described quantitatively on a molecular basis, we are still far from achieving this aim in the case of globular proteins. Even the knowledge of the crystal structure, *e.g.* of a family of proteins (Fig. 3), does not lead to satisfactory correlations with the observed thermodynamics and kinetics of cooperative transitions in solution.

Because of the many kinds of interactions in the three-dimensional folding of the polymer chain, the time constants for various transitions can vary by many orders of magnitude, and may be very appreciably increased or decreased by small external changes due to cooperative effects. It is not only fast conformational changes that are important to biological regulation processes[111]. It is conceivable that even processes such as the differentiation of cells, the phenomenon of a biological "clock" or the storage of information in the memory may in part be due to cooperative conformational changes with time constants of seconds – years. A time constant of one year corresponds to a difference in the free energy of activation of about – 35 kJ/mol in relation to the values given in Table 3, *i.e.* a quantity of energy that is compensated *e.g.* by the transfer of three tryptophan side chains from water into an organic phase (Fig. 4) or by rupture of about three ionic bonds (Fig. 11). Such slow conformational changes, on which very little investigation has been carried out so far, can probably be brought about within a single protein molecule, because of the specific three-dimensional interaction between the parts of the chain.

In biologically important processes, however, coupling with further reactions and interactions with other macromolecules is also to be expected, and the cooperativity and the specificity of responses to changes in the environment can be considerably increased in this way.

This work was partly supported by an EMBO long-term fellowship during a period spent in the Molecular Enzymology Laboratory (University of Bristol). I am very grateful to all those who have made information available to me before publication.

Received: August 4, 1971 [A 903 IE]
German version: Angew. Chem. *84*, 931 (1972)
Translated by Express Translation Service, London

[1] *R. E. Dickerson* and *I. Geis:* Struktur und Funktion der Proteine. Verlag Chemie, Weinheim 1971; The Structure and Action of Proteins. Harper & Row, New York 1969.

[2] *J. D. Watson:* The Molecular Biology of the Gene. Benjamin, New York 1971.

[3] *D. Eisenberg* and *W. Kauzmann:* The Structure and Properties of Water. Oxford University Press, London 1969.

[4] *L. P. Kayushin:* Water in Biological Systems. Plenum Publ. Corp., New York 1969.

[5] *E. Wicke*, Angew. Chem. *78*, 1 (1966); Angew. Chem. internat. Edit. *5*, 106 (1966).

[6] *J. Monod, J. Wyman,* and *J. P. Changeux*, J. Mol. Biol. *12*, 88 (1965).

[7] *B. Müller-Hill.* Angew. Chem. *83*, 195 (1971); Angew. Chem. internat. Edit. *10*, 160 (1971).

[8] *W. Kauzmann*, Advan. Protein Chem. *14*, 1 (1959).

[9] *R. Lumry* and *R. Biltonen* in *S. Timasheff* and *G. Fasman:* Structure and Stability of Biological Macromolecules. Dekker, New York 1969.

[10] *J. A. Schellman* and *C. Schellman* in *H. Neurath:* The Proteins. Vol. II. Academic Press, New York 1964.

[11] *M. Eigen,* Nobel Symposium 5, Almquist & Wiksell, Stockholm 1966; Angew. Chem. *80*, 892 (1968).

[12] *K. G. Denbigh:* The Principles of Chemical Equilibrium. Cambridge University Press, London 1968.

[13] *F. M. Pohl*, Habilitationsschrift, Universität Konstanz 1970.

[14] J. Mol. Biol. *52*, 1 (1970).

[15] *M. Levitt* and *S. Lifson*, J. Mol. Biol. *46*, 269 (1969).

[16] *G. N. Ramachandran* and *V. Sasisekharan*, Advan. Protein Chem. *23*, 283 (1968).

[17] *T. Funk, F. Eggers,* and *E. Grell*, 1. Eur. Biophys. Congress *5*, 37 (1971).

[18] *H. Gutfreund:* An Introduction to the Study of Enzymes. Blackwell Scientific Publications, Oxford 1967.

[19] *J. D. Shore* and *H. Gutfreund*, Biochemistry *9*, 4655 (1970).

[20] *K. Kirschner, M. Eigen, R. Bittman,* and *B. Voigt*, Proc. Nat. Acad. Sci. USA *56*, 1661 (1966).

[21] *H. Durchschlag, G. Puchwein, O. Kratky, I. Schuster,* and *K. Kirschner*, Eur. J. Biochem. *19*, 9 (1971).

[22] *S. F. Velick, J. P. Bagott,* and *J. M. Sturtevant*, Biochemistry *10*, 779 (1971).

[23] *M. Perutz*, New Scientist *50*, 676 (1971).

[24] *J. C. Kendrew*, Angew. Chem. *75*, 595 (1963).

[25] *D. Eisenberg* in *L. Boyer:* The Enzymes. 2nd Edit., Vol. I, Dekker, New York 1970.

[26] *D. M. Blow* and *T. A. Seitz*, Annu. Rev. Biochem. *39*, 63 (1970).

[27] *B. P. Schoenborn, A. C. Nunes,* and *R. Nathans*, Ber. Bunsenges. Phys. Chem. *74*, 1202 (1970).

[28] *B. S. Hartley*, Biochem. J. *119*, 805 (1970).

[29] *S. B. Needleman:* Protein Sequence Determination. Chapman & Hall, London, and Springer, Heidelberg 1970.

[30] *M. O. Dayhoff:* Atlas of Protein Sequence and Structure. National Biomedical Research Foundation, Silver Spring, Md. 1969.

[31] *J. J. Birktoft, B. W. Metthews,* and *D. M. Blow*, Biochem. Biophys. Res. Commun. *36*, 131 (1969).

[32] *D. M. Shotton* and *H. C. Watson*, Phil. Trans. Roy. Soc. London *B 257*, 111 (1970).

[33] *B. S. Hartley* and *D. M. Shotton* in *L. Boyer:* The Enzymes. 3rd. Edit. Vol. III, Dekker, New York 1971.

[34] *S. T. Freer, J. Kraut, J. D. Robertus, H. T. Wright,* and *Ng. H. Xuong*, Biochemistry *9*, 1997 (1970).

[35] *R. M. Stroud, L. M. Kay,* and *R. E. Dickerson*, Cold Spring Harbor Symp. Quant. Biol. *36*, 125 (1971).

[36] *D. M. Segal, G. H. Cohen, J. C. Powers,* and *P. E. Wilcos*, Cold Spring Harbor Symp. Quant. Biol. *36*, 85 (1971).

[37] *C. S. Wright, R. A. Alden,* and *J. Kraut*, Nature *221*, 236 (1969).

[38] *W. G. J. Hol*, Dissertation, Universiteit Groningen 1971.

[39] *T. L. Blundell, J. F. Cutfield, S. M. Cutfield, E. J. Dodson, D. C. Hodgkin, D. A. Mercola,* and *M. Vijayan*, Nature *231*, 506 (1971).

[40] *B. Lee* and *F. M. Richards*, J. Mol. Biol. *55*, 379 (1971).

[41] *C. Tanford*, J. Amer. Chem. Soc. *86*, 2050 (1964).

[42] *Y. Nozaki* and *C. Tanford*, J. Biol. Chem. *246*, 2211 (1971).

[43] *E. J. Cohn* and *J. T. Edsall:* Proteins, Aminoacids and Peptides. Reinhold, New York 1943.

[44] *M. H. Klapper*, Biochim. Biophys. Acta *229*, 557 (1971).

[45] *J. S. Rowlinson*, Discuss. Faraday Soc. *49*, 30 (1970).

[46] *R. Biltonen* and *R. Lumry*, J. Amer. Chem. Soc. *93*, 224 (1971).

[47] *A. Rich* and *N. Davison:* Structural Chemsitry and Molecular Biology. Freeman, San Francisco 1968.

[48] *P. Flory:* Statistical Mechanics of Chain Molecules. Wiley, New York 1969.

[49] *A. C. T. North* and *D. C. Phillips*, Progr. Biophys. Mol. Biol. *19*, 1 (1969).

[50] *F. M. Pohl*, Nature New Biol. *234*, 277 (1971).

[51] *E. L. Eliel, N. L. Allinger, S. J. Angyal,* and *W. A. Morrison:* Conformational Analysis. Interscience, New York 1965.

[52] *R. A. Newmark* and *M. A. Miller*, J. Phys. Chem. *75*, 505 (1971).

[53] *H. A. Scheraga*, Advan. Phys. Org. Chem. *6*, 103 (1968).

[54] *B. Pullmann* in *D. Daudel* and *A. Pullmann:* Aspects de la Chimie Quantique Contemporiar. Coll. Int. CNRS, Paris 1971.

[55] *J. Engel* and *G. Schwarz*, Angew. Chem. *82*, 468 (1970); Angew. Chem. internat. Edit. *9*, 389 (1970).

[56] *G. Schwarz* and *J. Engel*, Angew. Chem. *84*, 615 (1972); Angew. Chem. internat. Edit. *11*, 568 (1972).

[57] *D. C. Poland* and *H. A. Scheraga:* Theory of Helix-Coil Transitions. Academic Press, New York 1970.

[58] *J. Hermanns, D. Lohr,* and *D. Ferro*, Nature *224*, 175 (1919).

[59] *J. Kraut* in *L. Boyer:* The Enzymes. 3rd Edit., Vol. III, Dekker, New York 1971.

[60] *M. Joly:* A Physico-Chemical Approach to the Denaturation of Proteins. Academic Press, New York 1965.

[61] *O. B. Ptitsyn, A. K. Kron,* and *Yu. Ye. Eizner*, J. Polymer Sci. *C 16*, 3509 (1968).

[62] *G. I. Likhtenshtein* and *T. V. Troshkina*, Mol. Biol. *2*, 654 (1968).

[63] *A. C. Zettlemoyer:* Nucleation. Dekker, New York 1969.

[64] *J. Steinhardt* and *J. A. Reynolds:* Multiple Equilibria in Proteins. Academic Press, New York 1969.

[65] *H. Sund* and *K. Weber*, Angew. Chem. *78*, 217 (1966); Angew. Chem. internat. Edit. *5*, 231 (1966).

[66] *I. M. Klotz, N. R. Langerman,* and *D. W. Darnall*, Annu. Rev. Biochem. *39*, 25 (1970).

[67] *J. W. Teipel* and *D. E. Koshland, Jr.*, Biochemistry *10*, 792 (1971).

[68] *C. Tanford*, Advan. Protein. Chem. *23*, 121 (1969).

[69] *J. F. Brandts* in *S. Timasheff* and *G. Fasman;* Structure and Stability of Biological Macromolecules. Dekker, New York 1969.

[70] *F. M. Pohl*, Eur. J. Biochem. *4*, 373 (1968).

[71] *F. M. Pohl*, to be published.

[72] *J. F. Brandts, R. J. Oliveira,* and *C. Westort*, Biochemistry *9*, 1038 (1970).

[73] *S. A. Hawley*, Biochemistry *10*, 2436 (1971).

[74] *D. F. Hollis, G. McDonald,* and *R. Biltonen*, Proc. Nat. Acad. Sci. USA *58*, 1038 (1970).

[75] *D. N. Holcomb* and *K. E. van Holde*, J. Phys. Chem. *66*, 1999 (1962).

[76] *W. M. Jackson* and *J. F. Brandts*, Biochemistry *9*, 2294 (1970).

[77] *M. A. Eisenberg* and *G. W. Schwert*, J. Gen. Physiol. *34*, 583 (1951).

[78] *A. Rosenberg* and *C. K. Woodward*, J. Biol. Chem. *245*, 4677 (1970).

[79] *R. Lumry, R. Biltonen,* and *J. F. Brandts*, Biopolymers *4*, 997 (1966).

[80] *D. C. Poland* and *H. A. Scheraga*, Biopolymers *3*, 401 (1965).

[81] *T. Y. Tsong, R. P. Hearn, D. P. Wrathall,* and *J. M. Sturtevant*, Biochemistry *9*, 2666 (1970).

[82] *J. M. O'Reilly* and *F. E. Karasz*, Biopolymers *9*, 1429 (1970).

[83] *M. Eigen*, Quart. Rev. Biophys. *1*, 3 (1968).

[84] *A. N. Schechter*, Science *170*, 273 (1970).

[85] B. Havsteen in *S. J. Leach:* Physical Principles and Techniques of Protein Chemistry. Academic Press, New York 1969.

[86] *D. M. Crothers*, J. Mol. Biol. *9*, 712 (1964).

[87] *F. M. Pohl*, Eur. J. Biochem. *7*, 146 (1968).

[88] *M. Kunitz*, J. Gen. Physiol. *31*, 241 (1948).

[89] *F. H. Johnson, H. Eyring,* and *M. J. Pollisar:* Kinetic Basis of Molecular Biology. Wiley, New York 1954.

[90] *J. G. Wetmur* and *N. Davidson*, J. Mol. Biol. *31*, 349 (1968).

[91] *W. F. Harrington* and *G. M. Karr*, Biochemistry *9*, 3725 (1970).

[92] *J. F. Brandts*, J. Amer. Chem. Soc. *86*, 4291 (1964).

[93] *F. M. Pohl*, FEBS Lett. *3*, 60 (1969).

[94] *A. Kurosky, J. E. S. Graham, J. W. Dixon,* and *T. Hofmann*, Can. J. Biochem. *49*, 529 (1971).

[95] *C. H. Chervenka*, J. Amer. Chem. Soc. *83*, 473 (1961).

[96] *M. Eigen*, Angew. Chemie *75*, 489 (1963).

[97] *M. Ladzdunski, M. Delaage, J. P. Abita,* and *J. P. Vincent:* Structure-Function Relationships in Proteolytic Enzymes. Munksgaard, Copenhagen 1969.

[98] *J. J. Christensen, J. L. Oscarson,* and *R. M. Izatt*, J. Amer. Chem. Soc. *90*, 5949 (1968).

[99] *P. v. Hippel* and *T. Schleich* in *S. Timasheff* and *G. Fasman:* Structure and Stability of Biological Macromolecules. Dekker, New York, p. 417.

[100] *E. Lehr, M. Wenzel,* and *G. Werner*, Naturwissenschaften *57*, 521 (1970).

[101] *G. Nemethy* and *H. A. Scheraga*, J. Chem. Phys. *41*, 680 (1964).
[102] *A. Ben-Naim* and *S. Baer*, Trans. Faraday Soc. *89*, 4826 (1962).
[103] *R. Cerf*, C. R. Acad. Sci. Paris *271*, 60 (1970).
[104] *R. B. Merrifield*, Advan. Enzymology *32*, 221 (1969).
[105] *L. A. Cohen*, Annu. Rev. Biochem. *37*, 695 (1968).
[106] *L. Stryer*, Science *162*, 526 (1968).
[107] *D. J. Birkett*, *R. A. Dwek*, *G. K. Radda*, *R. E. Richards*, and *A. G. Salmon*, Eur. J. Biochem. *20*, 494 (1971).
[108] *T. Y. Tsong*, *R. L. Baldwin*, *P. McPhie*, and *E. L. Elson*, J. Mol. Biol. *63*, 453 (1972).
[109] *A. N. Schechter*, *R. F. Chen*, and *C. B. Anfinsen*, Science *167*, 886 (1970).
[110] *M. Brunori*, *E. Antonini*, *P. Fasella*, *J. Wyman*, *A. Rossi Fanelli*, J. Mol. Biol. *34*, 497 (1968).
[111] *C. Frieden*, J. Biol. Chem. *245*, 5788 (1970).
[112] *R. P. Hearn*, *F. M. Richards*, *J. M. Sturtevant*, and *G. D. Watt*, Biochemistry *10*, 806 (1971).
[113] *K. C. Aune*, *K. C. Goldsmith*, and *S. N. Timasheff*, Biochemistry *10*, 1617 (1971).

Crystal Chemistry of Complex Carbides and Related Compounds

By Hans Nowotny[*]

Numerous metal carbides can be discussed in a rather uniform way by means of structural features, mainly characterized by the mode of linking of octahedral and occasionally trigonal prismatic [M_6C] groups (M = transition element). From this point of view perovskite carbides ($M_3M'C$, M' = another transition or A-group element) and derivatives, β-Mn carbides ($M_3M'_2C$), κ-carbides, carbides with V_3AsC- and Cr_2AlC type structures and derivatives, η-carbides ($M_3M'_3C$) and carbides having the filled Mn_5Si_3 type structure will be treated. The high stability of these complex carbides is due to the strong bonding M—C and additional bonding of M—M' atoms forming an ordered parent lattice. Besides the interstitial principle of filling of lattice holes (by isolated carbon atoms), substitution with A-group elements may also take place. Thus in borocarbides extended structural elements occur.

1. Introduction

The review deals mainly with the structural aspects of some metallic carbides which occur in ternary systems of the type: two transition elements—carbon and transition element—A group element—carbon. The term complex carbide is arbitrarily introduced and stands for a double or higher carbide of intermediate character. There are more reasons than just classification for contrasting complex carbides with pseudoternary or pseudoquaternary compounds having their origin in binary carbides or nitrides such as (Ti,V)C_{1-x} or (Zr,Ta)(C,N) solid solutions. The latter carbonitride is found, for example, to be a constituent in cobalt based superalloys. Considering the compounds such as (Mo, Re)C or (W, Re)C having NaCl type structure[1], it is very likely, but not proven, that rhenium is able to stabilize the high-temperature modifications MoC_{1-x} and WC_{1-x} at much lower temperatures. Some kind of ordering may however occur in such solid solutions. Thus metal-metal short range order in carbides was found by analyzing the diffuse X-ray scattering[2]. Solid solutions of (Hf, Ta)C or (Nb, Mo)C_{1-x} apparently exhibit discontinuities of the electronic state[3], and clustering is indicated by miscibility gaps which have been detected at low temperatures for cubic carbide solid solutions such as TiC-HfC or VC-TaC[4]. In addition, ordering of carbon (and void) sites can be envisaged as is well known particularly for a number of subcarbides[5], carbohydrides *etc.*

Another peculiar case is encountered with the chromium-iron substitution in Fe_3C; chromium enters the lattice only in the eightfold position, thus a partial ordering of the metal atoms takes place[6]. The same seems to occur with $Cr_{21}W_2C_6$ within the solid solution (Cr, W)$_{23}C_6$, as one can assume from the numerous borides such as $Ni_{21}Hf_2B_6$ displaying metal ordering[7]. There are multicomponent carbides such as $Nb_3(Ni, Fe, Cr)_3C$, reported as a dispersion phase in stainless steels, which obviously derives from the η-carbide[*] Nb_3Ni_3C, and also phases such as $Nb_3Cr_{1-2}Al_{2-1}C$ which have been shown to exist only as a quaternary compound[8].

Relatively few true quaternary (and higher) carbides have been characterized so far. A number of metal carbides which correspond to intermediate carbides, develop from binary or ternary intermetallic compounds by uptake of carbon, *e. g.* $Nd_3InC_{0.7}$ or (Cr, W, Fe)$_{18}C$[9]. An interesting case involves the complete miscibility between rhenium metal and W_2C observed by *Kuz'ma et al.*[10] and confirmed by *Fackelman et al.*[11].

[*] Prof. Dr. H. Nowotny
Institut für Physikalische Chemie der Universität
A-1090 Wien IX, Währingerstrasse 42 (Austria)

[*] η-carbides, first detected as constituents in high speed steels by *A. Westgren* and *G. Phragmén*, Jernkontorets Ann. *111*, 525 (1927), are of formula $M_{2-3}M'_{4-3}C$ or $(M,M')_6C$, occasionally occurring with less carbon. They are characterized by a cubic cell with lattice parameters around 11 Å.

2. The Carbon Positions in Carbides

The determination of the carbon positions in metal carbides is usually accomplished by neutron diffraction; but difference Fourier synthesis can also be applied—as has been demonstrated by *Cromer et al.*[12] for $UMoC_2$ and by *Jeitschko et al.*[13] for Ti_3SiC_2. The carbon position within the perovskite carbide lattice is fairly well established for the compound Ti_3AlC[14]; however, it would seem to be desirable to investigate other perovskite carbides, particularly those containing heavier metal atoms, by neutron diffraction. The same is true for β-Mn carbides and κ carbides[*]. The precise carbon position for some of the H-phases[**] such as Cr_2AlC and V_2PC[15] can unambiguously be determined by X-ray experiments. In addition, neutron diffraction studies have confirmed the carbon positions in Nb_2SnC[16]. Similarly, the carbon positions in $Mo_{\sim 5}Si_3C_{0.6}$[17] with partially filled Mn_5Si_3 type structure and in the η-carbide W_6Fe_6C[18] have been determined by neutron diffraction.

Carbides, particularly transition element carbides, belong in a wider sense to interstitial compounds as defined by *Hägg*[19] and, more recently, by *Goldschmidt*[9]. The latter named author was aware of the formal character of geometrical conditions while discussing the size of interstitial atoms and proposed the term "inverse" interstitials for compounds such as MoS_2 where the metal atoms are inserted in a hexagonal close packed structure of sulfur atoms. Since very little information is available about the size and state of the interstitial atoms within metallic compounds, various concepts may be useful as guidelines.

It is obvious, therefore, that drastic structural changes can be expected depending on the metal-nonmetal ratio. Thus in the metal-rich boride Ni_3B[20] (having Fe_3C type structure) isolated boron atoms are present, while in the boron-rich boride YB_{66}[21] the metal atoms are inserted in a framework built up by boron atoms. A few examples of the following types of complex carbides will be discussed: (i) metal-rich carbides which reveal the usual interstitial concept (Section 3) and (ii) metal carbides which are characterized mainly by a substitutional mode between nonmetal and carbon (Section 4). Extended building elements are formed in borocarbides (Section 5).

Finally, it should be mentioned that minute amounts of other nonmetal elements (N, O, H *etc.*) are sometimes able to stabilize carbide structures, which either do not exist or cannot be prepared in the absence of these impurities.

3. Complex Carbides Consisting of $[M_6C]$ Groups

The strong tendency for ordering of the carbon atoms, as is clearly demonstrated for subcarbides or other carbides such as V_8C_7, does not support the assumption that carbon atoms because of their small size are just neutral particles filling the voids in a parent lattice. A more appropriate description is therefore based on the structural elements with the predominating octahedral and trigonal prismatic groups $[M_6C]$. The same building elements have also been found in a large class of complex carbides and, to some extent, in analogous transition element nitrides, some oxides, and some borides.

The occurrence and structural data of a number of representative compounds have recently been reviewed[22,23]. A few more complex carbides have been detected in the meantime, but a systematic inspection still reveals many gaps as far as analogous carbides and nitrides are concerned. Because of the high stability of many binary carbides of transition elements, the complex carbides are usually formed only at relatively low temperatures. In fact most of the complex carbides are formed by peritectic reactions *e.g.*:

$$TiC + (Ti,Si,C)_{liq.} \rightarrow Ti_3SiC_2$$

The variety of complex carbides is governed by the mode of linking of the structural elements; thus a few typical features always emerge[24].

1. The $[M_6C]$ groups can be linked by corners, by edges or by faces.

2. The transition element octahedra can be partially or completely filled.

3. An ordered metal parent lattice occurs, which occasionally exists as a binary compound.

4. The M—C distances are always relatively short compared to those in binary carbides.

5. There are no indications of bonding between the A-group element and carbon.

These features apply to a great many carbides (perovskite carbides[*], β-Mn carbides, κ-carbides, η-carbides), no matter whether the second metal is another transition element or an A-group element. However, H-phases have been observed only with A-group elements and the same is true for the partially filled Mn_5Si_3- and filled Re_3B-phases. As expected, the number of compounds with a more complicated structure type is smaller than those with simple crystal structure types.

3.1. Perovskite Carbides and Related Compounds ($M_3M'C$)

More than eighty such carbides have been reported so far; the perovskite type structure is the most regular structure of the complex carbides. A great many representatives contain transition elements of group III B and VIII such as in Sc_3AlC[25] or $Fe_3GeC_{0.45}$[26]. M components may also stem from group IV B and VII B such as in Ti_3AlC and Mn_3ZnC. One can add group VI B by considering the phase $(Cr, Pt)_3PtC_x$[27], while M components of group V B have been observed only in perovskite nitrides and oxides.

[*] β-Mn carbides display an arrangement of metal atoms corresponding to that of the manganese atoms in β-Mn (20 atoms per unit cell). Intermetallic compounds having β-Mn type structure are called π-phases. The term Kappa-carbides stems from the corresponding W—Co—C system, which is basic to the cemented carbides (hard metals); it was first investigated by *P. Rautala* and *J. T. Norton*; Plansee Proc. *1952*, 303.

[**] H-phase stands for hexagonal carbides or nitrides of formula M_2XC or M_2XN (M = transition element, X = A group metametal).

[*] The crystal structure of the perovskite carbides ($M_3M'C$) corresponds to an antitype of perovskite ($CaTiO_3$).

The chromium platinum carbide obviously leads to another branch of perovskite carbides such as VRu_3C or $ThRu_3C_{1-x}$ ($x = 0-0.1$), which were recently discovered by *Holleck*[28].

The perovskite carbide Fe_3CuC detected as a constituent in copper-containing cast iron[29] fits in the series $Fe_3\{Cu, Zn, Ga, Ge\}C$; nevertheless, the existence of Fe_3CuC appears remarkable in view of the low chemical affinity between Fe and Cu on the one hand, and Cu and C, on the other.

Rare earth perovskite carbides (except ytterbium) containing Al, In, Tl, Sn and Pb display a regularity inasfar as the lattice parameters increase proportionally with increasing radius of the trivalent rare earth ion[30]; this is in agreement with the behavior of the corresponding silicides and germanides[31]. Rare earth perovskite carbides containing gallium behave differently because of partial substitution of the metal atoms, *e.g.* $Nd_3(Nd, Ga)C_{0.2-0.8}$. It is not very likely that the so-called perovskite condition for ionic compounds can be applied to the corresponding carbides. As was pointed out by *Stadelmaier*[23] there are no satisfactory models available to explain the stability and occurrence of the perovskite carbides. With regard to the high metal-carbon ratio the interstitial concept may still constitute a first approach. Extending the radii criterion r_C/r_M to *ca.* 0.65 (nonmetal/transition metal) embraces all perovskite carbides. The problem at hand is closely related to the carbon solubility in γ-iron (austenite), where, however, the metal:carbon ratio is higher ($Fe_3FeC_{0.4}$). Substitution of the corner atom (M′) by a larger one (as *e.g.* in Fe_3CuC), obviously favors the condition for entry of a carbon atom into the octahedral void. In this way adjustment of the size of the two kinds of metal atoms (M and M′), that is the relative expansion and contraction, is responsible for the stability, as has been suggested by *Rosen* and *Sprang*[25]. Strong contraction —in order to meet the most favorable packing—can be observed for A group elements such as Mg, while small transition element atoms such as iron increase in average size; on the other hand, large atoms, *e.g.* of the lanthanum series, decrease in size because of the A group element. The arrangement of the metal atoms in the parent lattice (Cu_3Au type structure) provides another stabilizing factor in addition to the strong M—C bonding within the octahedral group $[M_6C]$. From the present data, including magnetic measurements mainly obtained on perovskite nitrides, no conclusive statements can be made on the role of electron concentration or type of electron transfer. The previously assumed electron transfer from the nonmetal atom to the transition element d-band is questionable. Measurements of the atomic scattering factor of nitrogen in the series Mn_3MnN—Mn_3GaN indicate the existence of uncharged nitrogen atoms; by no means is the donor role of the nonmetal supported[32].

3.1.1 Carbides of Filled-up U_3Si Type

Mn_3GeC_{1-x}, which has been described as a perovskite carbide[33], also occurs in a slightly modified arrangement, as was found by *Boller*[34]. Fig. 1 reveals the close relationship between these structures. The main difference consists of a slight twisting of the linked $[M_6C]$ octahedra along the *c*-axis. Thus the cell dimensions *c′* and *a′* correspond to 2*c* (perovskite) and $a/\sqrt{2}$ (perovskite) respectively. The short Mn—C distances (1.94 and 2.02 Å) are once again indicative of a strong interaction within the $[M_6C]$ group. Most likely, in Mn_3GeC there is only partial filling with carbon since the corresponding nitride has a somewhat larger cell volume. Complex nitrides are usually smaller than the analogous complex carbides—as is also the case for binary transition element carbides and nitrides.

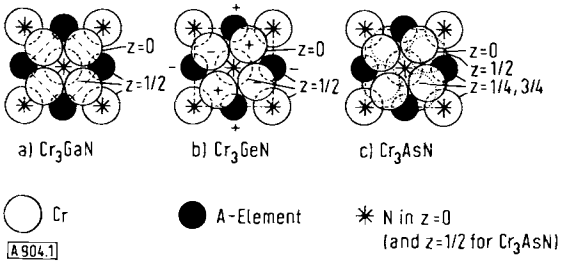


Fig. 1. Crystal structures of a) perovskite nitride (carbide), b) Cr_3GeN, and c) filled U_3Si viewed along [001] (*c* axis).

Another perovskite derivative was recently observed for Cr_3GeN[35], but no carbide having this arrangement has been found so far. The deformation of the octahedral group $[M_6N]$ generates a similarity to the white tin coordination. In the above mentioned series (Fig. 1a—1c) the coordination number of the Group A element (Ga, Ge, As) decreases from 12 to 10 to 8.

3.2. β-Manganese Carbides ($M_3M'_2C$)

From the standpoint of interstitial alloys this class of complex carbides having the filled β-Mn type structure belongs to the so-called π-phases described by *Goldschmidt*[9]. The partial lattice $\{M_3C\}$ consists—as is the case in the perovskite carbides—of a linking of fairly regular octahedral $[M_6C]$ groups by corners. Deviations in the carbon filling and in the ordering of the parent metal lattice $M_3M'_2$ also occur. The participating transition elements are mainly from group V B and VI B while a variety of the M′ components is observed (VII B to III A) if the analogous nitrides are also taken into consideration. As is shown in Table 1, the transition element as well as the A group element can be substituted, *e. g.* $(Mo,Cr)_3Al_2C$ or $Nb_3(Au,Ga)_2C$. The latter carbide, however, seems to be a quaternary compound. As constituents in high alloyed steels[36], the β-Mn carbides exhibit a manganese-like allotropy. Thus in the Fe—Cr—W—C system the χ-phase having an α-Mn type structure with respect to the metal positions transforms to β-Mn type structure on heating. The same mode of transformation was recently found within the Co—Cr—W—C system by *Ettmayer*[37]. There is no explanation available for the stability of the β-Mn carbide type. This is also true for the β-manganese type structure itself if there is a nonmetal-free β-Mn. As the interstices possess a nonvariant fourfold position, any filling with small nonmetal atoms appears to exert a stabilizing effect, since transition element-carbon bonds can be formed. It is interesting to note that Mo_3Al_2C compares

with $RbAg_4I_5$, where the Rb ions correspond to the carbon positions, while the metal parent lattice Mo_3Al_2 has the same arrangement as the iodine anion lattice. The small silver ions are randomly distributed over 72 positions and can thus be compared with the free electrons in the complex carbide.

Table 1. Complex carbides having filled β-Mn type structure.

Phase	Remarks
$Nb_3(Au,Ga)_2C_x$	amount of carbon unknown
Nb_3Al_2C	
Ta_3Al_2C	
Mo_3Re_2C	
W_3Re_2C	metal ordering likely
W-Fe-C	metal atoms disordered [39]
W-Mn-Fe-C	possibly derived from W-Fe-C
$Cr_9W_2Fe_{10}C$	partially filled [38]
Mo_3Al_2C	homogeneous range (Mo-Al)
$MoCr_3Al_2C$	solid solutions derived from Mo_3Al_2C
$(Mo,V)_3Al_2C$	
$(Mo,Mn)_3Al_2C$	

3.3. κ-Carbides and -Borides

According to the arrangement proposed by *Schönberg*[40] the $[M_6C]$ octahedra are linked by corners in such a way that trigonal metal prisms are formed between them. Although a number of ternary and quaternary κ-carbides have been detected, the amount of carbon and consequently the degree of filling is still uncertain. Besides the filling of the metal octahedra, it has been assumed that carbon atoms are also accommodated in the trigonal metal prisms, but unusually large metal-carbon distances result. As has been recognized from the formation of complex carbides in ternary and quaternary systems, aluminum is considered to be a suitable M′ component for stabilizing (Table 2). Since the lattice parameters of the Al-containing carbides are higher than those for the ternary carbides, it is very likely that aluminum atoms also occupy an additional crystallographic position; metal icosahedra are formed and complete resemblance of the parent lattice of the κ-carbides to the arrangement of Mn_3Al_{10} or Mn_3Al_9Si[41]. results. In addition to the metal atoms having the same positions within the same space groups, it is found that the atomic parameters are nearly the same. A characteristic feature of the κ-carbide phases is the c/a ratio equal to unity. The existence of the complex carbide Mo—Cu—Al—C indicates a lower degree of filling by carbon atoms inasfar as only strong Mo—C bonds can be expected. Nevertheless, the filling, or eventual filling, of the trigonal metal prism by carbon atoms must be regarded as a first step in the mixing of octahedral and trigonal prismatic $[M_6C]$ groups.

Very recently κ-borides have also been observed in the Hf—Mo(W)—B systems[42]. As can be seen from Table 2, the c/a ratio is once again approximately equal to one, and the atomic parameters for the metal atoms differ only slightly. A ternary phase in the above named systems was first reported by *Harmon*[43] and designated as a φ-phase in the region 50 at % of Hf, 20 at % Mo(W) and 30 at % B. A more detailed investigation confirmed the existence of ternary borides, the composition however was found to be less boron-rich and a formula Hf_9Mo_4B was adopted. In the case of the κ-boride one can rule out filling of the octahedra because of the short hafnium-octahedral void distance. On the other hand the filling of the trigonal prismatic void meets perfectly with the space requirements. In addition, further occupation by boron atoms is possible which leads, as in aluminum-containing κ-carbides, to completion of the metal icosahedron; in other words these boron atoms behave metal-like, as is already known for some other boron-containing intermetallics, such as $CeCo_3B_2$.

Table 2. κ-carbides and borides.

Phase	c/a	Phase	c/a	Phase	c/a
W-Mn-C	1.000	Mo-Mn-Al-C	0.999	Hf_9Mo_4B	0.99_1
$W_{9-10}Co_3C_4$	1.000	Mo-Fe-Al-C	1.000	$(Hf,W)_{13}B$	0.98_8
$W_{16}Ni_3C_6$	1.000	Mo-Ni-Al-C	0.995		
W-Mn-Al-C	0.986	$Mo_{12}Cu_3Al_{11}C_6$	0.989		

3.4. Carbides with V_3AsC Type Structure (Filled Re_3B Type)

It is a well established rule that a larger radius ratio nonmetal: metal shifts the octahedral environment to the trigonal prismatic groups. In some way this is a continuation of the building principle mentioned in Section 3.3.; thus a structural type of complex carbides has been detected, which equally combines octahedral and trigonal prismatic $[M_6C]$ groups[44,45]. The following complex carbides can be treated in the same way as above because the octahedral voids are filled by carbon (or nitrogen). The ordered parent lattice corresponds to the Re_3B type structure (or anti-$PuBr_3$ type), in which the boron atoms fill the voids of the trigonal metal prism (Fig. 2). As has

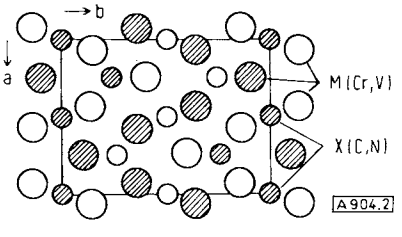


Fig. 2. Crystal structure of the filled Re_3B type. Small nonmetal atoms fill the M_6 octahedra.

already been shown there is no significant difference between a second participating transition element and an A group element in the complex carbides as fas as the structural features are concerned. Similarly, carbon may act like other non-metals or A group elements. As a result, the larger nonmetal or A group element must occupy the interstices of the trigonal prism in compliance with the larger ratio of radii nonmetal/transition metal. Thus V_3PC, for example, can topochemically be built up from the structural elements V_2C (octahedra) and VP (trigonal prisms). Conversely, for VCr_2C_2 a metal ordering is expected in which the vanadium atoms preferentially form the octahedral and the small chromium atoms the trigonal prismatic groups. In fact VCr_2C_2 is a perfect intermediate

between the cubic carbide (V, Cr)C_{1-x} and Cr_3C_2. The former represents the octahedral portion, while the latter consists of trigonal prisms.

Table 3. Lattice parameters of complex carbides and nitrides with filled Re_3B type structure.

Phase	a [Å]	b [Å]	c [Å]
V_3GaN	2.95_0	10.30	7.93_1
V_3GeN	3.01	10.30	7.79_3
V_3GeC	3.04_7	10.14	7.88_4
V_3PN	3.101	9.840	7.419
V_3PC	3.119	9.758	7.531
V_3AsN	3.130	10.18	7.590
V_3AsC	3.128	10.14	7.699
VCr_2C_2	2.870	9.30	6.99
$Cr_3(B,C)C$	2.870	9.260	6.982
Cr_3GeC	2.89_9	10.33_9	7.72_4
$Cr_3C(C,N)$	2.843	9.25_5	6.95_2
Cr_3PN	3.047	9.833	7.224
Cr_3PC	3.054	9.704	7.299
$Cr_3As(C,N)$ [a]	3.057	10.21	7.470

[a] Previously described as carbide.

In contrast to VCr_2C_2, the complex carbide VTa_2C_2 has, according to *Rudy*[46], a metal layer structure with the sequence $(hhc)_3$[*]. In the case of Cr_7BC_4[47] or $Cr_3(B,C)C$ and $Cr_3C_{1.4}N_{0.6}$[48] or $Cr_3C(C,N)$ carbon atoms occupy, at least partially, both kinds of voids. One must assume that the smaller nitrogen atoms enter only the octahedral sites. In Table 3 complex carbides and nitrides having the filled Re_3B type structure have been listed. The ratio $a/\sqrt{bc}$ increases with the A group number indicating less interaction between these atoms if the A group element is getting more electronegative. A similar behavior has been observed for H-phases, as is shown below (cf. Section 3.5).

3.4.1. The Compound V_4P_2C

The ternary system vanadium-phosphorus-carbon is distinguished by the occurrence of several complex carbides: V_5P_3C (filled Mn_5Si_3-type), V_3PC (see Section 3.4.), V_2PC (H-phase), and V_4P_2C recently detected by *Boller*[49]. The carbide V_4P_2C (Fig. 3) also combines the building elements

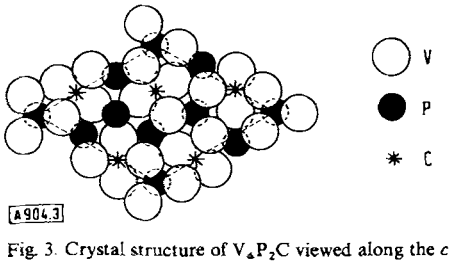


Fig. 3. Crystal structure of V_4P_2C viewed along the *c* axis.

of octahedra and trigonal prisms (parallel and perpendicular to the *c*-axis). As for V_3PC, the phosphorus atoms are filling the prisms, carbon the octahedral voids. Moreover, an irregular body-centered cube of metal atoms appears which is a common structural element in borides, silicides and phosphides[50].

[*] h signifies hexagonal close packed layer sequence 1212...; c a cubic close packed layer sequence 123123...; thus $(hhc)_3$ consists of nine layers of mixed type.

3.5. Complex Carbides Having the Cr_2AlC Type Structure (H-phases) and Related Structures

Almost seventy H-phases (mostly carbides) have been described. The crystal structure of the H-phase compares to that of the perovskite carbide in the same way as hexagonal close packing compares to cubic close packing. There is, however, no binary compound known which corresponds to the metallic parent lattice M_2M', *i. e.* a hexagonal close packed array with a superstructure $c' = 3c$ according to the sequence $M_AM_BM'_AM_BM_AM'_B$. Table 4, the major part of which is taken from the thesis work by *Jeitschko*[51], clearly shows the distinct dependency of the $c/3a$ ratio on the nature of the M' component. Thus, one can speak of a more metallic branch having a high $c/3a$ ratio and a less metallic (ionic) branch with a low $c/3a$ ratio, as is exemplified by the series: $V_2GaC(1.45_7) \rightarrow V_2GeC(1.36_1) \rightarrow V_2AsC(1.21_8) \rightarrow Ti_2SC(1.16_2)$.

Kudielka[52], who discovered the very first H-phase, namely Ti_2SC as a constituent in steels, pointed out that Hf_2SC is very likely a quaternary phase containing some iron. Deviations from the composition $M_2M'C$ are relatively rare, but nevertheless they do occur, *i.e.* incomplete filling of the transition element octahedra which are linked by edges. Some other H-phases, such as Ti_2PbC, also deviate from the ideal ratio $M/M' = 2$. In other words there is some partial Ti/Pb substitution corresponding to a lead defect. Ta_2GaC on the other hand exhibits a distortion which may be connected with stacking faults indicating derivative structure types (see the following Section).

With respect to the six layer type structure of $(hhh)_2$ there is a close relationship in cell dimensions with the MoC_{1-x}-phase[53], occasionally formulated as Mo_3C_2[46] and having a sequence $(cch)_2$, particularly if it is referred to the metallic branch of H-phases. Even more pronounced, however, is the relationship to the TiP type structure. Substituting two phosphorus atoms in Ti_4P_4 by two carbon atoms leads to the H-phase arrangement (Fig. 4). This represents another way of looking at the building elements of the H-phases—particularly for the less metallic branch. It clearly results from the analogy that both structural elements, the octahedral group $[M_6C]$ and a trigonal prismatic group $[M_6M']$ are building blocks in the H-phase. Thus the arrangements develop stepwise from the κ carbides to the filled-up Re_3B types and further to the H-phases. From the above mentioned series it can be seen that the ordered close packing of the metallic parent lattice (small *a*-axis) will be more and more replaced by the trigonal prismatic structural element (large *a*-axis). Consequently there is an M'—M' contact for the metallic branch such as V_2AlC or V_2GaC while no such contact can be assumed for phosphorus-, arsenic- or sulfur-containing H-phases. From this point of view H-phases are just another example of the topochemical mode of generation by two essential building groups, one characteristic of the large class of NaCl type structures (octahedra) and one characteristic of the NiAs type structures (trigonal prism). This is best demonstrated with V_2PC which is a sum of VC (octahedra)

+VP (trigonal prism). It is therefore not surprising that the H-phase parent lattice is an anti-type of MoS_2 which represents a stacking variant of the well known CdI_2 type structure.

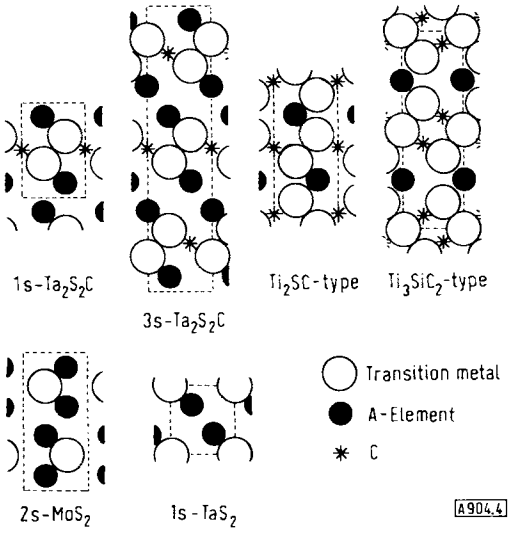


Fig. 4. Comparison of the different complex carbide layer structures [(11$\bar{2}$0) plane of hexagonal cell]. Ti_2SC (= Ti_2P_2 if * = •); 1 s-, 2 s-, 3 s- indicates the number of layers along the hexagonal axis.

Table 4. Complex carbides (H-phases).

Compound	$c/3a$	Compound	$c/3a$
Sc_2InC	—	V_2AlC	1.500
Ti_2CdC	1.550	V_2GaC	1.457
Ti_2AlC	1.490	V_2GeC	1.361
Ti_2GaC	1.448	V_2PC	1.182
Ti_2InC	1.400	V_2AsC	1.218
Ti_2TlC	1.476	Nb_2AlC	1.486
Ti_2GeC	1.400	$Nb_{1.2}Zr_{0.8}AlC$	1.497
Ti_2SnC	1.444	Nb_2GaC	1.443
Ti_2PbC	1.434	Nb_2InC	1.510
Ti_2SC	1.162	Nb_2SnC	1.414
Zr_2InC	1.486	Nb_2PC	1.172
Zr_2TlC	1.467	Nb_2AsC	1.196
Zr_2SnC	1.454	Nb_2SC	1.166
Zr_2PbC	1.445	$Nb_2SC_{0.4}$	1.168
Zr_2SC	1.190	Ta_2AlC	1.500
Hf_2InC	1.487	Ta_2GaC	1.458
Hf_2TlC	1.469	Cr_2AlC	1.495
Hf_2SnC	1.448	Cr_2GaC	1.458
Hf_2PbC	1.437	Cr_2GeC	1.365
Hf_2SC	1.190	Mo_2GaC	1.457
$Ti_{0.8}V_{1.2}SC$	1.142		

The transition element can partially be replaced by another transition element such as $(Nb,Zr)_2AlC$, however nothing is known about an M′/M′ substitution or replacement of carbon, *e.g.* by nitrogen, although a large number of H-phase nitrides also exists.

3.5.1. The Ti_3SiC_2 Structure

A ternary phase first reported by *Brukl*[54] was shown to be structurally closely related to the H-phase[55] (see Fig. 4). The Ti_3SiC_2 phase can be regarded as an intermediate between the H-phase and the cubic monocarbide arrangement. A double layer of $[Ti_6C]$ groups perpendicular to the hexagonal axis is present instead of the one $[Ti_6C]$ layer in the H-phase. The sequence of the parent lattice corresponds to the $(hhhc)_2$ scheme. In this context it is interesting to note that the ratio of the respective c-axes for the isotypic Ti_3GeC_2[56] and the H-phase Ti_2GeC is precisely 4/3 due to the additional TiC layer. This can again be expressed by a topochemical reaction according to: $Ti_2GeC + TiC = Ti_3GeC_2$. Because of the strongly bonded double layer of $[Ti_6C]$ groups, the lamellar character of Ti_3SiC_2 is very much pronounced. Only very recently *Nickl*[57] reported on stacking faults in titanium silicocarbides, thus indicating that an intergrowth of TiC layers and H-phase layers occurs.

3.5.2. Ta_2S_2C Type Structures

Similar layer arrangements have also recently been found in tantalum sulfocarbides[58] which exhibit a mechano-chemical transformation mode. The building elements consist of $[Ta_6C]$ layers and the well known transition element disulfide layer group. Ta_2S_2C (formed by sintering the powder components at 1200°C) behaves like a solid lubricant. Powdering the sintered mass in a mortar leads to platelet-like particles having a distinct texture. The crystal structure of the mechanically treated carbide (1 s-Ta_2S_2C) was found—ignoring the somewhat different c/a ratio—to be isotypic with the valence compound Ce_2O_2S. Annealing of 1 s-Ta_2S_2C at 1250°C (70 h) yields the initial 3 s-Ta_2S_2C state, which exhibits a more complex stacking corresponding to the arrangement of another valence compound, namely Bi_2Te_2S (tetradymite). Fig. 4 demonstrates the relationship of the hexagonal structure types. As can be seen in the (11$\bar{2}$0) plane, which lies perpendicular to the hexagonal layers (of metal, A group element (sulfur) and carbon atoms), 3 s-Ta_2S_2C consists of a sum of TaC layers and TaS_2 layers (1 s-TaS_2), while 1 s-Ta_2S_2C can be generated out of TaC layers and TaS_2 layers corresponding to the 2 s-MoS_2 type structure. The sequences of the layers along the c axis can be expressed as follows:

3s-Ta_2S_2C	-M-C-M-X-X-M-C-M-X-X-M-C-M-X-X-
Ti_3SiC_2	-M-C-M-C-M-X-M-C-M-C-M-X-
H-Phase	-M-C-M-X-M-C-M-X-
1s-Ta_2S_2C	-M-C-M-X-X-

M (transition metal), X (A group element), C (carbon)

As seen from the viewpoint of inverse interstitial compounds one has to mention that 3 s-Ta_2S_2C is an antitype structure of the complex carbide VTa_2C_2 mentioned in Section 3.4. inasfar as the partial lattice $[S_2C]$ and $[Ta_2V]$ on the one hand and $[Ta_2]$ and $[C_2]$ on the other perfectly correspond. Similarly, the H-phase is an antitype of alkali metal-niobium disulfide.

The partial filling of the metal octahedra in VTa_2C_2 is explained, as in the case of Mo_3C_2, by assuming that the carbon atoms repel each other if they come too close.

The complex compounds UBC[59] and Mo_2BC[60] consist of $[M_6C]$ or $[M_5BC]$ octahedra and $[M_6B]$ trigonal prisms; here the distinct boron-boron interaction (zigzag boron chains) is already noticeable.

3.6. Complex Carbides of the Filled Ti_2Ni Type (η-Carbides) and Filled Mn_5Si_3 Type

These complex carbides are characterized by $[M_6C]$ octahedra linked by planes. The first group, the so-called η-carbides, is of great interest from a practical point of view and has already been described in detail by *Stadelmaier*[23].

The filled or partially filled Mn_5Si_3 type structure reveals, in a particular way, the interstitial character inasfar as compounds with larger transition element atoms may also accommodate boron, germanium, and even metal atoms in the octahedral voids. Similarly to perovskite carbides there are many binary $M_5M'_3$ compounds which are able to take up carbon. In the case of rare earth silicides having this composition it has recently been shown that carbon can continuously be dissolved up to Ln_5Si_3C (Ln ≙ lanthanoid)[61]. For some of the intermediate complex carbides (Table 5) the amount of the stabilizing carbon has not been determined. Extended or complete solid solutions between such carbides also exist, *e.g.* $V_5(Si,Ge)_3C_x$. Furthermore, solid solutions occur between these carbides and the analogous binary compounds, *e.g.* $Mo_5Si_3C_x$ and Ti_5Si_3.

Table 5. Complex carbides of the filled Mn_5Si_3 type.

Phase	a[Å]	c[Å]	c/a	Remarks
$Zr_5Si_3C_x (x \simeq 0.2)$	7.91	5.58	0.705	
$Hf_5Al_3C_x$	8.052	5.690	0.707	
$Hf_5Si_3C_x$	7.89	5.56	0.705	
$V_5Si_3C_x$	7.12_1	4.83_2	0.679	
$V_5Ge_3C_x$	7.28	4.96	0.682	
$V_5P_3C_{0.7}$	6.924	4.799	0.692	
$V_5As_3C_{0.7}$	7.121	4.963	0.697	
$Nb_5Ga_3C_x$	7.72	5.27	0.682	
$Nb_5Si_5C_x$	7.52_1	5.23_8	0.697	
$Nb_5Ge_{3+y}C_x$	7.66	5.25	0.685	depends on amount of Ge
	7.628	5.39	0.707	
$Ta_5Ga_3C_x$	7.66_1	5.28_0	0.689_2	
$Ta_5Si_3C_x$	7.47_4	5.22_5	0.699	
$Ta_5Ge_3C_x$	7.58_1	5.23_5	0.690	
$Cr_5Si_3C_x$	6.993	4.72_6	0.676	
$Mo_{4.8}Si_3C_{0.6}$	7.28_6	5.04	0.692_6	
$Mo_5Ge_3C_x$	7.361	5.04_7	0.685	
$W_5Si_3C_x$	7.19	4.85	0.675	contains Cr

4. Complex Carbides Characterized by A Group Element—Carbon Substitution

Only A group elements larger than carbon are to be considered—that is to say no carbonitrides or carbohydrides, even though $Cr_3C(C,N)$ represents such an intermediate compound. On comparing this carbonitride with $Cr_3AsC_{0.75}N_{0.25}$ it is seen that carbon substitutes arsenic in a formal way, at least for the larger portion, while the other part plays the role of an interstitial atom. To some extent TiP (H-phase array) can also be regarded as a P/C substitution type.

4.1. Carbon in Cr-P and Cr-As Phases

A carbon-stabilized chromium phosphide of formula $Cr_6P_{2.6}C_{0.4}$ having Fe_2P type structure was recently detected[62]. As one can see from the change of the lattice parameters within the homogeneous region (Table 6), carbon obviously acts more in a substitutional phosphorus-carbon mode. This is also supported by the behavior of the isotypic compound $Cr_6As_{3-x}C_x$, which, however, develops from the high temperature phase Cr_2As[63]. It was shown from single crystal data that the electronic density at the arsenic positions is lower than expected for full occupation according to $Cr_6As_{2.8}$. These findings are, furthermore, in agreement with the short Cr—As distances and the relatively high density calculated for Cr_2As. Carbon dissolves up to $Cr_6As_{2.2}C_{0.8}$ (1000 °C, quenched). As is seen from Fig. 5 the volume increases only slightly from low

Table 6. Complex carbides based on partial substitution.

Compound	Type	a[Å]	c[Å]	c/a
$Cr_6P_{2.55}C_{0.45}$	Fe_2P	6.136	3.227	0.526
$Cr_6P_{2.75}C_{0.25}$		6.117	3.242	0.530
$Cr_6As_{2.2}C_{0.8}$	Fe_2P(ordered)	6.302	3.402	0.540

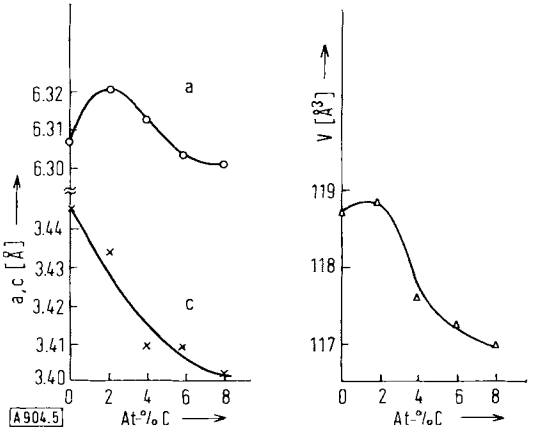


Fig. 5. Lattice parameters of $Cr_6As_{3-x}C_x$ as a function of the amount of carbon.

carbon concentrations, but then decreases because of a carbon/arsenic substitution. One can assume that take-up of carbon proceeds in a partially ordered way as is the case for Ni_6Si_2B (ordered Fe_2P type structure[64]); however, the ideal composition will not be reached. The behavior of carbon is also similar to that of boron in Cr_5PB_2[63].

5. Borocarbides of Transition Elements

The ease of replaceability between carbon and boron has been known for a long time regarding the solid solution $Fe_3(B,C)$; but more characteristic in this respect is the intermediate phase $Fe_{23}(B,C)_6$, discovered by *Carroll et al.*[65]. However, in contrast to the borocarbides already mentioned (UBC, Cr_7BC_4, Mo_2BC) the structural element of $Fe_{23}(B,C)_6$ (τ-phase) differs inasfar as the metal atoms form quadratic antiprisms whose voids are occupied by the non-metal atoms. The changing of the building elements (increase in coordination number) corresponds to the limit of the ratio of nonmetal-metal radii as proposed by *Hägg*[19] for the interstitial phases. No boro-

carbides of the transition elements of group IVB and VB appear to exist; this fact can be explained by the high stability of the corresponding monocarbides and diborides. There are obviously no borocarbides of tungsten or manganese either, although the latter case has not, as yet, been completely studied. On the other hand, there is a series of borocarbides of the transition elements of group III B (lanthanum and actinium series). As already mentioned, in UBC the carbon is octahedrally surrounded by five metal atoms and one boron atom; however, one can view the structural elements in a different way because of the occurrence of boron-boron chains. As is demonstrated in Fig. 6a the nonmetal atoms form a so-called branched chain.

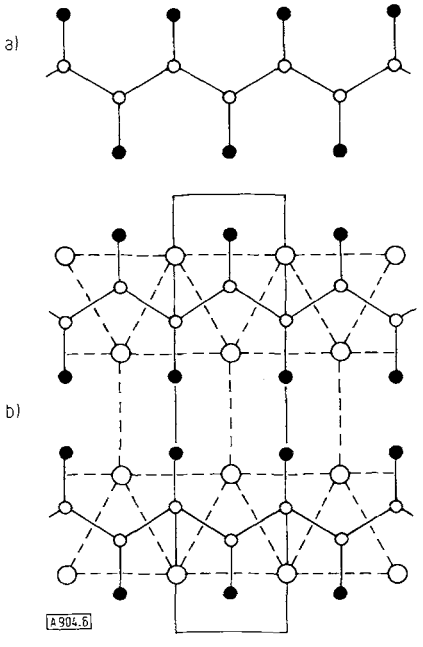


Fig. 6. a) Branched boron-carbon chain in UBC; b) Crystal structure of YBC.

While UBC seems to be the only ternary compound in this system, several borocarbides of thorium are known to exist[66], but no conclusive data are however available as yet. The compound of approximate composition ThB_2C is related to the AlB_2 type structure; thus, two-dimensional networks consisting of boron and carbon atoms were assumed. A complete structural characterization of ScB_2C_2 was later carried out by *Smith et al.*[67]. These authors found a two-dimensional boron-carbon network built up from 5- and 7-membered rings (Fig. 7a). The metal layers above and below can be regarded as a deformed hexagonal pack. Numerous borocarbides of elements of the lanthanum series have been reported by *Smith et al.*[68]; among these compounds GdB_2C_2 and analogous borocarbides were shown to exist which crystallize with a tetragonal unit cell; hence a two-dimensional boron-carbon network (4- and 8-membered rings) is likely to be present. According to these findings the compounds previously reported as lanthanoid borides of formula $LnB_x (x = 3-4)$[69] have now been identified as LnB_2C_2 compounds. A similar assumption has already been made by *Binder*[70].

5.1. Yttrium Borocarbides[71]

A detailed investigation of the ternary system yttrium-boron-carbon reveals the existence of the borocarbides YB_2C_2, YB_2C, YBC and $YB_{0.5}C$. The composition of the latter is not quite certain.

YB_2C_2: This borocarbide is obviously of the same structure type as LnB_2C_2. If it is assumed that no random distribution of boron and carbon atoms occurs, then the c-axis of the tetragonal cell must be doubled. Fig. 7b shows the arrangement of the atoms; the nonmetal network is built up of 4- and 8-membered rings; the cell parameters (a and $c/2$) in Table 7 correspond to those previously proposed for "YB_2C"[70]. There is no doubt that the same borocarbide is involved in both cases.

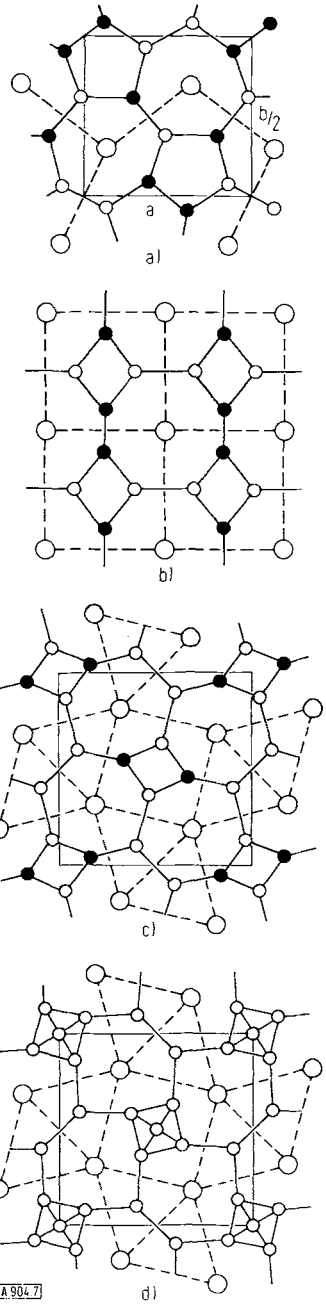


Fig. 7. a) Boron-carbon network in ScB_2C_2 (according to Ref. [67]). b) Boron-carbon network in YB_2C_2 (turned above and below by 90°); c) Boron-carbon network in YB_2C (turned above and below by 90°); d) Crystal structure of YB_4 (according to *C. E. Lundin*, in *F. H. Spedding* and *A. H. Daane*: The Rare Earths Wiley, New York, 1961).

YB_2C: The crystal structure has been proposed on the basis of single crystal patterns. From Fig. 7c one can recognize a close similarity to the architecture of YB_4 (Fig. 7d): Leaving out two boron atoms and substituting two further boron atoms by two carbon atoms yields YB_2C, which is a topochemical sum of the building elements of YB_2 (diboride type structure) and YB_2C_2. The arrangement of the metal atoms in the layer is well known from the U_3Si_2 type structure. The nonmetal atoms are again linked to a two-dimensional network (may be slightly puckered) consisting of 4- and 7-membered rings. Lattice parameters and atomic distances are given in Table 7.

Table 7. Yttrium borocarbides (lattice parameters and distances in Å).

	YB_2C_2	YB_2C	YBC
a	3.79_6	6.76_9	3.38_8
b	—	—	13.69_3
c	7.12_4	7.430	3.62_7
space group	D_{2d}^2–$P\bar{4}2c$	D_{4h}^{13}–$P4_2/mbc$	D_{2h}^{19}–Cmmm
Y–Y	3.68	3.60	3.71
B–B	1.76	1.75	1.98
C–C	1.28	—	—
B–C	1.62	1.64	1.65
Y–B	2.75	2.73	2.70
Y–C	2.68	2.55	2.55

YBC: By means of single crystal data the arrangement shown in Fig. 6 can be proposed. A close relationship to UBC occurs inasfar as branched boron-boron zigzag chains constitute the predominant structural element. As usual the boron atoms are accommodated in voids of a trigonal prism, however the surrounding of the carbon atoms differs. The fifth metal atom is missing and because of the large carbon-carbon distance no interaction takes place. Easy gliding of YBC crystals in the (010) plane is in agreement with the layer-like structure. Cell dimensions and interatomic distances are given in Table 7. The atomic parameters of boron and carbon, and therefore the atomic distances Y—B, Y—C, B—B, B—C and C—C, are a first approximation. No difference Fourier synthesis has, as yet, been carried out.

6. Discussion

6.1. Isolated Carbon Atoms

The concept of interstitial compounds applies in a similar way to the metal rich complex carbides. The dominant feature can be seen in the structural group $[M_6C]$ which mainly occurs as octahedra, but, sometimes, also as trigonal prisms. Thus, more complicated parent lattices than the simple cubic and hexagonal close packing must be envisaged. As seen from the viewpoint of critical radii ratio r_C/r_M there is a stepwise transition to metastable carbides and further to structural groups $[M_8C]$ consisting of square antiprisms; this occurs particularly frequently in the case of metal rich borides. Prediction on the basis of the radii criterion does not mean, however, that the size of the atoms in the carbide corresponds to the atomic radius in the elemental state. So far we have no unambiguous information about the electron transfer or the shape of the so-called atomic spheres in the carbides. At best, only the atomic distances and the coordination are precisely determined; consequently, in a first approach speculations about covalent radii (neutral state) and ionic radii (polar state) do not allow any discrimination. The large class of complex carbides reveals in a uniform way the strong bonding between transition metal atoms and carbon atoms, the M—C distances always being somewhat shorter than in the corresponding binary carbide, while the A group element atoms obviously do not form bonds with carbon. On the other hand transition element—A group element bondings contribute to the stabilization of complex carbides in addition to the M—M-bonds.

6.2. Carbon-Carbon and Carbon-Nonmetal Aggregates

A smaller amount of metal favors the nonmetal aggregation *per se* as is well known for borides and silicides. While these compounds display all kind of aggregates X_n (X = nonmetal), namely: X_2, X_3, X_4, X-chains, branched chains, double chains, nets *etc.*, the aggregation mode for carbides is much less pronounced. Carbon pair formation has been observed in dicarbides such as CaC_2 *etc.*; other examples are sesquicarbides such as Pu_2C_3 or $Sc_{15}C_{19}$. C_3-aggregates are, so far, only known for B_4C. No carbon-chain formation takes place in metal carbides; it was earlier assumed to occur in Cr_3C_2, but could not be confirmed by neutron diffraction studies. Nevertheless the carbon atoms in Cr_3C_2 come relatively close together which also might be a hint that no "CrC" can exist. In this context, carbon-carbon aggregation is indicative of competition between carbide formation and metal-graphite decomposition. As is immediately seen from the decreasing stability of carbides with increasing group number Ti → Ni, this parallels the decreasing atomic size of the metal and increasing carbon:metal radii ratio. All attempts to prepare graphite compounds of transition metals have so far failed; however, alkali metal and alkaline earth metal graphite compounds have been known for some time. It is of interest to note that borocarbides fill this gap by formation of branched chains or two-dimensional networks. There is no doubt that, here, metal-nonmetal covalent bonds between the nonmetal atoms play a significant role in the stabilization of such metal carbides.

In conclusion one may ask whether cage-like carbides can be formed analogous to those of the borides and silicides (clathrates).

Received: June 21, 1971 [A 904 IE]
German version: Angew. Chem. *84*, 973 (1972)

[1] *L. K. Borusevich* and *E. I. Gladyshevskii*, Porosh. Met. *4*, 22 (1964).
[2] *Ya. S. Umanski* and *V. I. Fadeeva*, Fiz. Metal. Metalloved. *20*, 719 (1965).
[3] *E. N. Denbnorentskaya*, Porosh. Met. *7*, 57 (1967).
[4] *R. Kieffer, H. Nowotny, A. Neckel, P. Ettmayer*, and *L. Usner*, Monatsh. Chem. *99*, 1020 (1968).
[5] *H. Nowotny* and *F. Benesovsky*, Planseeber. Pulvermet. *16*, 204 (1968).

[6] *H. Kudielka* and *H. Möller*, Z. Kristallogr. Kristallgeometrie Kristallphys. Kristallchem. *118*, 213 (1963).

[7] Cf. *E. Ganglberger*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *97*, 494 (1966).

[8] *E. Reiffenstein*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *96*, 1543 (1965); *97*, 1428 (1966).

[9] *H. J. Goldschmidt:* Interstitial Alloys. Butterworths, London 1967.

[10] *Yu. B. Kuz'ma*, *B. I. Lakh*, *V. Ya. Markiv*, *B. I. Stadnyk*, and *E. I. Gladyshevskii*, Sov. Powder Met. Metal Ceram. No. 4, (16) 286 (1963).

[11] *J. M. Fackelman*, *R. W. Getz*, and *D. P. Mock*, AIME Symp., French Lick, Ind., Oct. 1965.

[12] *D. T. Cromer*, *A. C. Larson*, and *R. B. Roof, Jr.*, Acta Crystallogr. *17*, 272 (1964).

[13] *W. Jeitschko*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *95*, 319 (1964).

[14] *W. Jeitschko*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *94*, 672 (1963).

[15] *H. Boller*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *99*, 672 (1968).

[16] *H. Boller*, *K. Yvon*, and *H. Nowotny*, II. Int. Colloqu. Semi-Metallic Compounds, Enschede 1967.

[17] *E. Parthé*, *W. Jeitschko*, and *V. Sadagopan*, Acta Crystallogr. *19*, 1031 (1965).

[18] *J. Leciejewicz*, J. Less-Common Metals *7*, 318 (1964).

[19] *G. Hägg*, Z. Phys. Chem. (B) *6*, 221 (1930); *12*, 33 (1931).

[20] *S. Rundquist* and *S. Pramatus*, Acta Chem. Scand. *21*, 191 (1967).

[21] *S. M. Richards* and *J. S. Kaspar*, Acta Crystallogr. *B 25*, 237 (1969).

[22] *H. Nowotny* and *P. Ettmayer*, J. Inst. Metals *97*, 180 (1969).

[23] *H. H. Stadelmaier* in *B. C. Giessen*: Developments in the Structural Chemistry of Alloy Phases. Plenum Press, New York 1969.

[24] *E. Parthé* and *W. Jeitschko*, Acta Crystallogr. *19*, 1031 (1965).

[25] *S. Rosen* and *P. G. Sprang*, 13th Annu. Conf. Appl. X-ray Analysis, Denver, Col. 1965.

[26] *H. H. Stadelmaier*, Z. Metallk. *52*, 758 (1961).

[27] *E. Ganglberger*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *96*, 1781 (1965).

[28] *H. Holleck*, J. Nucl. Mater. *39*, 226 (1971); KFK 1485, Durham-Conf., July 1971.

[29] *N. Janakiev*, Berg. Hüttenmänn. Monatsh. *116*, 6 (1971).

[30] *H. Haschke*, *H. Nowotny*, and *F. Benesovsky*. Monatsh. Chem. *97*, 716, 1045, 1469 (1966); *98*, 273, 2157 (1967).

[31] *E. Parthé*, Colloqu. Int. Derivés Semi-Métalliques, CNRS, Paris 1967.

[32] *M. Barberon*, *R. Madar*, *E. Fruchart*, *G. Lorthioir*, and *R. Fruchart*, Mater. Res. Bull. *5*, 903 (1970).

[33] *L. J. Hütter* and *H. H. Stadelmaier*, Z. Metallk. *50*, 199 (1959).

[34] *H. Boller*, Monatsh. Chem. *99*, 2444 (1968).

[35] *H. Boller*, Monatsh. Chem. *100*, 1471 (1969).

[36] *W. Koch*: Metallkundliche Analyse. Verlag Stahleisen, Düsseldorf 1956, p. 272.

[37] *P. Ettmayer*, Inst. Metals Meeting, Wien, Sept. 1968.

[38] *H. J. Goldschmidt*, Research *10*, 289 (1957).

[39] *K. Kuo*, Trans. AIME *8*, 97 (1956).

[40] *N. Schönberg*, Acta Met. *2*, 837 (1954).

[41] *P. I. Kripyakevich*, Zh. Strukt. Khim. *4*, 177, 282 (1963).

[42] *P. Rogl*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *102*, 971 (1971).

[43] *P. Harmon* in *E. Rudy*: Compendium on Phase Diagram Data, AFML-Rep. 1969.

[44] *P. Ettmayer*, *G. Vinek*, and *H. Rassaerts*, Monatsh. Chem. *96*, 1259 (1965).

[45] *H. Boller* and *H. Nowotny*, Monatsh. Chem. *99*, 721 (1968).

[46] *E. Rudy*, J. Less-Common Metals *20*, 49 (1970).

[47] *Y. D. Kondrashev*, Kristallografiya *11*, 559 (1966).

[48] *P. Ettmayer* and *R. Kieffer*, Radex Rundsch. *1970*, 191.

[49] *H. Boller*, Monatsh. Chem., in press.

[50] *H. Nowotny*, *H. Boller*, and *O. Beckmann*, J. Solid State Chem. *2*, 462 (1970).

[51] *W. Jeitschko*, Dissertation, Universität Wien 1964.

[52] *H. Kudielka*, Z. Kristallogr. Kristallgeometrie Kristallphys. Kristallchem. *121*, 165 (1965).

[53] *H. Nowotny*, *E. Parthé*, *R. Kieffer*, and *F. Benesovsky*, Monatsh. Chem. *85*, 255 (1954).

[54] *Ch. E. Brukl*, Tech. Rep. AFML-TR-65-2, Vol. II, Part II.

[55] *W. Jeitschko* and *H. Nowotny*, Monatsh. Chem. *98*, 329 (1967).

[56] *H. Wolfgruber*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *98*, 2403 (1967).

[57] *J. Nickl*, Int. Conf. Crystal Growth, Zürich, Sept. 1970.

[58] *H. Nowotny*, *H. Boller*, and *O. Beckmann*, Monatsh. Chem. *101*, 945 (1970).

[59] *L. E. Toth*, *H. Nowotny*, *F. Benesovsky*, and *E. Rudy*, Monatsh. Chem. *92*, 794 (1961).

[60] *W. Jeitschko*, *H. Nowotny*, and *F. Benesovsky*, Monatsh. Chem. *94*, 65 (1963).

[61] *I. Mayer* and *I. Shidlovsky*, Inorg. Chem. *8*, 1240 (1968).

[62] *H. H. Baurecht*, *H. Boller*, and *H. Nowotny*, Monatsh. Chem. *102*, 373 (1971).

[63] *W. Wolfsgruber*, *H. Boller*, and *H. Nowotny*, Monatsh. Chem. *99*, 1230 (1968).

[64] *S. Rundquist* and *F. Jellinek*, Acta Chem. Scand. *13*, 425 (1959).

[65] *K. G. Carroll*, *L. S. Darken*, *R. M. Fischer*, and *L. Zwell*, Nature (London) *174*, 978 (1954).

[66] *L. E. Toth*, *H. Nowotny*, *F. Benesovsky*, and *E. Rudy*, Monatsh. Chem. *92*, 956 (1961).

[67] *G. S. Smith*, *Q. Johnson*, and *P. C. Nordine*, Acta Crystallogr. *19*, 668 (1965).

[68] *P. K. Smith* and *P. W. Gilles*, J. Inorg. Nucl. Chem. *29*, 375 (1967).

[69] *B. Post*, *D. Moskowitz*, and *F. W. Glaser*, J. Amer. Chem. Soc. *78*, 1800 (1956).

[70] *I. Binder*, J. Amer. Ceram. Soc. *43*, 287 (1960).

[71] *J. Bauer* and *H. Nowotny*, Monatsh. Chem. *102*, 1129 (1971).

Reactions of Enamines with *N*-Dichloromethylene--*N*,*N*-dimethylammonium Chloride[1]

By *Heinz Günter Viehe, Thérèse van Vyve,* and *Zdenek Janousek*[*]

The highly electrophilic salt *(1)* reacts with enamines *(2)* containing β-hydrogens to give the amide chlorides *(3)*, some examples of which are given in Table 1. Thus *(1)* behaves analogously to phosgene—which produces β-(chlorocarbonyl)enamines *(4)* with *(2)*[2]—and to Vilsmeier reagents[3].

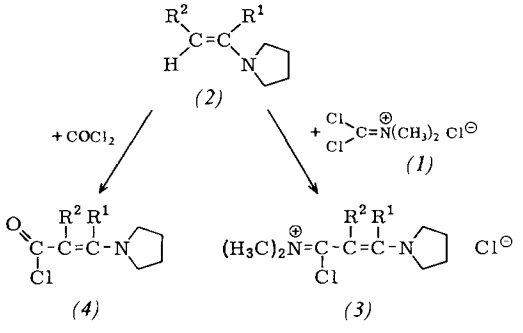
Table 1. Properties of a few compounds of type *(3)*.

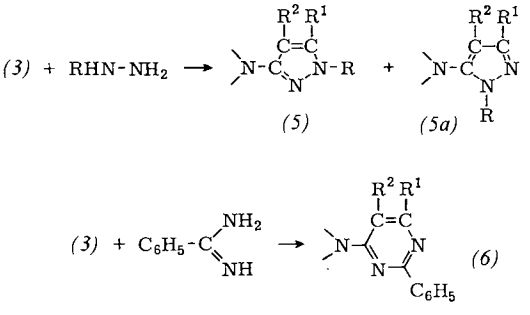
	R^1	R^2	Yield (%)	UV in CH_2Cl_2 (nm)
(3a)	$-(CH_2)_4-$		95	389
(3b)	$-(CH_2)_3-$		90	370
(3c)	H	C_6H_5	92	366
(3d)	$(CH_2)_2$-*o*-C_6H_4-		96	387

Table 2. Properties of a few compounds of type *(7)*. [R^1 and R^2 for *(a)* and *(c)* as in Table 1.]

Cpd.	Yield (%)	B.p. (°C/torr)	IR (cm^{-1})	NMR($CDCl_3$, TMS—O) δ(ppm)
(7a)	60	115–120/0.2	1710, 1640	3.6(1H/m), 2.8(6H/s, 1.6–2.6(8H/br.)
(7c)	92	130/0.1	1730, 1640	10.0(1H/d), 7.4(5H/m), 4.5(1 H/d). 2.9, 3.0(6 H/2s)

Compounds *(3)* react like *(4)* with dinucleophiles such as hydrazine and amidines to give aminopyrazoles *(5)* and *(5a)* or aminopyrimidines *(6)* respectively.



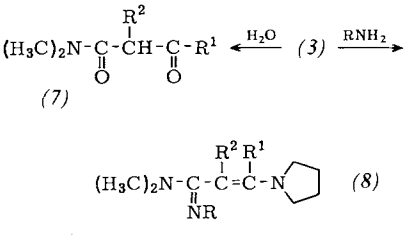


or yellow oil, which in some cases crystallizes (Table 1). Hydrolysis of *(3)* with water yields the corresponding β-ketoamide *(4)*. The enaminoamidines *(8)* are formed by aminolysis in ether.

Table 3. Properties of a few compounds of type *(8)*, $R^1 + R^2 = -(CH_2)_4-$.

R	Yield (%)	B.p. (°C/torr)	NMR($CDCl_3$, TMS = 0) δ(ppm)
H	60	180/1	7.6(1H/s), 2.8(6H/s), 2.4–1.4(16H/br.)
CH_3	65	140/2	2.8(9H/d), 2.4–1.4(14H/m), 3.2(2H/m)
C_6H_5	65	160/0.05	6.8–7.2(5H/m), 3.2(2H/m), 3.0(6H/s), 2.4–1.4(14 H/m)

Hydrolysis of *(3)* affords tertiary β-ketoamides *(7)* (Table 2); aminolysis of *(3)* gives enaminoamidines *(8)* (Table 3).



Synthesis of (3):

1 mole of enamine *(2)* in CH_2Cl_2 solution is added dropwise at 20 °C to a stirred suspension of *(1)* (1 mole) in the same solvent. Stirring is then continued at room temperature until *(1)* is completely dissolved. About two thirds of the solvent are distilled off and an excess of dry ether is added, whereupon the product *(3)* separates as an orange

Cyclization of (3a) with hydrazine:

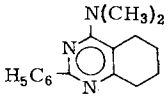
A solution of *(3a)* (9.34 g) in CH_2Cl_2 (50 ml) is added dropwise to a stirred solution of hydrazine dihydrochloride

[*] Prof. Dr. H. G. Viehe, Dipl. Chem. Th. van Vyve, and Dr. Z. Janousek
Laboratoire de Chimie Organique
96, Naamsestraat, B-3000 Louvain (Belgium)

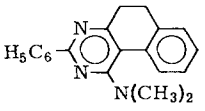
(2.33 g) in CH_2Cl_2 (100 ml). The mixture is boiled under reflux for 5 hours then cooled to 0°C and treated with 15 ml of concentrated KOH. The organic layer is separated, dried over solid K_2CO_3, filtered, and finally evaporated. 3.4 g (60%) of a mixture of *(5)* and *(5a)* is obtained.

Reaction of phenylhydrazine with *(3)* gave analogously a 56% yield of a mixture of isomers *(5)* and *(5a)* in a ratio of about 1:1 (determined by gas chromatography).

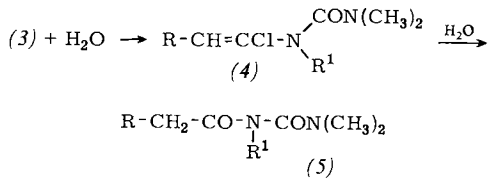
Cyclization of *(3a)* and of *(3d)* with benzamidine gave the pyrimidines *(6a)* and *(6d)* in 37 and 30% yield, respectively.



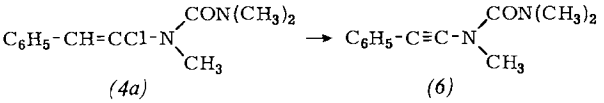
(6a)



(6d)



Compounds *(3)* are generally yellowish stable salts (Table 1) which on hydrolysis first form the *N*-(1-chloroalkenyl)ureas *(4)* and then the *N*-acylureas *(5)*, whereas with hydrogen sulfide the analogous dithio compounds are formed. Compounds *(4)* are of particular interest as starting materials for the hitherto unknown ethynylureas *(6)*. They are formed from *(4)* by treatment with potassium *tert*-butoxide in anhydrous THF. *(6)*, $R = C_6H_5$, is a colorless stable and



(4a) *(6)*

Table 1. Properties of a few compounds of type *(3)*.

	R	R'	Yield (%)	M.p. (°C)	NMR ($CDCl_3$, TMS—O) δ(ppm)
(3a)	C_6H_5	CH_3	97	82–5	3.74(9H/s), 7.47 and 7.80(6H/2mult.)
(3b)	Cl	CH_3	85	154	3.76(3H/s), 3.78(6H/s), 8.11(1H/s)
(3c)	$-(CH_2)_4-$		86	liq.	6.23(1H/t), 4.16(2H/t), 3.78(6H/s), 1.7–2.6(6H/br.)
(3d)	H	CH_3	90	liq.	3.80(6H/s), 3.89(3H/s), 5.90(1H/d), 6.41(1H/d)

The structures of all the new compounds were confirmed IR, NMR, and mass spectrometrically.

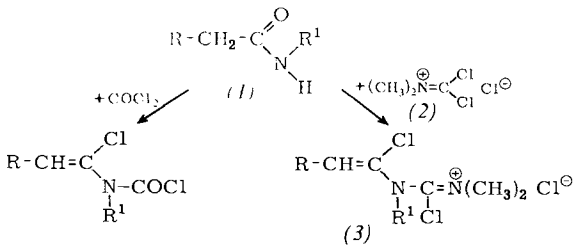
Received: July 6, 1972 [Z 683a IE]
German version: Angew. Chem. *84*, 991 (1972)

[1] Immonium Chemistry, Part 4.–Part 3: *H. G. Viehe, Z. Janousek,* and *M. A. Deffrenne*, Angew. Chem. *83*, 616 (1971); Angew. Chem. internat. Edit. *10*, 575 (1971).
[2] *A. Halleux* and *H. G. Viehe*, J. Chem. Soc. (C) *1970*, 991.
[3] *Y. Ito, S. Katsuragawa, M. Okano,* and *R. Oda*, Tetrahedron *23*, 2159 (1967).

Reaction of Secondary Acetamides with *N*-Dichloromethylene-*N*,*N*-dimethylammonium Chloride[1]

By *Zdenek Janousek, Juliette Collard,* and *Heinz Günter Viehe*[*]

Secondary acetamides of the general formula *(1)* react with phosgeneimmonium chloride similarly as with phosgene itself[2], to give a new class of chloroformamidinium salts *(3)*.



(3)

[*] Dr. Z. Janousek, Miss J. Collard, and Prof. H. G. Viehe
Laboratoire de Chimie Organique, Université de Louvain
96, Naamsestraat, B-3000 Louvain (Belgium)

distillable liquid. Its chemical behavior is similar to that of the recently described *N*-alkynylamides[3].

Synthesis of compounds (3):

1 mole of the acetamide *(1)* and 2 moles of *(2)* are boiled under reflux in chloroform for 30—60 min. The solvent is then evaporated and the residue is washed with anhydrous ether to remove the dimethylcarbamoyl chloride formed as a by-product.

Hydrolysis of (3a) to (4a):

2.5 g of *(3a)* (8.54 mmoles) is added to 10 ml of a stirred suspension of $NaHCO_3$ in water, the resulting mixture being kept about neutral during the addition. After about 5 minutes the mixture is extracted with methylene chloride and the extract is dried over potassium carbonate, filtered, and finally evaporated. Yield: 1.8 g (88.5%) of *(1)*, $R = C_6H_5$, $R^1 = CH_3$.

Hydrolysis of (3a) to (5a):

A solution of *(3a)* [from 10 g (67 mmoles) of *(1a)*] in chloroform (40 ml) is treated with 10 ml of water and an excess of $NaHCO_3$ for a period of 2 hours. The organic layer is separated off and then dried over K_2CO_3. Fractional distillation affords 10.1 g (71%) of *(5a)*, b.p. 135°C/0.2 torr.

Dehydrochlorination of (4a) to (6):

A solution of potassium *tert*-butoxide (0.176 g, 1.55 mmoles) in anhydrous THF (5 ml) is added to a stirred solution of 0.37 g (1.55 mmoles) of *(4a)* in THF (2.5 ml) at room temperature. After 10 minutes, 10 ml of anhydrous ether is added and stirring is continued for 30 minutes. The pre-

cipitate is filtered off and the filtrate is evaporated to remove solvent; the oily residue is distilled at 140 °C/0.4 torr [yield of *(6)*: 0.20 g (64%); colorless stable oil].

Received: July 6, 1972 [Z 683b IE]
German version: Angew. Chem. *84*, 993 (1972)

[1] Immonium Chemistry, Part 5.–Part 4: *H. G. Viehe, Th. van Vyve,* and *Z. Janousek*, Angew. Chem. *84*, 991 (1972). Angew. Chem. internat. Edit. *11*, 916 (1972).

[2] *J. H. Ottenheym* and *J. W. Garritsen*, British Pat. 901 169, *(1962)*; Chem. Abstr. *58*, 6810, *(1963)*; *H. Ulrich*: The Chemistry of Imidoyl Halides. Plenum Press, New York *1968* p. 207.

[3] *H. G. Viehe*, Lecture at the Nottingham Symposium on Acetylenes, July 1971; *E. Goffin* and *Y. Legrand*, Dissertations, Université de Louvain, in preparation.

Synthesis of the First Oxide of Tetrasulfur Tetranitride

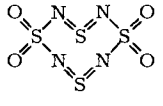
By *Herbert W. Roesky* and *Olaf Petersen*[*]

We reported recently the synthesis of $S_3N_3O_3Cl$, the *S,S,S'*-trioxide of a six-membered sulfur-nitrogen ring[1]. We have now succeeded in isolating the first oxide of the S_4N_4 ring.

N,N'-Bis(trimethylsilyl)sulfur diimide *(1)*[2] reacts with the anhydride of fluorosulfuric acid with cleavage of trimethylfluorosilane and trimethylsilyl fluorosulfate to give $S_4N_4O_4$ *(2)*.

$$2\ (CH_3)_3Si\text{-}N{=}S{=}N\text{-}Si(CH_3)_3 + 2\ FSO_2\text{-}O\text{-}SO_2F \longrightarrow$$

(1)



$$+ 2\ (CH_3)_3SiF + 2\ (CH_3)_3SiOSO_2F$$

(2)

(2) is a yellow solid which sublimes at 80—90 °C under oil-pump vacuum. Decomposition point: 115 to 120 °C. The compound is not formed on reaction of *(1)* with SO_2Cl_2. In the presence of moisture it decomposes with loss of SO_2 and turns brown in color. The given structure follows from complete elemental analysis and the MS and IR data.

The mass spectrum contains the molecular ion at $m/e = 248$ with a relative intensity of only 0.1%. This is accompanied by the following characteristic ions: $m/e = 216$, $S_4N_4O_2$ (16%); 184, S_4N_4 (1%); 170, $S_3N_3O_2$ (13%); 138, S_3N_3 (1%); 124, S_3N_2 (4%); 110, S_3N (1.5%); 92, S_2N_2 (8%); 78, S_2N (14%); 64, SO_2 (17%); 48, SO (16%); 46, NS (100%); 32, S (9%); 28, N_2 (17%).

In the IR spectrum absorptions occur at (cm^{-1}): 1420 (s), 1400 (s), 1328 (vs), 1280 (w), 1218 (m), 1202 (m), 1175 (s), 1137 (vs), 1115 (vs), 1072 (w), 1018 (w), 980 (w), 895 (w), 850 (w), 830 (w), 715 (s), and 704 (s). The bands at 1420 and 1400 cm^{-1} are assigned to asymmetric S=O stretching vibrations.

[*] Prof. Dr. H. W. Roesky and Dipl.-Chem. O. Petersen
Anorganisch-chemisches Institut I der Universität
6 Frankfurt, Robert-Mayer-Strasse 7–9 (Germany)

Experimental:

To a solution of *(1)* (0.1 mol) in CCl_4 (200 ml) in a 500-ml two-necked flask fitted with dropping funnel is added dropwise over 3h a solution of $F_2S_2O_5$ (0.1 mol) in CCl_4 (100 ml). The mixture is then boiled under reflux for 4h and the solvent and volatile products subsequently removed by evaporation and condensation into a trap under vacuum. The residue remaining in the flask is sublimed under oil-pump vacuum. Four sublimations are required for complete purification of the product. Yield 2.5 g (5%).

Received: July 18, 1972 [Z 685 IE]
German version: Angew. Chem. *84*, 946 (1972)

[1] *H. W. Roesky*, Angew. Chem. *83*, 253 (1971); Angew. Chem. internat. Edit. *10*, 266 (1971).

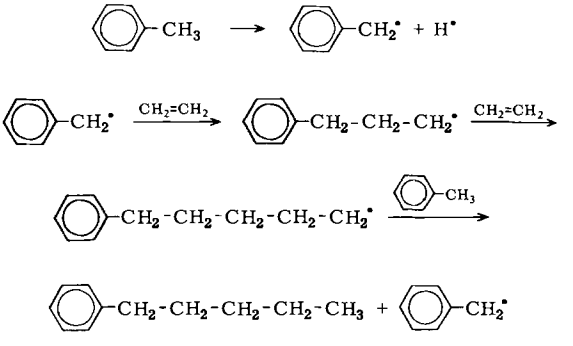
[2] *U. Wannagat* and *H. Kuckertz*, Angew. Chem. *74*, 117 (1962); Angew. Chem. internat. Edit. *1*, 113 (1962).

Side-Chain Alkylation of Toluene with Ethylene[1]

By *Ernst Oltay*, *Johannes M. L. Penninger*, and *Hendrik Maatman*[*]

In the presence of metallic Na or K as a catalyst, with or without promoter, the three hydrogen atoms of the methyl group in toluene can be stepwise alkylated with ethylene, the most highly alkylated product formed being 3-ethyl-3-phenylpentane[2–4]. In the presence of butyl-Li and a di-tertiary amine, toluene reacts with ethylene to give a straight-chain homologous series[5, 6].

We have found that toluene reacts with ethylene in the absence of a catalyst even at as low a temperature as ≈ 400 °C and a pressure of 50 atm to give alkylbenzenes having straight alkyl chains (for instance, *n*-propylbenzene and *n*-pentylbenzene). The reaction proceeds *via* free radicals.



Compounds yielding benzyl radicals catalyze the reaction. Thus the conversion of toluene and the selectivity of the side-chain alkylation to give straight-chain alkylbenzenes are favored by addition of benzyl chloride and benzyl bromide (Table 1).

All compounds were isolated by preparative gas chromatography and identified by NMR, IR, and MS, as well as by their gas-chromatographic retention times. The new reaction is of general applicability.

[*] Prof. Dr. E. Oltay, Dr. ir. J. M. L. Penninger, and H. Maatman
Technische Hochschule Twente, Laboratory for Industrial Chemistry
Enschede, Postbus 217 (Netherlands)

Table 1. Side-chain alkylation of toluene with ethylene. Cr-Ni-Mo steel autoclave (314 cm^3), 20 g (217 mmol) toluene, 7 g (250 mmol) ethylene, 380 °C, 55 atm, 2 h.

$C_6H_5CH_2Br$ [wt.-%]	Toluene conversion [%]	Yield [mol-%] *n*-propyl-benzene	*n*-pentyl-benzene	all straight chain alkyl-benzenes
—	10.6	32.7	12.4	45.1
0.1	13.3	42.1	25.1	67.2
0.5 [7]	19.3	56.7	25.5	82.2
1.0	24.0	60.9	14.5	75.4

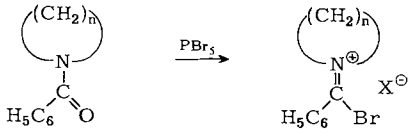
Received: July 17, 1972 [Z 686 IE]
German version: Angew. Chem. *84*, 947 (1972)

[1] Side-Chain Alkylation of Alkylbenzenes with Olefins, Part 1.
[2] *H. Pines, J. A. Vesely*, and *V. N. Ipatieff*, J. Amer. Chem. Soc. *77*, 554 (1955); *H. Pines* and *V. N. Ipatieff*, US-Pat. 2721887 (1955).
[3] *St. E. Voltz*, J. Org. Chem. *22*, 48 (1957).
[4] *J. P. Napolitano* and *R. D. Clossen*, US-Pat. 3449455 (1969).
[5] *G. G. Eberhardt*, Belg. Pat. 633482 (1963).
[6] *G. G. Eberhardt* and *W. A. Butte*, J. Org. Chem. *29*, 2928 (1964).
[7] We obtained almost identical results with an equivalent amount of benzyl chloride.

The Mechanism of the Bischler-Napieralski Reaction[1]

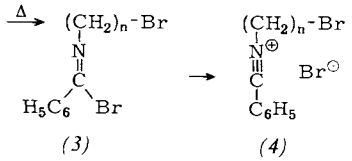
By *Gábor Fodor, J. Gal*, and *B. A. Phillips*[*]

The fragmentation of cyclic benzamides of type *(1)* upon the action of phosphorus pentabromide[2] leads to α, ω-dibromoalkanes and benzonitrile. Our recent studies have revealed that the first step of this reaction is in fact the formation of the α-bromoiminium tribromide *(2a)* which can be isolated[3] in more than 90% yield. Reduction of this compound with an olefin (*e.g.* cyclohexene) results in the quantitative formation of the monobromide *(2b)*[4]. Mild heating of *(2b)* gave the *N*-(ω-bromoalkyl)imidoyl bromide (with $n = 5$) which was also synthesized *via* its hydrobromide from *N*-(5-bromoamyl)benzamide and carbonyl bromide[4] (or phosphorus pentabromide) followed by reduction of Br_3^- to Br^-, and mild heating.



(1)

(2a), X = $Br_3^{\ominus}$
(2b), X = $Br^{\ominus}$

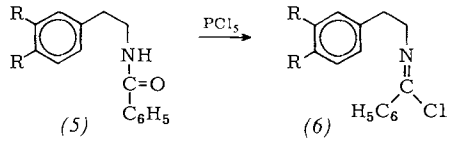


(3) *(4)*

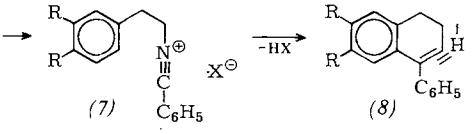
Imidoyl bromides—unlike imidoyl chlorides[5]—have not been previously known in pure form. We have found that imidoyl bromides equilibrate with nitrilium bromides *(4)* and hence are the intermediates which occur after the bromoiminium bromide in the degradation of the amide *(1)*[6].

[*] Prof. Dr. G. Fodor, Dr. J. Gal, and B. A. Phillips
Department of Chemistry, West Virginia University
Morgantown, West Virginia 26506 (USA)

However, if unlike in the amide degradation there is an internal nucleophile present, it should react with the carbon of the nitrilium group. This is the case in the Bischler-Napieralski ring closure reaction of *N*-acyl-2-arylethylamines *(5)* under the influence of P_2O_5, $POCl_3$ or $ZnCl_2$ to give the 3,4-dihydroisoquinolines *(8)*. To prove this we have converted *N*-[2-(3,4-dimethoxyphenyl)-ethyl]benzamide *(5a)* at room temperature with phosphorus pentachloride in CCl_4 into the crystalline hydrochloride of the benzimidoyl chloride *(6a)* (80% yield). This salt loses hydrogen chloride slowly at room temperature (more rapidly at 85 °C) and gives quantitatively the cyclized product, *i.e.* 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline hydrochloride *(8a)*.



(5) *(6)*



(7) *(8)*

(a), R = CH_3O
(b), R = H

The reaction can be followed with NMR using $CDCl_3$ as solvent: *(6a)* shows a singlet at 3.82 ppm for the six methoxy protons which is converted to two singlets at 3.80 and 4.09 ppm as the cyclization to *(8a)* proceeds. The aromatic region is also informative in that the original peak at 6.82 ppm integrating for three protons changes to two singlets at 6.94 and 7.13 ppm which integrate for one proton each.

Addition of a Lewis acid ($ZnCl_2$, $SnCl_4$, *etc.*) enhanced the rate of cyclization. This could be explained through a push-pull displacement of chlorine from the imide carbon in *(6)* by the nucleophilic arene carbon, synchronously with attack of the Lewis acid upon the chloride ion. Alternatively, one can suppose intermediary formation of the nitrilium ion *(7a)*, which could then react very fast[7] with the aromatic carbon.

In order to slow down the cyclization, and detect the nitrilium ion, *N*-(2-phenylethyl)benzamide *(5b)* was converted into the crystalline imidoyl chloride hydrochloride[8] and then into the base *(6b)*, which was distilled at 132 °C/0.045 torr. If stannic chloride is added to a solution of *(6b)* in a NMR tube, the triplet at 4.02 ppm of the methylene adjacent to nitrogen disappears and a new CH_2 triplet appears at 4.68 ppm, indicating nitrilium ion *(7b)* formation. Upon standing at 25 °C this triplet is slowly (faster upon heating) displaced to 4.20 ppm, which is the chemical shift of the methylene protons at C-3 in the hydrochloride of the 3,4-dihydroisoquinoline *(8b)*. Moreover, the *N*-(2-phenylethyl)benzonitrilium ion could also be trapped as the crystalline hexafluoroantimonate. It reacts subsequently in solution to give the dihydroisoquinolinium hexafluoroantimonate.

N-(2-Phenylethyl)benzonitrilium complexes have previously been obtained from a metal halide complex of the nitrile and 2-phenylethyl chloride[9], reminiscent of the Ritter reaction[10]. The product was also cyclized into the

isoquinoline[9]; previously, however, nitrilium salts have not been trapped, let alone suggested as intermediates in the Bischler-type cyclization reaction. The results of our investigation explain why certain phenylethylamines gave under forcing conditions, but in absence of an appropriate Lewis acid, a nitrile besides an olefin[11]. Actually, these were von Braun products arising from decomposition of the imidoyl chloride at relatively high temperatures. This failure of the Bischler cyclization is partly due to the weak nucleophilicity of the aromatic *ortho* carbon, as well as to the inability of phosphorus oxychloride to form a stable complex anion.

Nitrilium ions, however, cannot be formed as intermediates, in the cyclization of *N*-alkyl-*N*-(2-phenylethyl)-amides *via* chloroiminium chloride, to the quaternary isoquinolinium salt. In this case the nucleophilic displacement of the chlorine atom is the only reasonable pathway.

The knowledge of this mechanism now enables us to carry out the Bischler-Napieralski reaction in high yields—at 20—80 °C depending on substituents in the arene, instead of refluxing with $POCl_3$ in high-boiling solvents. The two-step process of isolating the imidoyl chloride and cyclizing the nitrilium salt nevertheless gives an appreciable improvement in yields even in the case of "unactivated" aromatic rings. Therefore, we think that the long list[12] of amides which have failed to undergo dihydroisoquinoline ring closure will be appreciably shortened when using this improved technique.

We feel that the system

imidoyl halide$\rightleftharpoons$nitrilium salt

can make smooth ring closure possible in other fields, *e.g.* in the synthesis of 4-quinolones from 2-amino-*N*-aryl-acrylamides, or of complex fused heterocycles. Furthermore, correlation of the mechanism of the von Pechmann and von Braun amide degradations with the Bischler-Napieralski and the Ritter reactions will probably lead to a better understanding and improvement of the Vilsmeier aldehyde and the Hoesch ketone syntheses when generating nitrilium salts as reactive intermediates.

Received: July 17, 1972 [Z 687 IE]
German version: Angew. Chem. *84*, 947 (1972)

[1] Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society for support of this work and also to the Research Corporation.

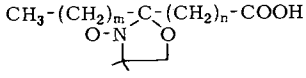
[2] *J. v. Braun*, Ber. Dtsch. Chem. Ges. *37*, 2915 (1904); *H. v. Pechmann, ibid. 33*, 611 (1900).
[3] *B. A. Phillips* and *G. Fodor*, 162nd ACS National Meeting, Washington 1971, Paper ORGN 019.
[4] *B. A. Phillips*, Dissertation, West Virginia University 1972.
[5] *H. Ulrich*: The Chemistry of Imidoyl Halides. Plenum Press, New York 1968.
[6] *J. Gal, B. A. Phillips*, and *R. Smith*, Can. J. Chem., in press.
[7] *I. Ugi, F. Beck*, and *V. Fetzer*, Chem. Ber. *95*, 125 (1962) found an initial first-order kinetics in the hydrolysis of imidoyl chlorides which they ascribed to the formation of a nitrilium ion in the rate-determining step.
[8] According to *H. Decker* and *W. Kropp*, Ber. Dtsch. Chem. Ges. *42*, 2075 (1909), so-called unactivated phenylethylamides cyclize under the action of phosphorus pentachloride and (subsequently) of aluminum chloride. Furthermore, *H. J. Barber et al.*, J. Soc. Chem. Ind. *69*, 82 (1950) isolated an imidoyl chloride during the synthesis of phenylanthridines.
[9] *M. Lora-Tamayo* and *R. Madronero et al.*, Chem. Ber. *94*, 199 (1961).
[10] *J. J. Ritter* and *P. P. Minieri*, J. Amer. Chem. Soc. *70*, 4045, 4048 (1948).
[11] *A. McCoubrey* and *D. W. Mathieson*, J. Chem. Soc. *1949*, 696; *A. J. Hill* and *W. M. Holliday*, ACS National Meeting, Chicago 1950, Paper 58 N.
[12] *W. M. Whaley* and *T. R. Govindachari*, Org. Reactions *6*, 74 (1951).

Folding of Fatty Acid Chains in Liquid Crystalline Bilayers

By *Hugo Limacher* and *Joachim Seelig*[*][**]

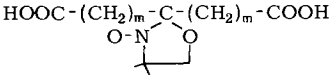
Spin label studies have shown that several types of motion can occur in lipid bilayers: exchange of molecules between the half-layers[1], lateral diffusion of molecules within the half-layers[2], rigid body rotation of hydrocarbon chains around their long molecular axes[3–5], the rapid isomerization of carbon-carbon bonds between *trans* and *gauche* conformations[4–7].

Here we wish to compare two different methods, both employing spin labels, for measuring the energy difference, E_σ, between *trans* and *gauche* conformations of hydrocarbon chains in bilayers. In our model both the intramolecular bond rotation potential and interactions between adjacent hydrocarbon chains contribute to E_σ. Since the *intra*molecular bond rotation potential is known from several sources (*e.g.* studies of macromolecules in solution[8]), it is possible to extract information about the *inter*molecular interactions in bilayers from measurements of E_σ.



(1), n = 2-12

In our first approach, which has been described previously[4, 6], we measured the order parameter S_3 for spin labeled stearic acids *(1)* in two different liquid crystalline bilayers. The carboxyl group of the spin label is fixed at the lipid-water interface and the order parameter decreases continuously as the label group is translated along the chain towards the center of the bilayer. A plot of log S_3 *versus* the distance of the label group from the bilayer surface yields straight lines in the central part of the bilayers. The slope of the plot measures the chain flexibility in the liquid crystalline phase. Applying a linear Ising model to these data, one can easily obtain values for E_σ[6]. The composition of the liquid crystalline bilayers[9] and the corresponding results for E_σ are listed in Table 1 (fourth row). A more direct way of measuring E_σ results on use of spin labels of type *(2)*[10]. The chain length is selected to be nearly the same as the thickness of the bilayer[10]. An



(2), m = 6, 7

equilibrium then exists between folded (B) and extended configurations (A) of the hydrocarbon chains, as illustrated in Figure 1. In the folded form B both carboxyl groups

[*] Dipl.-Phys. H. Limacher and Priv.-Doz. Dr. J. Seelig [***]
Biozentrum, Universität Basel
Klingelbergstrasse 70, CH-4056 Basel (Switzerland)

[**] We are much indebted to Dr. *C. J. Scandella* for critically reading the manuscript and for making valuable comments.

[***] To whom correspondence should be addressed.

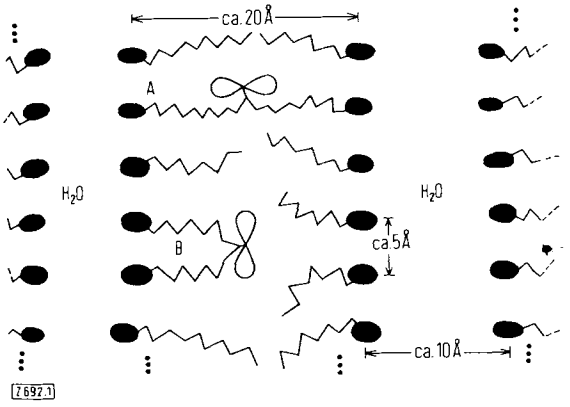


Fig. 1. Schematic diagram of the spin label orientation within the bilayer.

are on the same side of the bilayer, whereas in the extended form A the polar groups are on opposite sides of the bilayer. In homogeneously oriented samples of liquid crystals the EPR signals arising from the two different configurations are well resolved[10], so that the relative concentrations of A and B can be obtained directly from the resonance spectra. From these concentrations one can evaluate the equilibrium constant K of the transition $A \rightleftarrows B$. We have measured the temperature dependence of this equilibrium constant for two labels of type *(2)* in the liquid crystalline bilayers mentioned above. Increasing temperature shifts the equilibrium towards the folded

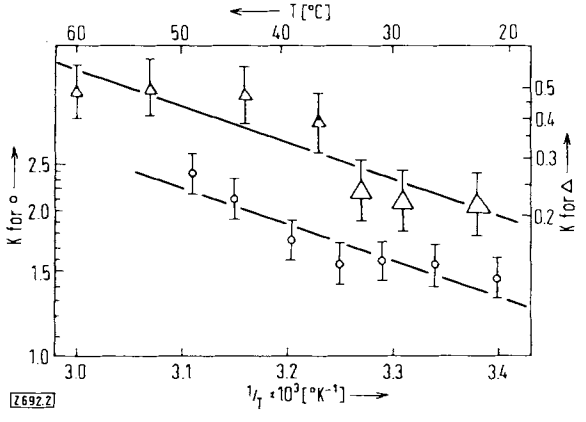


Fig. 2. Temperature dependence of the equilibrium constant K on a logarithmic scale. – ○, spin label *(2)*, $m = 6$; △, spin label *(2)*, $m = 7$.

configuration (Fig. 2). The slope of the straight line affords the reaction enthalpy ΔH (Table 1, first row). In the notation of the rotational isomeric model[8] the transition from the extended to the folded configuration can be written as

$$t\,t\,t\,t\,t\,t\,t \rightarrow t\,g\,g\,t\,g\,g\,t$$

(t and g denote the *trans* and *gauche* rotational states, respectively. All *gauche* conformations must exhibit the same angular rotation, *i.e.* either $+120°$ or $-120°$). The equilibrium constant K can be expressed in terms of the statistical probabilities p of the two configurations. One can easily show, using the linear Ising model, that

$$K = p_{tggtggt}/p_{ttttttt} = \sigma^4 \qquad (1)$$

where

$$\sigma = \exp(-E_\sigma/RT)\,. \qquad (2)$$

To a first approximation E_σ can be assumed to be temperature independent. Then

$$(\partial \ln K/\partial T) = \Delta H/RT^2 = 4(\partial \ln \sigma/\partial T) = 4E_\sigma/RT^2 \qquad (3)$$

and

$$E_\sigma = \Delta H/4\,. \qquad (4)$$

The third row in Table 1 lists the values of E_σ calculated from ΔH using eq. (4). These values are in good agreement with the values of E_σ obtained by our first method. Subtracting the internal rotation potential[8] $E_{rot} \approx 500$—700 cal mol^{-1} from E_σ yields the intermolecular energy contribution ΔW to the flexibility of the fatty acid chains (Table 1, fifth row).

ΔW can be interpreted as the energy required per CH_2 unit to overcome at least partially the van der Waals attraction between parallel chain segments. For monomolecular layers of stearic acid with a perfectly parallel arrangement of the hydrocarbon chains an interaction energy of -470 cal mol^{-1} per CH_2 unit has been calculated[11]. The melting behavior of polyethylene can be described reasonably well with an interaction energy of -680 cal mol^{-1} per CH_2 unit[12]. Our experimental results for liquid crystalline bilayers are consistent with these atomistic calculations.

The entropy ΔS of the folding process can also be determined from K and ΔH. The positive ΔS values (Table 1, second row) show that the transition from the extended to the folded form substantially increases the disorder of the system.

Table 1. Thermodynamic parameters for folding of fatty acids in liquid crystalline bilayers.

	Label *(2)*, $m = 6$, in sodium caprylate 35 wt.-% caprylic acid 35 wt.-% water 30 wt.-%	Label *(2)*, $m = 7$, in sodium caprylate 28 wt.-% decanol 42 wt.-% water 30 wt.-%
ΔH [cal mol^{-1}]	3230	5190
ΔS [e.u.] at 25 °C	*ca.* 11.6	*ca.* 14.5
E_σ [cal mol^{-1}]	810	1290
E_σ [cal mol^{-1}] determined with label *(1)*	820	1200
ΔW [cal mol^{-1}]	100–300	500–700

It seems that spin labels of type *(2)* might be used as rulers to measure the thickness of bilayer membranes, including biological membranes with bilayer structure. A label long enough to pass easily through the bilayer will be in the extended form, while a label too short to span the bilayer will be in the folded form. Only spin labels whose length is comparable with the bilayer thickness will exhibit resonance spectra representing both configurations.

Received: July 24, 1972 [Z 692 IE]
German version: Chem. *84*, 950 (1972)

[1] *R. D. Kornberg* and *H. M. McConnell*, Biochemistry *10*, 1111 (1971).
[2] *R. D. Kornberg* and *H. M. McConnell*, Proc. Nat. Acad. Sci. USA *68*, 2564 (1971); *P. Deveaux* and *H. M. McConnell*, J. Amer. Soc. *94*, 4475 (1972); *E. Sackmann* and *H. Träuble*, *ibid. 94*, 4482, 4492, 4499 (1972); *C. J. Scandella*, *P. Deveaux*, and *H. M. McConnell*, Proc. Nat. Acad. Sci. USA, in press.
[3] *W. L. Hubbell* and *H. M. McConnell*, Proc. Nat. Acad. Sci. USA *64*, 20 (1969).
[4] *J. Seelig*, J. Amer. Chem. Soc. *92*, 3381 (1970).
[5] *W. L. Hubbell* and *H. M. McConnell*, J. Amer. Chem. Soc. *93*, 314 (1971); *P. Jost*, *L. J. Libertini*, *V. C. Hebert*, and *O. H. Griffith*, J. Mol. Biol. *59*, 77 (1971).
[6] *J. Seelig*, J. Amer. Soc. *93*, 5017 (1971).
[7] *B. G. McFarland* and *H. M. McConnell*, Proc. Nat. Acad. Sci. USA, *68*, 1274 (1971).
[8] *P. J. Flory*: Statistical Mechanics of Chain Molecules. Interscience, New York 1969.
[9] *P. Eckwall*, *L. Mandell*, and *K. Fontell* in *G. H. Brown*: Liquid Crystals. Gordon and Breach, New York 1969, part II, p. 325.
[10] *J. Seelig*, *H. Limacher*, and *P. Bader*, J. Amer. Chem. Soc., in press.
[11] *L. Salem*, J. Chem. Phys. *37*, 2100 (1962).
[12] *E. Schrader* and *H. G. Zachmann*, Ber. Bunsenges. Physik. Chem. *73*, 823 (1970); *C. W. Bunn*, J. Polymer Sci. *16*, 323 (1955).

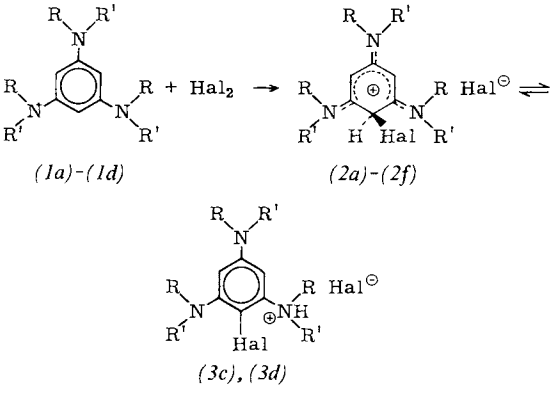
σ-Complexes in Halogenation of Aminobenzenes—Isolation and Secondary Reactions[1]

By *Peter Menzel* and *Franz Effenberger*[*]

σ-Complex intermediates in electrophilic aromatic substitution have so far been established only for protonation and alkylation[2, 2a]. Due to exceptional mesomeric stabilization, they can be isolated in the case of protonation and alkylation of 1,3,5-tripyrrolidinobenzene[3a, b].

The primary isotope effect found in bromination of 1,3,5-tri-*tert*-butylbenzene[4] and the observation that bromination of *N*,*N*-dialkylanilines is reversible even below 100 °C[5] clearly indicate long-lived halo σ-complex intermediates in these cases. Steric factors are held responsible for the additional stabilization in the first instance, electronic influences in the second example. The intermediate identified NMR-spectroscopically for the bromination of 2-hydroxynaphthalene-6,8-disulfonic acid, however, is no σ-complex but rather the tautomeric quinonoid form[6]; corresponding quinonoid intermediates have been isolated from the bromination of sterically hindered phenols[7].

If bromine is added to tris(dialkylamino)benzenes *(1)* in dry chloroform at −60 °C, deep-red colored solutions are formed from which the dark-red σ-complexes may be precipitated by addition of ether. While *(2a)* and *(2b)* are stable for some time at ambient temperature, *(2c)* and *(2d)* rearrange to give the *N*-protonated aminobromobenzenes *(3c)* and *(3d)* respectively. When the aminobenzenes *(1)* are chlorinated with sulfuryl chloride or chlorine under like conditions, *(2e)* is obtained in crystalline form; *(2f)*



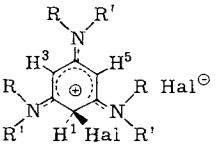
(1a)-(1d) *(2a)-(2f)*

(3c), (3d)

	R	R'	Hal
(a)	—$(CH_2)_4$—		Br
(b)	CH_3	CH_3	Br
(c)	—$(CH_2)_5$—		Br
(d)	—$(CH_2)_2$—O—$(CH_2)_2$—		Br
(e)	—$(CH_2)_4$—		Cl
(f)	CH_3	CH_3	Cl

can be detected by NMR spectroscopy but may be isolated only with the less nucleophilic tetrafluoroborate as gegenion. By anion exchange with $AgBF_4$, all the halides *(2a)* to *(2f)* are converted to the tetrafluoroborates, which, as expected, are more stable, and thus better suited for further investigations. The structure of the σ-complexes *(2)* has been unequivocally established both by chemical reactions and spectroscopically; some characteristic NMR and UV data are given in Table 1.

Table 1. ^{1}H-NMR and UV-spectroscopic data of halogen σ-complexes *(2a)* to *(2f)*.



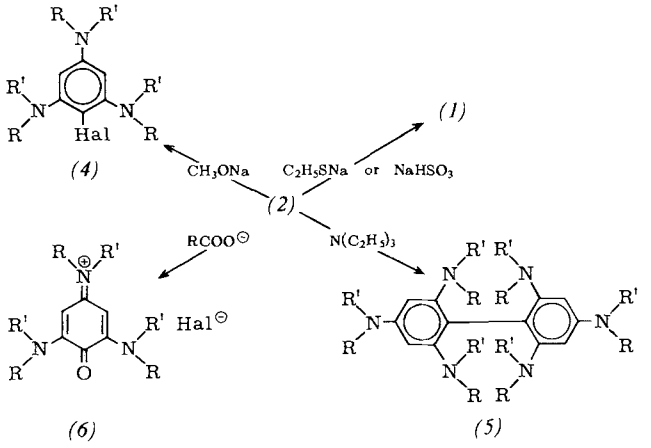
	^{1}H-NMR data [a] H^1	$H^{3,5}$	UV absorption bands (in $CHCl_3$) λ_{max} [nm] (ε)
(2a)	6.12	4.8	250 (16200), 360 (14300), 490 (4600)
(2b)	5.78	4.99	250 (12900), 355 (10500), 484 (3600)
(2c)	5.92	5.28	256 (13900), 368 (9300), 488 (3000) [b]
(2d)	6.44	5.61	250 (18800), 365 (14200), 488 (5500) [b]
(2e)	6.13	4.79	250 (13200), 348 (13900), 466 (6100)
(2f)	5.88	5.01	

[a] δ values (ppm) relative to TMS als internal standard. Solution: 0.5 M in $CDCl_3$.
[b] UV spectrum of the tetrafluoroborate.

The σ-complexes formed as intermediates in normal arene halogenation suffer immediate deprotonation. Since we isolate the σ-complexes *(2)* in crystalline form, the secondary reactions can be directed along different routes. Deprotonation to give the halobenzenes *(4)* is the course taken with strong bases while highly nucleophilic or reducing agents cleave off a halogen cation thus re-forming *(1)*. Tertiary amines produce the biphenyls *(5)* from *(2a)* and *(2b)*, most likely *via* radical intermediates. These biphenyls are also formed when *(1)* is treated with iodine or iodine chloride under the reaction conditions described. From

[*] Dr. P. Menzel and Prof. Dr. F. Effenberger
Institut für Organische Chemie der Universität
7000 Stuttgart 1, Azenbergstr. 14—18 (Germany)

the reaction of *(2)* with carboxylate ions, quinone iminium salts *(6)* are isolated besides *(1)*. We have ascertained that these compounds do not arise from interaction with atmo-



spheric oxygen. However, as to whether highly reactive cyclohexadienylium dications are precursors for the formation of *(6)* or whether the σ-complexes *(2)* are oxidized to *(6)* by carbonic acid hypohalites that are formed as intermediates, has yet to be investigated.

Received: July 31, 1972 [Z 695 IE]
German version: Angew. Chem. *84*, 954 (1972)

[1] Electrophilic Substitution of Aromatic Compounds, Part 6.—Part 5: *P. Fischer, W. Kurtz*, and *F. Effenberger*, Chem. Ber., in print.—For support of this work, we are indebted to the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft. We also thank *W. Kinza, K. Hermann*, and *G. Pilidis* for some of the experiments.

[2] *G. A. Olah, R. H. Schlossberg, R. D. Porter, Y. K. Mo, D. P. Kelly*, and *G. D. Meteescu*, J. Amer. Chem. Soc. *94*, 2034 (1972) and literature cited therein.

[2a] Note added in proof: *Olah et al.* [J. Amer. Chem. Soc. *94*, 3667 (1972)] now report the detection by NMR of σ-complexes for nitration and chlorination of persubstituted benzenes where follow-up reaction to give the substitution product is not possible.

[3] (a) *F. Effenberger* and *R. Niess*, Angew. Chem. *79*, 1100 (1967); Angew. Chem. internat. Edit. *6*, 1067 (1967); (b) *R. Niess, K. Nagel*, and *F. Effenberger*, Tetrahedron Lett. *1968*, 4265.

[4] *P. C. Myhre*, Acta Chem. Scand. *14*, 219 (1960).

[5] *F. Effenberger* and *P. Menzel*, Angew. Chem. *83*, 535 (1971); Angew. Chem. internat. Edit. *10*, 493 (1971).

[6] *M. Christen* and *H. Zollinger*, Helv. Chim. Acta *45*, 2057 (1962).

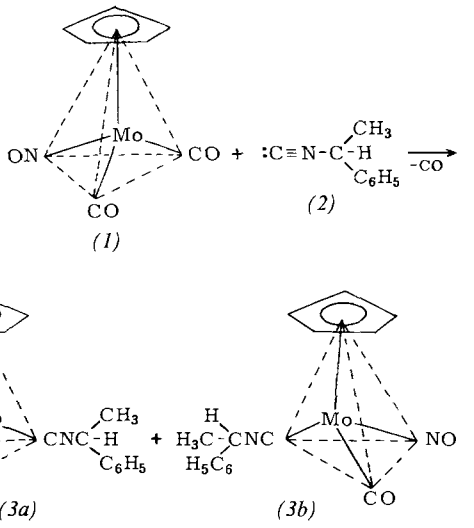
[7] *V. V. Ershov* and *A. A. Volod'kin*, Bull. Acad. Sci. USSR Div. Chem. Sci. *1962*, 680; Chem. Abstr. *57*, 12337c (1962).

Walden Inversion at an Asymmetric Molybdenum Atom[1]

By *Henri Brunner* and *Marta Lappus*[*]

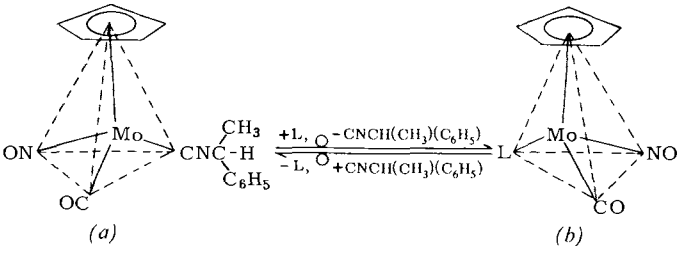
The isocyanide ligand in the molybdenum complex *(3)* can be replaced by nucleophiles. We have shown that these reactions occur with inversion of configuration at the asymmetric Mo atom.

On reaction of *(1)* with the optically active isocyanide *(2)*[2], $[\alpha]_{589}^{25} = +40°$ (pure liquid), in the molar ratio 1:1, the diastereoisomeric replacement products *(3a)*, $[\alpha]_{589}^{25} = +275°$, and *(3b)* $[\alpha]_{589}^{25} = -365°$, are formed,



and they can be separated by fractional crystallization from benzene/pentane. The rotations given are reached after 20 recrystallizations. *(3a)* and *(3b)* are configurationally stable in the solid state and in benzene solution (up to +50 °C)[3].

If the isocyanide *(2)* is added to a 10^{-2} M solution of *(3a)* in benzene in the molar ratio 1:1, the rotation falls to values near 0° within about 2 h at room temperature. This loss of optical activity is to be ascribed to back-side attack by *(2)* on the complex *(3a)*. It results in an equilibrium between *(3a)* and *(3b)* that, like *(2)*, shows only very low optical rotation.



$C_5H_5MO(CO)(NO)L$	*(3a), (3b)*	*(4a), (4b)*	*(5a), (5b)*
L	$(+)_{589}$-CNCH(CH$_3$)(C$_6$H$_5$)	CNC$_6$H$_{11}$	P(C$_2$H$_5$)$_3$

If the more nucleophilic cyclohexyl isocyanide is used, the decrease of rotation is complete in only about 1.5 h under similar conditions. If in this case a three-fold excess of cyclohexyl isocyanide is used and the reaction is stopped after about 10 min, chromatographic working up gives a mixture in which *(4b)* predominates but which also contains *(4a)* and, according to ^{1}H-NMR analyses, 10 to 20% of *(3a)*, *(3b)*.

Table 1. Specific rotations of *(3a)*, *(4b)* [a] and *(5b)* in benzene solution (*ca.* 10^{-3} M solution).

	(3a)	*(4b)* [a]	*(5b)*
$[\alpha]_{589}^{25}$ (°)	+220	−37	−205
$[\alpha]_{579}^{25}$ (°)	+270	−44	−235
$[\alpha]_{546}^{25}$ (°)	+350	−60	−215
$[\alpha]_{436}^{25}$ (°)	−330	− 8	+190
$[\alpha]_{365}^{25}$ (°)	−475	+27	+615

[a] In admixture with *(4a)*, *(3a)*, and *(3b)* [see text].

[*] Prof. Dr. H. Brunner and Dipl.-Chem. M. Lappus
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

The opposite signs of the rotatory values of the comparable isocyanide complexes *(3a)* and *(4b)* (Table 1) prove the inversion of configuration on reaction of *(3a)* with CNC_6H_{11} as our investigations up to now have shown that small changes on the ligands do not influence the optical rotations and CD spectra of these compounds appreciably.

Treatment of *(3a)* with $P(C_2H_5)_3$ in benzene for 2h at room temperature gives the complex *(5b)*, which can be isolated in 50% yield by chromatography on Al_2O_3. Table 1 contains the rotatory values at different wave lengths. The CD spectra of *(3a)* and *(5b)* are opposite to each other. In this case also, the nucleophile probably attacks the complex at the back-side, thus replacing the isocyanide ligand with Walden inversion.

(5b) is configurationally stable in solution, but racemizes slowly in the presence of $P(C_2H_5)_3$. This racemization is also to be ascribed to rear attack by the nucleophile on the complex; it occurs considerably more slowly than the reaction of *(3a)* with $P(C_2H_5)_3$. Since however this reaction cannot be wholly excluded it leads to reduction in the optical purity of *(5b)*, although to a considerably smaller extent than during reaction of *(3a)* with cyclohexyl isocyanide.

Received: July 28, 1972 [Z 6961E]
German version: Angew. Chem. *84*, 955 (1972)

[1] Part 14 of Optically Active Transition Metal Complexes. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 13: *H. Brunner* and *W. A. Herrmann*, Chem. Ber., in the press.

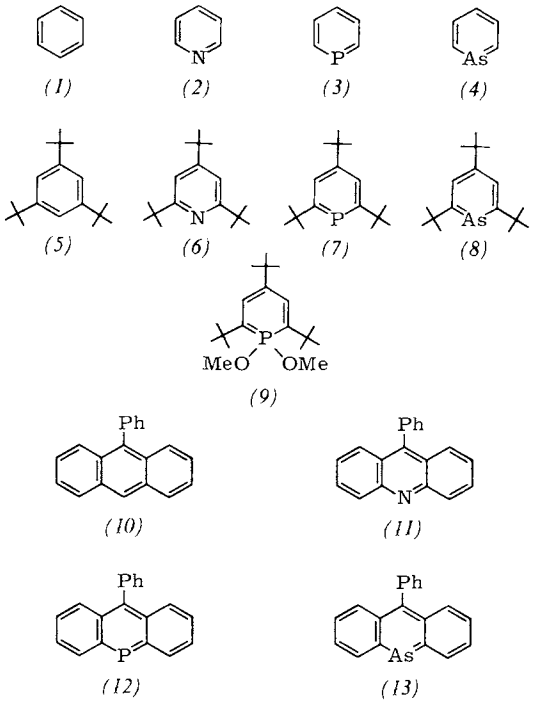
[2] *H. Brunner* and *M. Vogel*, J. Organometal. Chem. *35*, 169 (1972).

[3] *H. Brunner, H.-D. Schindler, E. Schmidt*, and *M. Vogel*, J. Organometal. Chem. *24*, 515 (1970).

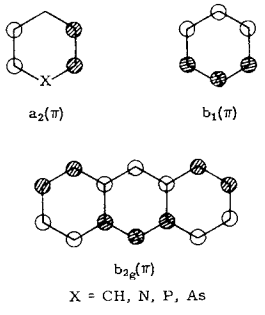
Photoelectron Spectroscopy and Conjugation—Direct Proof of the Unusual Sequence of the Two Highest Occupied π-Molecular Orbitals in the Phosphorin (Phosphabenzene) and the Arsenin (Arsabenzene) System[1]

By *Werner Schäfer, Armin Schweig, Friedrich Bickelhaupt*, and *Hans Vermeer*[*]

In 1970 we found[2] by approximate quantum chemical calculations[3] for phosphorin *(3)* the unusual sequence of the two highest occupied π-molecular orbitals: $b_1(\pi)$ as HOMO ("highest occupied MO") before $a_2(\pi)$ (*i.e.* π-MO with non-zero coefficient on the heteroatom energy-richer than the π-MO with the node; cf. representation of the two MO's), this contrasting with the situation for pyridine *(2)*. In two later papers[4, 5] we were able, by comparative photoelectron (PE) spectroscopic studies on 2,4,6-tri-*tert*-butylpyridine *(6)*[6], 2,4,6-tri-*tert*-butylphosphorin *(7)*[6] and 2,4,6-tri-*tert*-butyl-1,1-dimethoxyphosphorin *(9)*[7], to render this hitherto unique heterocyclic MO sequence very probable. We now record here, on the basis of PE spectra of 9-phenylanthracene *(10)*, 9-phenylacridine *(11)*, 10-phenyldibenzo[*b*,*e*]phosphorin (10-phenyl-9-phosphaanthracene) *(12)*[8] and 10-phenyldibenzo[*b*,*e*]arsenin (10-phenyl-9-arsaanthracene) *(13)*[9], an unambiguous proof of the correctness of the sequence proposed for the phosphorin *(3)*[10, 11] and we extend our considerations and conclusions to the arsenin *(4)*[10, 11].



The six-membered ring systems *(1)* to *(9)* suffer from two main disadvantages for proof of reversal in the MO sequence on changing from the azabenzenes *(2)* and *(6)* to the phospha- and arsa-benzenes *(3)*, *(4)* and *(7)* to *(9)*: 1. The two initial MO's $e_{1g}(\pi)$ in *(1)* and $e''(\pi)$ in *(5)* are degenerate, and 2. lacking experience with the new types of system, we do not know *a priori* how the orbital energies of the MO's $b_1(\pi)$ and $a_2(\pi)$ alter under the influence of the phosphorus and arsenic ring atoms in the phospha- and arsa-benzenes (the position is different with azabenzenes, where the effect of aza replacement is known from long experience).



These difficulties (which permit only circumstantial evidence) can be avoided (and a direct proof made possible) if one can find a non-degenerate MO of a benzenoid hydrocarbon that fulfills the following conditions: 1. It must be known from the symmetry and topology that this MO has a non-zero coefficient in one specific atom; 2. the sign of the coefficients on the two neighboring atoms must be the same as on the specified atom (these two conditions make

[*] Prof. Dr. A. Schweig and Dipl.-Chem. W. Schäfer
Fachbereich Physikalische Chemie der Universität
355 Marburg, Biegenstrasse 12 (Germany)
Prof. Dr. F. Bickelhaupt and Drs. H. Vermeer
Scheikundig Laboratorium der Vrije Universiteit
De Lairessestraat 174, Amsterdam-Z (The Netherlands)

this MO related to the "$b_1(\pi)$ MO" of benzene); 3. the aza, phospha, and arsa homologs can be obtained from the selected hydrocarbon by replacement of this specific atom; 4. it must be possible to observe the chosen test MO experimentally in the hydrocarbon and in the derived heterocycles separately from all the other MO's and without a change in the sequence.

These four conditions are fulfilled in an ideal manner by the $b_{2g}(\pi)$ HOMO of the anthracene derivatives *(10)* to *(13)*[12, 13] (cf. the representation of this MO). Comparing the HOMO ionization potentials (IP) of compounds *(10)* to *(13)* with the IP values that, from previous work[2, 4, 5], are probable for the $b_1(\pi)$ MO's [$e_{1g}(\pi)$ in *(1)* and $e''(\pi)$ in *(5)*] of compounds *(1)* to *(4)* or *(5)* to *(7)* thus shows sequence reversal if the behavior is similar and absence of reversal if behavior is different.

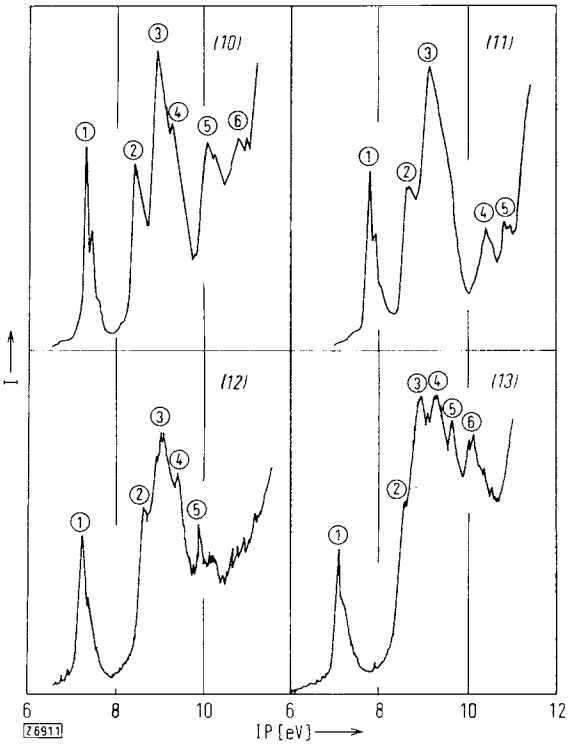


Fig. 1. Photoelectron spectra [18] for 9-phenylanthracene *(10)*, 9-phenylacridine *(11)*, 10-phenyl-9-phosphaanthracene *(12)* and 10-phenyl-9-arsaanthracene *(13)*. The vertical ionization potentials (in eV) are: for *(10)*, ① 7.25, ② 8.45, ③ 9.00, ④ 9.25, ⑤ 10.05, ⑥ 10.80; for *(11)*, ① 7.80, ② 8.65, ③ 9.15, ④ 10.40, ⑤ 10.85; for *(12)*, ① 7.25, ② 8.65, ③ 9.00, ④ 9.30, ⑤ 9.90; for *(13)*, ① 7.05, ② 8.60, ③ 8.95, ④ 9.25, ⑤ 9.70, ⑥ 10.10 [19].

Figure 1 shows the PE spectra of *(10)* to *(13)*. In Figure 2 the IP values of the probable $b_1(\pi)$ MO's [$e_{1g}(\pi)$ in *(1)* and $e''(\pi)$ in *(5)*] of *(1)* to *(4)* (9.24[14], 10.5[15], 9.1[16], and 8.7[16] eV) on the one hand and of *(5)* to *(7)* (8.15, 9.3[4] and 8.0[4] eV) on the other are plotted against the HOMO IP's of *(10)* to *(13)* (7.25, 7.80, 7.25 and 7.05 eV). There is very good correspondence in both cases, and the two straight lines are strictly parallel[17]. These results provide the first direct and unambiguous proof that the hitherto unique MO sequence — π-MO with non-zero coefficient on the hetero atom [$b_1(\pi)$] higher in energy than the π-MO with its node on the hetero atom [$b_1(\pi)$] — does in fact exist in the phosphorin and in the arsenin system.

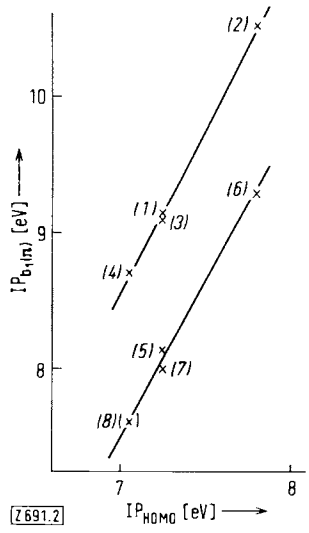


Fig. 2. Correlation between the ionization potentials of the $b_1(\pi)$ MO's [e_{1g} for *(1)* and e'' for *(5)*] probable from previous work [2, 4, 5] in the six-membered ring systems *(1)* and *(8)* (ordinates) and the HOMO ionization potentials of the anthracene systems *(10)* to *(13)* (abscissae).

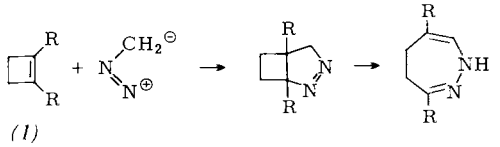
Received: August 3, 1972 [Z 691 IE]
German version: Angew. Chem. *84*, 993 (1972)

[1] Part 15 of Theory and Application of Photoelectron Spectroscopy. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 14: *A. Schweig, U. Weidner*, and *G. Manuel*, Angew. Chem. *84*, 899 (1972); Angew. Chem. internat. Edit. *11*, 837 (1972).
[2] *H. Oehling* and *A. Schweig*, Tetrahedron Lett. *1970*, 4941.
[3] CNDO/2-Methode, cf.: *J. A. Pople* and *D. L. Beveridge*: Approximate Molecular Orbital Theory. McGraw-Hill, New York 1970.
[4] *H. Oehling, W. Schäfer*, and *A. Schweig*, Angew. Chem. *83*, 723 (1971); Angew. Chem. internat. Edit. *10*, 656 (1971).
[5] *A. Schweig, W. Schäfer*, and *K. Dimroth*, Angew. Chem. *84*, 636 (1972); Angew. Chem. internat. Edit. *11*, 631 (1972).
[6] *K. Dimroth* and *W. Mach*, Angew. Chem. *80*, 489 (1968); Angew. Chem. internat. Edit. *7*, 460 (1968).
[7] *W. Mach*, Dissertation, Universität Marburg 1968.
[8] *P. de Koe* and *F. Bickelhaupt*, Angew. Chem. *80*, 912 (1968); Angew. Chem. internat. Edit. *7*, 889 (1968).
[9] *H. Vermeer* and *F. Bickelhaupt*, Tetrahedron Lett. *1970*, 3255.
[10] *A. J. Ashe, III*, J. Amer. Chem. Soc. *93*, 3293 (1971).
[11] Meanwhile an *ab initio* calculation has been made on *(3)* by *D. T. Clark* and the compounds *(3)* and *(4)* have been measured by *E. Heilbronner*; the unpublished results [16] of these two investigations provide a welcome confirmation of our previous findings.
[12] We have proved that the phenyl group in 9-phenylanthracene *(10)* does not influence the results of our work. For anthracene we have measured the vertical ionization potentials (in eV) for the first four PE bands as: ① 7.40, ② 8.55, ③ 9.15 and ④ 10.30. The phenyl group lowers the HOMO IP inappreciably, by 0.15 eV. Very recently the IPs of anthracene were also measured by *H. D. Eland*, Int. J. Mass Spectrom. Ion Phys. *9*, 214 (1972) and *P. A. Clark, F. Brogli*, and *E. Heilbronner*, Helv. Chim. Acta *55*, 1416 (1972). The values found by these authors are in very good agreement with those measured by us.
[13] The anthracene derivatives have a further considerable advantage over the benzene derivatives: comparing the HOMO photoelectron bands of *(10)* and its hetero homologs *(11)* to *(13)* proves clearly that bands ① in *(11)* to *(13)* cannot arise by ionization of the free electron pair on the hetero atoms. Such a direct proof is not possible for the series of six-membered rings.
[14] *A. D. Baker, D. P. May*, and *D. W. Turner*, J. Chem. Soc. *B 1968*, 22; *D. W. Turner, C. Baker, A. D. Baker*, and *C. R. Brundle*: Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970.
[15] *R. Gleiter, E. Heilbronner*, and *V. Hornung*, Angew. Chem. *82*, 878 (1970); Angew. Chem. internat. Edit. *9*, 901 (1970).
[16] *E. Heibronner*, personal communication.
[17] From Fig. 2 we expect an HOMO IP of 7.5 to 7.6 eV for the arsenin *(8)* that has not yet been synthesized.
[18] The He-I (584 Å) photoelectron spectra were measured with a PS-16 spectrometer from Perkin-Elmer Ltd., Beaconsfield, England.
[19] Our investigations of the higher PE bands not discussed here will be reported later.

A General Synthetic Route to Seven-membered Heterocycles from Cyclobutenes and 1,3-Dipoles

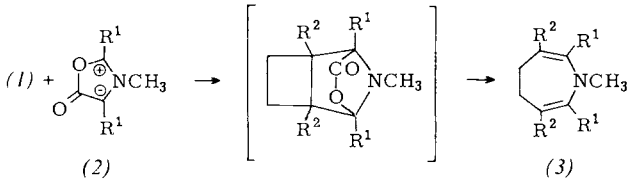
By *Hans-Dieter Martin* and *Mirko Hekman*[*]

Addition of diazomethane to the cyclobutenes *(1)* and subsequent fission of the internal σ-bond of the adduct affords seven-membered heterocycles according to the scheme ④ + ③ → ⑦[**][1].



(1)

We report here on the reaction of cyclobutenes *(1)* with the mesoionic oxazolone *(2)*[2], which leads to dihydroazepines *(3)* [*(3)*: NMR (CCl_4): δ=2.32 (3 H, S), 2.86

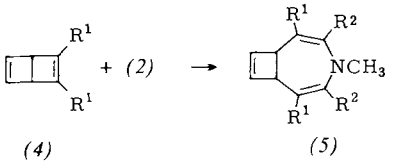


(2) *(3)*

$R^1 = C_6H_5$, $R^2 = CO_2CH_3$

(4 H, S), 3.22 (6 H, S), 7.33 ppm (10 H, M).—UV in CH_3CN: $\lambda_{max}(\varepsilon)$=241 (17400), 307 nm (9100).—M.p. 120°C].

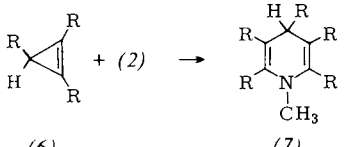
The still more reactive Dewar-benzene derivative *(4)*[3] adds one molar equivalent of *(2)*, yielding the bicyclic, thermally not very stable 4-azabicyclo[5.2.0]nonatriene *(5)*. Systems of this type have hitherto been accessible only by addition of nitrenes to cyclooctatetraene[4]. [*(5)*: NMR ($CDCl_3$): δ=2.32 (3 H, S), 3.30 (6 H, S), 4.30 (2 H, S), 6.32 (2 H, S), 7.40 ppm (10 H, M).—UV in CH_3CN: $\lambda_{max}(\varepsilon)$=233 (17400), 313 nm (10000).—Mass spectrum: M^+ at m/e=401.]



(4) *(5)*

$R^1 = CO_2CH_3$, $R^2 = C_6H_5$

The appreciably more strained cycloadducts from cyclopropenes undergo relatively ready ring opening to six-membered heterocycles[1]. Triphenylcyclopropene *(6)* and *(2)* give a 63% yield of dihydro-1-methylpentaphenylpyridine *(7)* [NMR ($CDCl_3$): δ=2.56 (3 H, S), 4.42 (1 H, S),



(6) R = C_6H_5 *(7)*

[*] Dr. H.-D. Martin and Dipl. Chem. M. Hekman
Organisch-chemisches Institut der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] ⑦ means the number of ring atoms contributed by each of the reactants and the ultimate size of the ring formed.

6.90—7.80 ppm (25 H, M).—UV in CH_3CN: $\lambda_{max}(\varepsilon)$= 222 (sh, 30400), 268 (14700), 345 nm (sh, 6300).—M.p. 209 C].

Experimental for synthesis of (5):

Compound *(4)* (1 g, 5.1 mmol) in benzene (50 ml) is warmed at 35 C and *(2)* (2.5 g, 10 mmol) is added portionwise with stirring during 20 min. Stirring is continued for 10 min after cessation of gas evolution and the excess of *(2)* is then filtered off. The filtrate is concentrated in a rotatory evaporator. Methanol (about 40 ml) is added to the concentrated solution. Crystallization begins in about 5 min and is completed by storage for a day at −15 C. Recrystallization from methanol affords white crystals which, being thermally unstable, melt between 132 and 136 C. Yield: 20% (400 mg).

Received: August 2, 1972 [Z 693 IE]
German version: Angew. Chem. *84*, 995 (1972)

[1] *H. Prinzbach* and *H.-D. Martin*, Chimia *23*, 37 (1969).

[2] *H. O. Bayer, R. Huisgen, R. Knorr*, and *F. C. Schaefer*, Chem. Ber. *103*, 2581 (1970).

[3] *L. Watts, J. D. Fitzpatrick*, and *R. Pettit*, J. Amer. Chem. Soc. *87*, 3253 (1965).

[4] *S. Masamune* and *N. T. Castellucci*, Angew. Chem. *76*, 569 (1964); Angew. Chem. internat. Edit. *3*, 582 (1964); *A. G. Anastassiou, S. W. Eachus, R. L. Elliott*, and *E. Yakali*, Chem. Commun. *1972*, 531.

The Synthesis of the 1-Methoxy-4,5:10,11-bis-(tetramethylene)-6,8-didehydro[13]annulenyl Anion, an Aromatic 13-Membered Carbocyclic System[1]

By *Eugene LeGoff* and *Franz Sondheimer*[*]

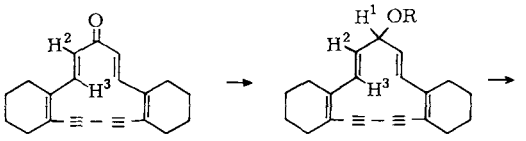
(4n+1)-Membered conjugated carbocyclic anions contain (4n+2) π-electrons, and are therefore expected to be aromatic (diatropic)[2]. The properties of the known 5-, 9- and 17-membered ring anions are in agreement with this prediction[2, 3], but it has previously not been possible to prepare an example of a 13-membered ring system. We now report the synthesis of a didehydro[13]annulenyl anion, which, as expected, proved to be strongly diatropic.

Reduction of 4,5:10,11-bis(tetramethylene)-6,8-didehydro[13]annulenone *(1)*[4] in ether with ethanolic $NaBH_4$ for 2 h at room temperature, followed by chromatography on silicic acid, gave 80% of the alcohol *(2)* as pale yellow crystals, which decomposed on attempted melting point determination. [m/e = 290.—UV (in ether): $\lambda_{max}(\varepsilon)$ = 257 (13100), *ca.* 300 sh (5500), 321 (7400), 335 nm (7200).—IR (in $CHCl_3$): 3600 w, 3425 m (OH), 2200 m (C≡C), 1715 w, 1640 w, 1580 m (C=C), 975 s cm^{-1} (*trans* C=C).—NMR: see Table 1.]

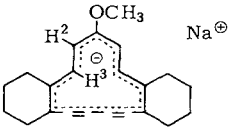
Methylation of *(2)* in ether with MeI and Ag_2O for 15 hours at room temperature led to 90% of the ether *(3)*, an unstable pale yellow oil. [m/e = 304.—UV (in ether): $\lambda_{max}(\varepsilon)$ = 257 (12700), *ca.* 300 sh (5300), 320 (7100), 335 nm (6900).—IR (in CCl_4): 2205 m (C≡C), 1730 m, 1630 w, 1585 w (C=C), 975 s cm^{-1} (*trans* C=C).—NMR: see Table 1.]

[*] Prof. Dr. E. LeGoff[**] and Prof. Dr. F. Sondheimer
Chemistry Department, University College
Gordon Street, London WC1H OAJ (England)

[**] On sabbatical leave from Michigan State University, East Lansing, Michigan (U.S.A.)



(1) (2), R = H (3), R = CH_3



(4)

[2] *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972).
[3] *J. Griffiths* and *F. Sondheimer*, J. Amer. Chem. Soc. *91*, 7518 (1969), and references given therein.
[4] *P. D. Howes*, *E. LeGoff*, and *F. Sondheimer*, Tetrahedron Lett. *1972*, 3691.
[5] *E. J. Corey* and *M. Chaykovsky*, J. Amer. Chem. Soc. *87*, 1345 (1965); *G. G. Price* and *M. C. Whiting*, Chem. and Ind. *1963*, 775.
[6] Complete conversion of *(3)* to *(4)* has been assumed in calculating the ε values.
[7] The lithium salt corresponding to *(4)* [NMR (100 MHz): $\tau = 1.82$ (d, $J = 16$ Hz, H^2), 5.96 (s, OCH_3), 15.74 (d, $J = 16$ Hz, H^3)] could be obtained by treatment of *(3)* with MeLi in [D_8]-THF at *ca.* −40 °C [3], but this procedure was less satisfactory than the dimsyl sodium reaction.

Table 1. ^{1}H-NMR parameters of compounds *(1)*–*(4)* at 60 MHz; τ values in ppm.

Proton	*(1)* in $CDCl_3$	*(2)* in $CDCl_3$	*(3)* in $CDCl_3$	*(4)* in [D_6]-DMSO
H^1	—	5.0–5.5 m [a]	5.1–5.7 m	—
H^2	3.77 d ($J = 17$ Hz)			1.72 d ($J = 16.2$ Hz)
H^3	0.77 d ($J = 17$ Hz)	3.97 d ($J = 15$ Hz)	4.02 d ($J = 15$ Hz)	15.74 d ($J = 16.2$ Hz)
Allylic CH_2	7.55–8.1 m	7.4–8.1 m	7.4–8.0 m	6.05–6.65 m
Nonallylic CH_2	8.1–8.6 m	8.1–8.6 m	8.1–8.55 m	7.6–8.15 m [b]
OCH_3	—	—	6.57 s	5.87 s

[a] This assignment was confirmed by the addition of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) [Eu(fod)$_3$].
[b] The lower limit of this band cannot be determined accurately due to the overlap of the solvent band.

Abstraction of H^1 from *(3)* by addition of a solution of dimsyl sodium in DMSO (prepared from NaH and DMSO)[5] at room temperature afforded a deep red solution of the sodium salt *(4)*. [UV (in DMSO): λ_{max} (ε) = 348 sh (8200), *ca.* 440 sh (6000), *ca.* 500 sh nm (4400)[6], with absorption >700 nm.]

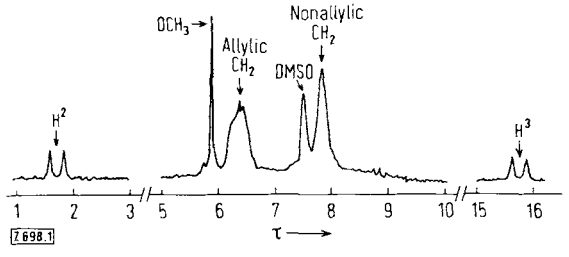


Fig. 1. ^{1}H-NMR spectrum of *(4)* in [D_6]-DMSO at 60 MHz.

The NMR spectrum of *(4)* [Table 1, Figure 1] was obtained by treatment of *(3)* with [D_5]-dimsyl sodium in [D_6]-DMSO (from NaH and [D_6]-DMSO)[7]. The very high field resonance of the inner olefinic protons and the low field resonances of the outer olefinic, allylic and nonallylic protons clearly demonstrate *(4)* to be strongly diatropic. This is also shown by the relatively low field resonance of the methoxyl protons (cf. anisole: $\tau = 6.22$). It is clear that the downfield shift of the outer protons due to the diamagnetic ring current far outweighs the small upfield shift to be expected of the negative charge. The diatropic (4n + 2) π-electron system *(4)* presumably contains a reasonably coplanar carbon skeleton, unlike the related 4n systems *(1)* and protonated *(1)*, which are not appreciably paratropic[4].

Received: July 31, 1972 [Z 698 IE]
German version: Angew. Chem. *84*, 996 (1972)

[1] Unsaturated Macrocyclic Compounds. Part 96. — Part 95: *K. Stöckel*, *P. J. Garratt*, *F. Sondheimer*, *Y. De Julien de Zelicourt*, and *J. F. M. Oth*, J. Amer. Chem. Soc., in the press.

Sequence of Orbitals in Sulfones and Sulfodiimides[1]

By *Bahman Solouki*[*], *Hans Bock*[*], and *Rolf Appel*[**]

Compared with dialkyl sulfoxides R_2SO[2] the number of "sulfur valence electrons" in dialkyl sulfones R_2SO_2 is raised to a total of 12. The 3d atomic orbitals of sulfur must therefore be included in any description of the σ- and π-bonds[3,4] ($d_{SO}^{R_2SO} = 1.47$ Å, $d_{SO}^{R_2SO_2} = 1.45$ Å[3]). Combination of four oxygen 2p, two σ-bonding, and two sulfur 3d orbitals allows construction of the qualitative MO diagram in Figure 1.

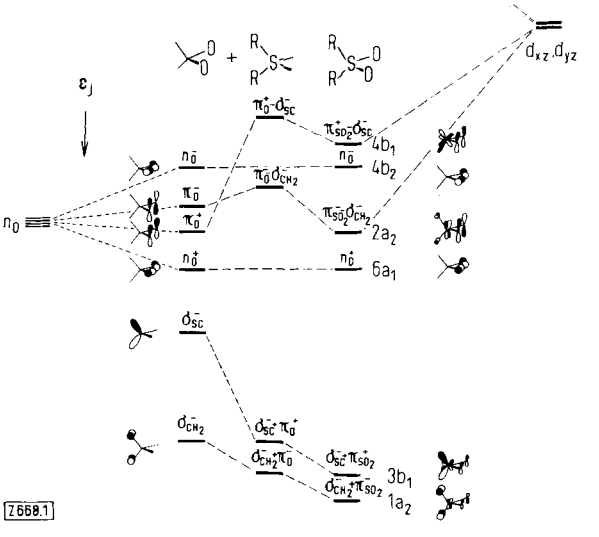


Fig. 1. Qualitative MO diagram for dialkyl sulfones.

[*] Prof. Dr. H. Bock and Dipl.-Chem. B. Solouki
Chemische Institute der Universität
6 Frankfurt 70, Ludwig-Rehn-Str. 14 (Germany)
[**] Prof. Dr. R. Appel
Anorganisch-chemisches Institut der Universität
53 Bonn, Meckenheimer Allee 168 (Germany)

The qualitatively derived sequence of the four highest occupied molecular orbitals, which can also be reproduced by CNDO/2 calculations[5], is substantiated by comparison of the ionization potentials determined by photoelectron spectroscopy for isoelectronic series of compounds and by the additional "transannular π-interaction" in an unsaturated five-membered ring sulfone.

In the photoelectron (PE) spectra of the isoelectronic series $(CH_3)_2SX_2$ (X = O→NH) the first four bands exhibit varying shifts towards lower ionization potentials (Fig. 2 and Table 1).

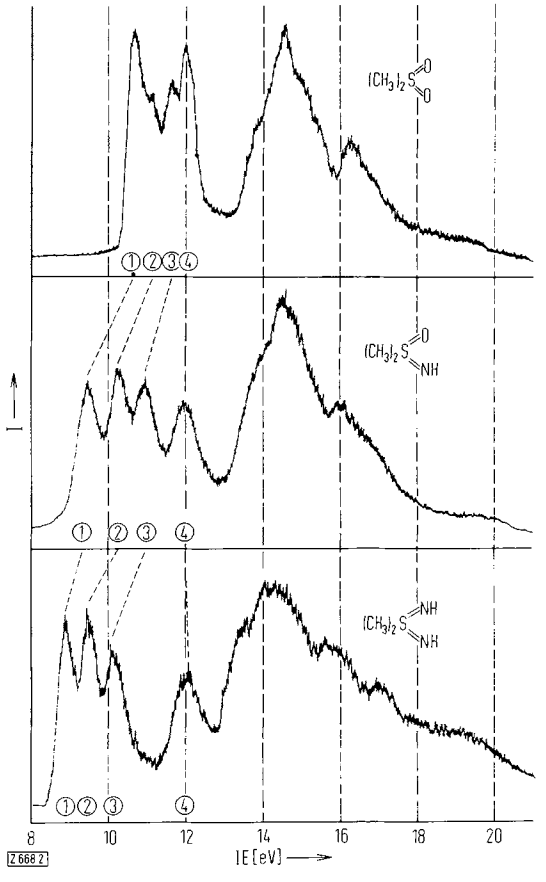
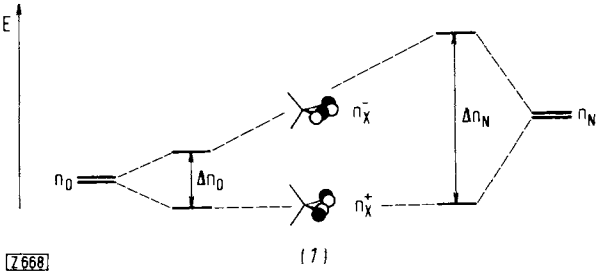


Fig. 2. PE spectra of dimethyl sulfone, dimethylsulfonimide, and dimethylsulfodiimide.

Table 1. Vertical ionization potentials IE_n (eV) of dimethyl sulfone and derivatives.

Cpd.	IE_1	IE_2	IE_3	IE_4	IE_5
$(CH_3)_2SO_2$	10.65	11.18	11.65	12.0	
$(CH_3)_2S(NH)O$	9.5	10.29	10.94	12.0	
$(CH_3)_2S(NH)_2$	8.87	9.4	10.0	12.06	
$(CH_3)FSO_2$	12.53	12.53	12.53	13.91	15.57
F_2SO_2	13.75	13.92	15.16	15.29	16.68
$(CH_3)ClSO_2$	11.6	11.94	12.36	12.6	13.32
Cl_2SO_2	12.41	12.41	13.17	13.67	14.06
2,5-Dihydrothiophene 1,1-dioxide	10.44	10.66	11.25	11.63	11.99

The differences in the PE spectra on replacement of oxygen by an NH group can be discussed in terms of the qualitative MO diagram (Fig. 1) with the aid of *Koopmanns'* theorem[6]. In so doing attention must be paid to structural modifications in the molecular skeleton such as the increased π-bond length ($d_{SO} = 1.45$ Å, $d_{SN} = 1.53$ Å[7]) and the widened angle XSX ($\sphericalangle$ OSO = 117.9°, $\sphericalangle$ NSN = 122.2°[7]) which suggest an enhanced spatial interaction between the nitrogen lone pairs. If n_N lies above n_O according to *(1)* and if the splitting Δn_N is greater than Δn_O then n_X^- should be raised more than n_X^+. A comparison of the



(1)

PE ionization potentials (Table 1), shows that IE_4 remains roughly constant and IE_2 decreases additively as expected from Figure 1 with decreasing energy of the center of gravity of the electron pair orbitals. The qualitative MO diagram thus suggests assignment of PE band 4 to the MO $6a_1$ and the PE band 2 to the MO $4b_2$. The splitting of the bands 1 and 3, again for a constant center of gravity, is greatest in the unsymmetrical dimethylsulfonimide, and can be rationalized according to the CNDO/2 calculations in terms of a larger N contribution to the higher MO $4b_1$ and a larger O contribution to the MO $2a_2$.

The qualitative orbital sequence for dimethyl sulfone (Fig. 1) is also in accord with the substituent effects in the isoelectronic series X_2SO_2 (X = CH_3→F or CH_3→Cl). Thus the replacement of methyl groups by fluorine (Fig. 3) should lead to a lowering of all orbitals by the "perfluoro effect"[6]. The $4b_1$ orbital should be lowered particularly drastically since no antibonding σ_{sc}^- contribution has to be considered in this case (Fig. 1). In contrast, the orbitals $4b_2$ and $2a_2$ should exhibit less pronounced lowering owing to the more effective antibonding admixture of fluorine orbitals. These arguments are confirmed by *ab initio*[4] and CNDO/2 calculations[5] for F_2SO_2 and explain the correlation diagram of the PE ionization potentials (Fig. 3 and Table 1).

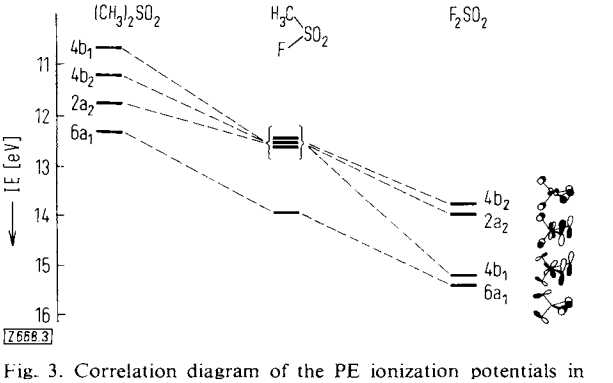
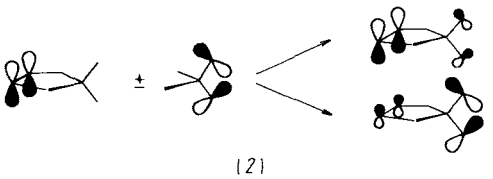


Fig. 3. Correlation diagram of the PE ionization potentials in the isoelectronic series $(CH_3)_2SO_2 \rightarrow F_2SO_2$.

As a final argument in favor of the derived dialkyl sulfone MO scheme (Fig. 1) we would like to cite the transannular interaction in 2,5-dihydrothiophene 1,1-

dioxide. The occupied π_{CC} orbital is of b_2 symmetry (group C_{2v}) and can therefore mix only with the $4b_2$ orbital of the sulfone group according to *(2)*. The first PE band of the five-membered ring sulfone (Table 1: IE_1) is to be assigned to the π level on the basis of the



[2]

observed vibrational fine structure ($1200 \pm 100\,cm^{-1} \triangleq \tilde{\nu}_2$ and $560 \pm 100\,cm^{-1} \triangleq \tilde{\nu}_3$). Comparison of the ionization potentials IE_{n+1} of the unsaturated five-membered ring (Table 1) shows that, as expected, equal contributions are found for $n = 1,3,4$. The small lowering for $n = 2$ suggests that the second highest occupied molecular orbital in dialkyl sulfones does have b_2 symmetry.

Received: June 16, 1972 [Z 668 IE]
German version: Angew. Chem. *84*, 944 (1972)

[1] Photoelectron Spectra and Molecular Properties, Part 13.—Part 12: *H. Bock, S. Elbel, W. Ensslin, W. Fuss, P. Mollère* and *G. Wagner*, Chimia *26*, 249 (1972).

[2] *H. Bock* and *B. Solouki*, Angew. Chem. *84*, 436 (1972); Angew. Chem. internat. Edit. *11*, 436 (1972).

[3] *H. H. Szmant:* "The Sulfur-Oxygen Bond" in *A. Senning:* Sulfur in Organic and Inorganic Chemistry. Dekker, New York 1971, and further literature cited there.

[4] *R. L. DeKock* and *D. R. Lloyd*, Proc. Roy. Soc. A, in press.

[5] *B. Solouki*, Dissertation, Universität Frankfurt.

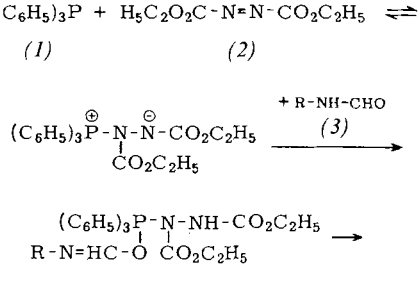
[6] *C. R. Brundle* and *M. B. Robin* in *F. C. Nachod* and *J. J. Zuckermann:* Determination of Organic Structures by Physical Methods. Academic Press, New York 1971, Vol. III.

[7] *N. S. Webb* and *R. A. Gloss*, Tetrahedron Lett. *1967*, 1043; *H. Oberhammer* and *W. Zeil*, Z. Naturforsch. *24a*, 1612 (1969).

Synthesis of Isocyanides from *N*-Monosubstituted Formamides, Phosphanes, and Azodicarboxylic Acid Derivatives

By *Barbro Beijer, Ernst von Hinrichs*, and *Ivar Ugi*[*]

The mechanism proposed[1] for the reaction of phthalimide with alcohols, triphenylphosphane *(1)*, and diethyl azodicarboxylate *(2)* induced us to investigate whether the



combination of *(1)* and *(2)* was suitable for removal of water from *N*-monosubstituted formamides *(3)* and thus for the synthesis of isocyanides *(4)*. An isocyanide synthesis of this type would have the advantage over all others[2] of occurring without addition of a base, which would be of interest for the several isocyanides that racemize or decompose in the presence of bases[2]. The results of such reactions are collected in Table 1.

Table 1. Preparation of isocyanides from *N*-monosubstituted formamides *(3)* with *(1)* and *(2)*.

(4), R =	Yield (%)
Methyl	0
tert-Butyl	0
Cyclohexyl	39
Phenyl	38
Benzyl	25
p-Nitrophenyl	0
2,6-Dimethylphenyl	53
2,4,6-Trimethylphenyl	58
$-CH_2-CO_2CH_3$	0
$-CH(CH_3)-CO_2CH_3$	0
$-CH[CH(CH_3)_2]-CO_2CH_3$	0

The yields are about the same whether *(2)* or dimethyl azodicarboxylate is used, but *N*-phenylazodicarboximide gives yields that are about 10% lower. If *(1)* is replaced by tri-*n*-butylphosphane in the synthesis of cyclohexyl isocyanide, the yield amounts to 30%, but no isocyanide is formed when trimethyl phosphite, hexamethylphosphorotriamide, or 2-methoxy-3-methyl-1,3,2-oxazaphospholidine is employed[3].

Example:

Triphenylphosphane (524 mg, 2 mmol) *(1)* is dissolved in anhydrous tetrahydrofuran (THF) (5 ml) under N_2 and is treated at 20 °C under N_2 with diethyl azodicarboxylate *(2)* (174 mg, 2 mmol) in anhydrous THF (5 ml). Finally, *N*-cyclohexylformamide *(3)*, R = cyclo-C_6H_{11} (254 mg, 2 mmol) in anhydrous THF (2 ml). After being kept for 24 h at 20 °C the mixture is worked up, giving 39% (85 mg) of *(4)*, R = cyclo-C_6H_{11}. If *(1)* and *(2)* are used in 100% excess, the yield is 70%.

Received: August 7, 1972 [Z 700 IE]
German version: Angew. Chem. *84*, 957 (1972)

[1] *O. Mitsunobu, M. Wada*, and *T. Sano*, J. Amer. Chem. Soc. *94*, 679 (1972).

[2] *P. Hoffmann, G. Gokel, D. Marquarding*, and *I. Ugi* in *I. Ugi:* Isonitrile Chemistry. Academic Press, New York 1971, p. 9.

[3] *T. Mukayama* and *Y. Kodaira*, Bull. Chem. Soc. (Japan) *39*, 1297 (1966).

2-Cyclopropene-1-carboxylic Acids from Trimethylsilylacetylenes

By *Oleg M. Nefedov, Igor E. Dolgij, Galina P. Okonnischnikova*, and *Inna B. Schwedova*[*]

We have investigated the thermal, catalyzed reaction of trimethylsilylacetylenes *(1)* with alkyldiazoacetates *(2)*.

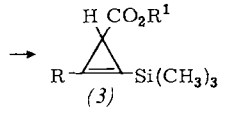
[*] B. Beijer [**], Dipl.-Chem. E. v. Hinrichs, and Prof. Dr. I. Ugi
Laboratorium für Organische Chemie der Technischen Universität
8 München, Arcisstrasse 21 (Germany)

[**] Permanent address: Institutionen för organisk Kemi, Chalmers Tekniska Högskola och Göteborgs Universitet, Göteborg (Sweden)

[*] Prof. Dr. O. M. Nefedov, Dr. I. E. Dolgij, Dipl.-Chem. G. P. Okonnischnikova, and Dipl.-Chem. I. B. Schwedova
N. D. Zelinsky Institute for Organic Chemistry, Academy of Sciences of the USSR
Moscow, B-334, Leninsky Prospekt 47 (USSR)

Dropwise addition of a solution of *(2)*, $R^1 = CH_3$, in an equal volume of *(1)* in the presence of 6×10^{-4} mol $CuSO_4$/mol *(2)* at 100—110 °C to an excess of *(1)* [total molar ratio *(1)* : *(2)* = 6 : 1 to 10 : 1] leads—depending on the nature of R in *(1)*—to formation of the 2-substituted 3-trimethylsilyl-2-cyclopropene-1-carboxylates *(3)* [yields and properties, see Table 1].

$$R\text{-}C{\equiv}C\text{-}Si(CH_3)_3 + N_2CH\text{-}CO_2R^1$$
(1) *(2)*

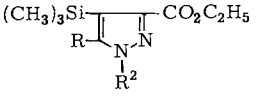


(3)

Table 1. Properties of the cyclopropenecarboxylates *(3)*, $R^1 = CH_3$.

R	Yield (%)	B.p. (°C/torr)	d_4^{20}	n_D^{20}	IR (cm^{-1}) $\nu_{C=C}$
$(CH_3)_3Si$[4]	5—8	85—87/10	0.9020	1.4500	1900
$(CH_3)_3C$[4]	10	76.5—77.0/8	0.8892	1.4435	1820
CH_3	54	67—69/10	0.9280	1.4460	1830
n-C_5H_{11}	50	118/15	0.9074	1.4490	1820
n-C_8H_{17}	35	151—151.5/7	0.8901	1.4538	1830

On the other hand, reaction of *(1)*, $R = (CH_3)_3Si$ with the ethyl ester *(2)*, $R^1 = C_2H_5$, under the same conditions, gives the pyrazoles *(4a)* and *(4b)* in about 60% yield [*(4a)*: m. p. 138.5 °C, from $CH_3OH/n\text{-}C_7H_{16}$ (5:1)[1]; *(4b)*: m. p. 70.8—70.9 °C, from $CH_3OH/n\text{-}C_7H_{16}$ (5:1)[2]].

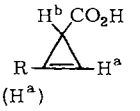


(4a), R = $(CH_3)_3Si$, R^2 = H
(4b), R = $(CH_3)_3Si$, R^2 = $CH_2\text{-}CO_2C_2H_5$
(4c), R = $(CH_3)_3C$, R^2 = $CH_2\text{-}CO_2C_2H_5$

Similarly, reaction of *(2)*, $R^1 = C_2H_5$, with an excess of *(1)*, $R = (CH_3)_3C$, affords the pyrazole *(4c)* [m.p. 73—74 °C, from C_2H_5OH[3], yield: 5%] and small amounts of *(3)*, $R = (CH_3)_3C$, $R^1 = C_2H_5$.

The difference in behavior between *(2)*, $R^1 = CH_3$, and *(2)*, $R^1 = C_2H_5$, may be due to the lower thermal stability of the methyl ester, which favors the formation of methoxycarbonylcarbene and, consequently, of *(3)*.

The action of dilute aqueous or aqueous-alcoholic solutions of NaOH, KOH, Na_2CO_3, K_2CO_3 or other bases at 20 °C or higher temperatures on *(3)* leads successively to hydrolytic cleavage of the trimethylsilyl group and hydrolysis of the ester group with quantitative formation of the free carboxylic acids *(5)* [Table 2]. These, particularly when R = H, are converted at temperatures above 50 °C into polymeric products that are only sparingly soluble in organic solvents.



(5)

Received: June 28, 1972 [Z 681 IE]
German version: Angew. Chem. *84*, 946 (1972)

[1] IR Spectrum in KBr: 1730 ($\nu_{C=O}$) and 3150 cm^{-1} (ν_{N-H}).
[2] IR Spectrum in KBr: 1725 and 1755 cm^{-1} (both $\nu_{C=O}$).
[3] IR Spectrum in KBr: 1718 and 1750 cm^{-1} (both $\nu_{C=O}$).
[4] *I. E. Dolgij, G. P. Okonnischnikova*, and *O. M. Nefedov*, Izv. Akad. Nauk SSSR, Ser. Khim. *1970*, 197.

A New Route to Triple-Decker Sandwich Compounds[1]

By *Albrecht Salzer* and *Helmut Werner*[*]

We recently reported the synthesis of tris (η-cyclopentadienyl)dinickel cation[2]—the first representative of a new class of metal π-complexes—which was assumed to have a "triple-decker sandwich structure"[3]. Reaction *(1)* proceeds almost quantitatively.

$$2\ Ni(C_5H_5)_2 + R^{\oplus}X^{\ominus} \longrightarrow [Ni_2(C_5H_5)_3]^{\oplus}X^{\ominus} + C_5H_5R \qquad (1)$$
$R = C(C_6H_5)_3, C_7H_7$; $X = BF_4, PF_6$

Attempts to prepare the complexes *(2b)* and *(2c)* by reaction of substituted bis(η-cyclopentadienyl)nickel compounds such as *(1b)* and *(1c)* with $R^{\oplus}X^{\ominus}$ gave unsatisfactory results. The products were either oils that proved difficult to handle or still contained considerable amounts of the reagent $R^{\oplus}X^{\ominus}$ which was exceptionally difficult to remove.

We therefore sought a new route to the cations of *(2a)* to *(2c)*, returning to our previously voiced opinion regarding

[*] Prof. Dr. H. Werner and A. Salzer
Anorganisch-chemisches Institut der Universität
CH—8001 Zürich, Rämistrasse 76 (Switzerland)

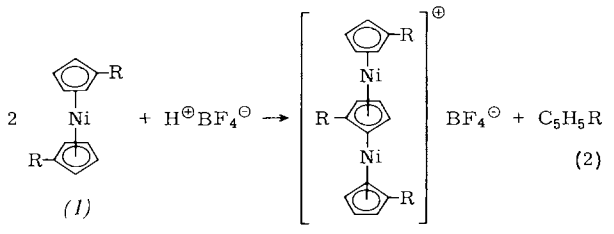
Table 2. Properties of the cyclopropenecarboxylic acids *(5)*.

R	M.p. (°C)	IR (cm^{-1}) $\nu_{C=C}$	$\nu_{C=O}$	NMR (CCl_4) δ (ppm) H^a	H^b
H[4]	147—148 (from C_6H_6/C_2H_5OH)	—	—	—	—
CH_3	42.5—43.0 (from hexane)	1820	1690	6.23	2.00
$(CH_3)_3C$[4]	41.5 (from C_6H_6)	1790	1700	6.08	2.06
n-C_5H_{11} [a]	oil	1815	1690	6.02	2.00
n-C_8H_{17} [b]	oil	1805	1690	6.02	2.00

[a] $n_D^{20} = 1.4610$; $d_4^{20} = 0.9783$.
[b] $n_D^{20} = 1.4676$; $d_4^{20} = 0.9596$.

the mechanism of the reaction between *(1a)* and carbo cations[2, 5]. Accordingly, a primary one-electron transfer and subsequent radical addition, or direct attack by $R^{\oplus}$ on *(1a)*, is assumed to yield a diene(dienyl)nickel cation $[Ni(C_5H_5)(C_5H_5R)]^{\oplus}$ which undergoes an ion-molecule reaction with an additional molecule of *(1a)* to give *(2a)*. If this were the case one could expect a *proton* to react with the sandwich complex *(1)* in an analogous fashion to $R^{\oplus}$.

We have now actually succeeded in preparing good yields of the compounds *(2a)* – *(2c)* by reaction of *(1a)* – *(1c)* with 50% aqueous HBF_4 in propionic anhydride as solvent[6].



(1) *(2)*

(a), R = H
(b), R = CH_3
(c), R = *tert.*-C_4H_9

(2b) is obtained as a blackish violet microcrystalline powder, and *(2c)* as platelets having a metallic sheen. The properties of *(2b)* and *(2c)* closely resemble those of *(2a)*: the compounds dissolve without decomposition only in nitromethane, are insoluble in nonpolar solvents, and react with water, ethanol, or acetonitrile to give *(1b)* and *(1c)* respectively. In the solid state *(2b)* and *(2c)* are only slightly sensitive to air and are stable for weeks in a nitrogen atmosphere.

Like that of *(2a)*[2], the NMR spectra of *(2b)* and *(2c)* exhibit separate signals for the protons of the two outer rings and the inner ring[7]. Whereas the eight protons of the two outer rings give a sharp singlet, the signals of the four protons of the inner ring are split into a multiplet, weakly in *(2b)* and more strongly in *(2c)* (Fig. 1).

It is noticeable (see Table 1) that the signals of the ring protons of *(2b)* are shifted 0.1 ppm *upfield* compared to *(2a)*. In the case of *(2c)* the signal of the outer rings is unchanged compared to *(2a)* while those of the inner ring are shifted 0.15 ppm *downfield*. *Nesmeyanov et al.* have recently also reported similar differential effects of the methyl and the *tert*-butyl group on the chemical shifts of the ring protons of substituted ferrocenes and substituted cobaltocenium salts[8].

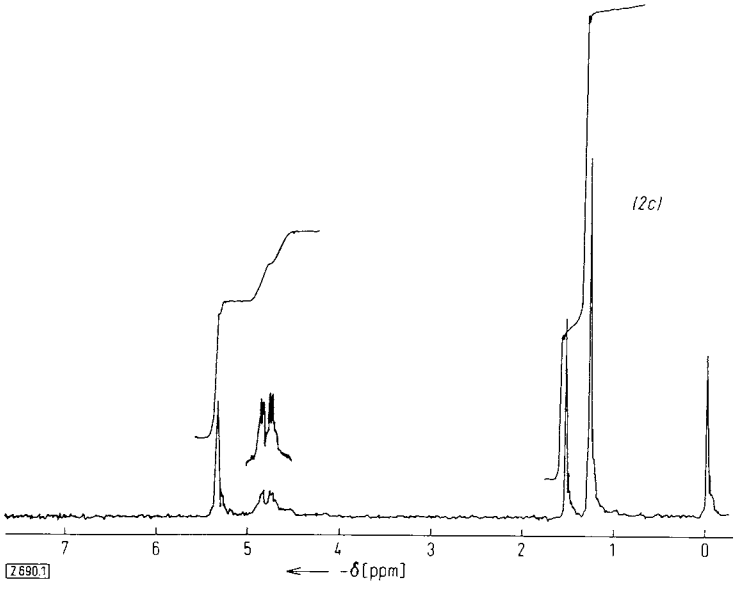


Fig. 1. ^{1}H-NMR spectrum of *(2c)* in CD_3NO_2.

Table 1. ^{1}H-NMR data for the compounds *(2a)*, *(2b)*, and *(2c)* [solvent: CD_3NO_2; TMS as internal standard; chemical shifts in ppm].

Compound	δ	
(2a)	4.7	(5 H, s)
	5.4	(10 H, s)
(2b)	2.0	(6 H, s)
	2.2	(3 H, s)
	4.6	(4 H, m)
	5.3	(8 H, s)
(2c)	1.8	(18 H, s)
	2.05	(9 H, s)
	4.85	(4 H, m)
	5.4	(8 H, s)

IR measurements indicate a pronounced resemblance between the spectra of compounds *(1)* and those of the cations of *(2)*, thus supporting the proposed triple-decker sandwich structure.

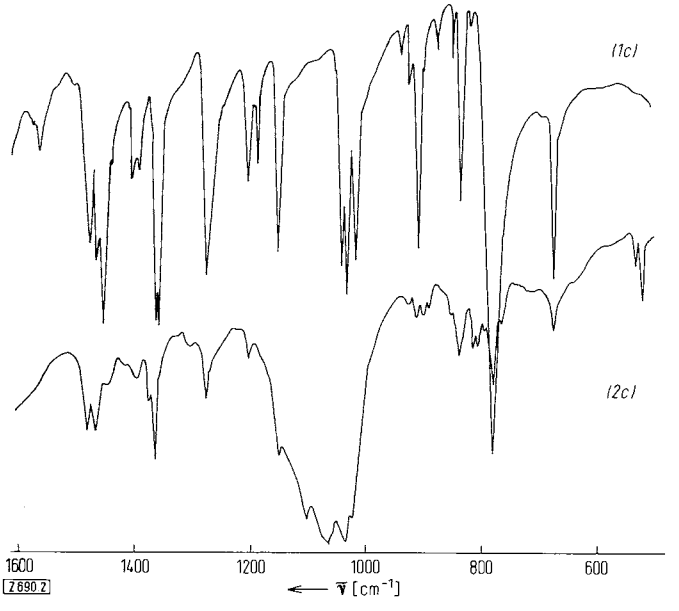
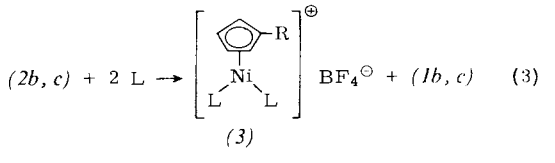


Fig. 2. IR spectra of *(1c)* and *(2c)* in KBr.

Like *(2a)*[9], *(2b)* and *(2c)* readily react with Lewis bases, losing their upper deck and forming cationic monocyclopentadienylnickel compounds *(3)*. The reactions according to eq. (3) proceed quantitatively.



(3)

(3)

L = $P(C_6H_5)_3$, $P(OCH_3)_3$, $P(OC_6H_5)_3$;
2 L = Norbornadiene

Preparation, properties, and reactions of the new η-cyclopentadienyl(diolefin)nickel complexes will be reported in detail elsewhere.

Tris(η-methylcyclopentadienyl)dinickel tetrafluoroborate (2b)

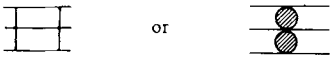
A 50% aqueous solution of HBF_4 (0.4 ml) is added very slowly with exclusion of air to a solution of *(1b)* (650 mg, 3 mmol) in propionic anhydride (5 ml). After brief mixing the resulting dark brown solution is carefully added dropwise to vigorously stirred diethyl ether (75 ml). The blackish violet, finely crystalline precipitate is isolated by filtration through a G 3 frit and washed several times with ether. Vacuum drying affords 620 mg of *(2b)* (93% yield based on *(1b)*).

Received: July 20, 1972 [Z 690 IE]
German version: Angew. Chem. *84*, 949 (1972)

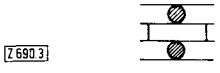
[1] Studies on the Reactivity of Metal π-Complexes, Part 6. This work was supported by the Schweizerischer Nationalfonds. Part 5: [9].

[2] *H. Werner* and *A. Salzer*, Synth. Inorg. Metal-org. Chem. *2*, 239 (1972).

[3] In our first publication [2] we designated the ion $[Ni_2(C_5H_5)_3]^+$ as a double sandwich complex. In the meantime Prof. *E. Schumacher* has pointed out that, according to Webster's dictionary, a triple deck can be pictured as



whereas a double sandwich is probably



Z 690 3

We have therefore decided to adopt the designation triple decker sandwich (in agreement with earlier suggestions [4]).

[4] *E. Schumacher* and *R. Taubenest*, Helv. Chim. Acta *47*, 1525 (1964).

[5] *H. Werner, G. Mattmann, A. Salzer*, and *T. Winkler*, J. Organometal. Chem. *25*, 461 (1970).

[6] The results of elemental analysis (C, H, F, Ni) are in very good agreement with the calculated values.

[7] According to measurements by Dr. *T. L. Court*.

[8] *A. N. Nesmeyanov, N. S. Kochetkova, E. V. Leonova, E. I. Fedin*, and *P. V. Petrovskii*, J. Organometal. Chem. *39*, 173 (1972).

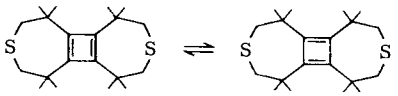
[9] *A. Salzer* and *H. Werner*, Synth. Inorg. Metal-org. Chem. *2*, 249 (1972).

Synthesis of a Cyclobutadiene Stabilized by Steric Effects[**]

By *Horst Kimling* and *Adolph Krebs*[*]

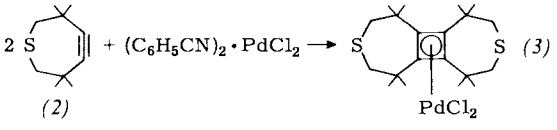
In our investigations of the stabilization of strained cyclic compounds by large substituents we have isolated a compound to which we assign the cyclobutadiene structure *(1)* on the basis of its mode of formation, its reactions and its spectroscopic data; the substituents on the four-membered ring correspond to four *tert*-butyl groups if the two S bridges are neglected.

Starting material for the synthesis of *(1)* was the 3,3,6,6-tetramethyl-1-thiacycloheptyne *(2)*[1], treatment of which with $(C_6H_5CN)_2PdCl_2$ in tetrahydrofuran (24 hours' boiling under reflux) afforded the yellow cyclobutadiene complex *(3)* (80%). Elemental analyses and spectroscopic data (Table 1) prove the structure *(3)*.

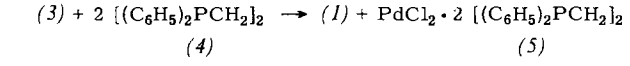


(1a) *(1b)*

A suspension of *(3)* in chloroform or methylene dichloride reacts with ethylenebis(diphenylphosphane) *(4)* completely within 1 h at 45 °C under N_2, yielding the $PdCl_2$-phosphane complex *(5)* as a white precipitate. Evaporation of the solvent from the supernatant solution and recrystallization of the residue from chloroform affords transparent yellowish crystals of *(1)*.

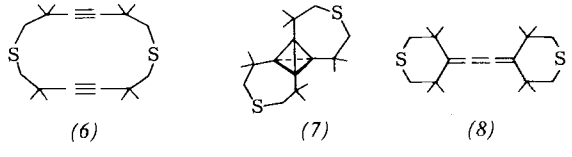


(2) *(3)*



(4) *(5)*

The most intense signal in the mass spectrum of *(1)* is that of the molecular ion at $m/e = 336$, as was confirmed by low-voltage spectra; fragmentation occurs similarly to that of *(3)* and *(10)*. The ^{1}H-NMR spectrum with only two sharp signals indicates a highly symmetrical structure. The occurrence of C=C double bonds is shown by a ^{13}C-NMR signal in the olefinic region and by a Raman band at 1590 cm^{-1}; the diacetylene *(6)* and tetrahedrane *(7)* formulas are thus eliminated as alternatives. The cumulene structure *(8)* also cannot be brought into accord with the ^{13}C-NMR and UV spectra: the two central C atoms of the butatriene chain should appear in the ^{13}C-NMR spectrum of *(8)* at $\delta = -200$ to -220 ppm (relative to TMS), similarly to the central C atom of allene[2]; and the UV spectrum of *(1)* shows only a maximum at 227 nm with an extinction decreasing very slowly to the visible region, whereas tetraalkylbutatrienes show maxima at considerably longer wavelengths[3].



(6) *(7)* *(8)*

(1) is very sensitive towards oxygen with which it affords, amongst other, unidentified, products, a colorless compound to which we assign the structure of the furan *(9)* on the basis of its spectroscopic data (Table 1).

The cyclobutadiene structure of *(1)* is supported by the reaction with nickel dibromide: this gives the deep violet cyclobutadiene complex *(10)* (10%), that can also be prepared from *(2)* and nickel dibromide. *(10)* was characterized by elemental analysis and spectra (Table 1); its UV spectrum is in good agreement with that of the tetramethylcyclobutadiene-nickel dichloride complex[4]. With dimethyl acetylenedicarboxylate, *(1)* gives a 1:1 adduct, whose spectroscopic data accord with structure *(11)* or *(12)* (Table 1).

X-ray analysis is in progress for unambiguous proof of structure *(1)* and decision between *(1a)* and *(1b)*.

[*] Dr. H. Kimling and Priv.-Doz. Dr. A. Krebs
Organisch-Chemisches Institut der Universität
69 Heidelberg, Im Neuenheimer Feld 7 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft.

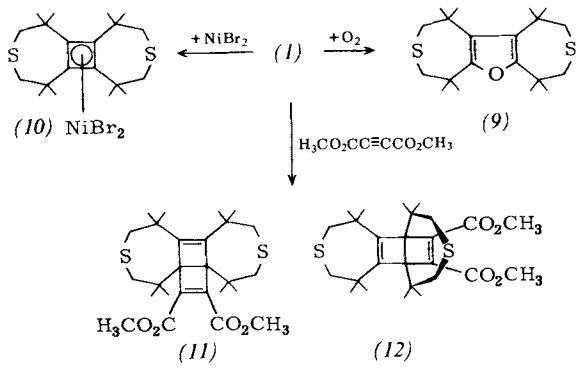


Table 1. Physical data for compounds *(1)*, *(3)*, *(9)*, *(10)*, and *(11)* or *(12)*.

(1)	M.p. 240 °C MS: m/e = 336 (M), 321 (M − CH_3), 280 (M − C_4H_8), 265 (M − CH_3 − C_4H_8), 209 (M − CH_3 − $2C_4H_8$) Rel. mol. wt. (cryoscopic, camphor): 355 ^{1}H-NMR (60 MHz, $CDCl_3$): δ = 2.50 (s, 8 H, CH_2), 1.26 ppm (s, 24 H, CH_3) ^{13}C-NMR (22.63 MHz, $CDCl_3$, broad band decoupled): δ = −27.0 (CH_3), −41.6 ($C_{quat.}$), −52.1 (CH_2), −146.5 ppm ($C_{olef.}$) Raman (cryst.): $\nu_{C=C}$ 1590 cm^{-1}
(3)	M.p. 305 °C (dec.) MS: m/e = 479, 477, 476 (M − Cl), 336 (M − $PdCl_2$), 280 (M − $PdCl_2$ − C_4H_8), 265 (M − $PdCl_2$ − C_4H_8 − CH_3), 209 (M − $PdCl_2$ − $2C_4H_8$ − CH_3) ^{1}H-NMR (60 MHz, benzonitrile): δ = 3.84 and 2.54 (AB, J_{AB} = 15 Hz, each 4 H, CH_2), 1.67 and 1.53 ppm (2 s, each 12 H, CH_3) UV (CH_2Cl_2): λ_{max} (ε) = 228 (7400), 251 (10800), 273 (6500), 340 nm (3000)
(9)	M.p. 260—261 °C MS: m/e = 352 (M), 337 (M − CH_3), 305 (M − CH_3 − S), 296 (M − C_4H_8), 281 (M − C_4H_8 − CH_3), 225 (M − $2C_4H_8$ − CH_3) ^{1}H-NMR (60 MHz, $CDCl_3$): δ = 2.66 and 2.62 (2 s, each 4 H, CH_2), 1.51 and 1.35 ppm (2 s, each 12 H, CH_3) UV (cyclohexane): λ_{max} (ε) = 219 nm (9000)
(10)	M.p. 320 °C (dec.) MS: m/e = 556, 554, 552 (M), 475, 473 (M − Br), 336 (M − $NiBr_2$), 280 (M − $NiBr_2$ − C_4H_8), 265 (M − $NiBr_2$ − C_4H_8 − CH_3), 209 (M − $NiBr_2$ − $2C_4H_8$ − CH_3) ^{1}H-NMR (60 MHz, $CDCl_3$): δ = 4.34 and 2.50 (AB, J_{AB} = 15 Hz, each 4 H, CH_2), 1.93 and 1.44 ppm (2 s, each 12 H, CH_3) UV ($CHCl_3$): λ_{max} (ε) = 260 (10400), 308 (3600), 500 nm (1100)
(11) or *(12)*	M.p. 180—181 °C MS: m/e = 478 (M), 463 (M − CH_3), 447 (M − OCH_3), 419 (M − CO_2CH_3), 407 (M − CH_3 − C_4H_8) ^{1}H-NMR (60 MHz, benzene): δ = 3.39 (s, 6 H, OCH_3), 3.57 and 2.26 (AB, J_{AB} = 14.4 Hz, 4 H, CH_2), 3.19 and 2.32 (AB, J_{AB} = 15.2 Hz, 4 H, CH_2), 1.37, 1.30, 1.27 and 1.23 ppm (4 s, each 6 H, CH_3) UV (cyclohexane): λ_{max} (ε) = 210 (9300), 245 nm (sh, 2000) IR (KBr): ν = 1715, 1635, 1260 cm^{-1}

Received: August 2, 1972 [Z 694 IE]
German version: Angew. Chem. *84*, 952 (1972)

[1] *A. Krebs* and *H. Kimling*, Tetrahedron Lett. *1970*, 761; Nachr. Chem. Techn. *19*, 272 (1971).

[2] *R. A. Friedel* and *H. L. Retcofsky*, J. Amer. Chem. Soc. *85*, 1300 (1963); *R. Steur, J. P. C. M. van Dongen, M. J. A. de Bie, W. Drenth, J. W. de Haan*, and *L. J. M. van de Ven*, Tetrahedron Lett. *1971*, 3307.

[3] *F. Bohlmann* and *K. Kieslich*, Chem. Ber. *87*, 1363 (1954); *H. D. Hartzler*, J. Amer. Chem. Soc. *93*, 452 (1971).

[4] *R. Criegee* and *G. Schröder*, Liebigs Ann. Chem. *623*, 1 (1959).

[5] *J. Haase*, Sektion Röntgen- und Elektronenbeugung der Universität Ulm, Karlsruhe (Germany).

1,3-Oxazolidine-2-thiones from Alkyl Isothiocyanates and Carbonyl Compounds

By *Dieter Hoppe*[*]

1,3-Oxazolidine-2-thiones *(6)* are of interest because some of the naturally occurring members[1] show antithyroid activity. They are obtained in good yield, by bond formation between C-4 and C-5[2], on treatment of alkyl isothiocyanates (mustard oils) *(1)* with bases (potassium *tert*-butoxide or sodium hydride in tetrahydrofuran) and carbonyl compounds *(3)*. The decisive intermediate is the α-metalated alkyl isothiocyanate *(2)*, which adds to the carbonyl compound, giving the anion of the 2-hydroxyalkyl isothiocyanate *(4)*. Cyclization to the anion *(5)* and protonation by glacial acetic acid affords the oxazolidine-2-thione *(6)* (Table 1).

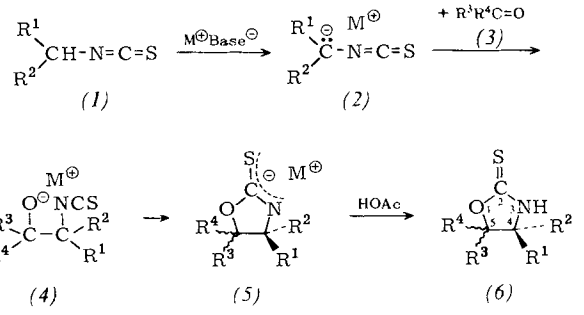


Table 1. 1,3-Oxazolidine-2-thiones *(6)* synthesized.

(6)	R^1	R^2	R^3	R^4	Base [a]	*trans*/*cis*	Yield (%)
(a)	H	$CO_2C_2H_5$	H	C_6H_5	KOtBu	4.5 : 1	68 [b]
					NaH	2 : 1	78 [b]
(b)	H	$CO_2C_2H_5$	H	$(CH_3)_2CH$	KOtBu	1 : 1	100 [c]
					NaH	1.5 : 1	90 [c]
(c)	H	$CO_2C_2H_5$	CH_3	CH_3	KOtBu	—	67 [d]
(d)	H	$CO_2C_2H_5$	$-(CH_2)_5-$		KOtBu	—	80 [b]
(e)	H	$CO_2C_2H_5$	C_6H_5	C_6H_5	KOtBu	—	40 [d]
					NaH		63 [d]
(f)	CH_3	$CO_2C_2H_5$	H	C_6H_5	KOtBu	1 : 2	90 [b]
(g)	CH_3	$CO_2C_2H_5$	H	$C_6H_5CH=CH$	NaH	1 : 1	95 [c]
(h)	H	C_6H_5	H	C_6H_5	KOtBu	2 : 1	75 [b, d]
(i)	H	$CH=CH_2$	H	C_6H_5	KOtBu	1 : 1	15 [b]

[a] In tetrahydrofuran; KOtBu = K *tert*-butoxide.
[b] After chromatographic purification or separation of isomers.
[c] Crude product [content of *(6)* over 95% according to NMR spectroscopy].
[d] After purification by recrystallization.

[*] Dr. D. Hoppe
Organisch-Chemisches Institut der Universität
34 Göttingen, Windausweg 2 (Germany)

If the isothiocyanate *(1)* does not possess a further group stabilizing the anion *(2)* and stronger nucleophilic bases such as butyllithium or Grignard reagents are used, then attack on the isothiocyanate group predominates, affording thioamides[3]. Diastereomeric oxazolidine-2-thiones *(6)*, $R^1 \neq R^2$ and $R^3 \neq R^4$, are readily separable by chromatography on silica gel or, for *(6f)* and *(6h)*, even by crystallization: *cis-(6f)* (m.p. 104°C) is obtained in 58% yield by crystallizing the crude product from tetrachloromethane. Evaporation of the mother liquor and crystallization of the residue by ether/petroleum ether yields 22% *trans-(6f)* (m.p. 112°C). The compounds *(6)* were identified by IR-, NMR-, and mass spectra and afforded satisfactory CH-analyses. Characteristic IR absorptions are found between 3100 and 3200 cm^{-1} (NH proton) and near 1500 cm^{-1} (thiocarbamate).

Experimental:

a) With potassium *tert*-butoxide: A solution of the alkyl isothiocyanate *(1)* (0.040 mol) and the carbonyl compound *(3)* (0.040 mol) in anhydrous tetrahydrofuran (THF) is added dropwise with stirrring to potassium *tert*-butoxide (0.042 mol) in THF (30 ml) at −60 to −50°C (nitrogen atmosphere). The mixture is stirred for a further 15 min at this temperature, allowed to warm to 0°C, and then poured into a solution of glacial acetic acid (3.0 g) in THF (10 ml). The solvent is distilled off in a vacuum (bath temperature max. 40°C), and the residue is taken up in dichloromethane (100 ml) and treated with water (30 ml). The organic phase is separated, shaken with water (30 ml), and dried over sodium sulfate. On evaporation of the solvent the oxazolidinethione *(6)* remains as a yellow to brown viscous oil. It is purified by crystallization from carbon tetrachloride or chloroform or by chromatography on silica gel with chloroform/ethyl acetate.

b) With sodium hydride: Procedure is as in a), but with sodium hydride (0.044 mol), one-tenth of the solution of *(1)* and *(3)* being added dropwise at 10°C. If hydrogen evolution does not occur, the temperature is raised slowly to a maximum of 35°C. As soon as reaction begins, the remainder of the solution is added dropwise, the whole is stirred for 15 min, then the mixture is cooled to 10°C and worked up as described above.

Received: July 28, 1972 [Z 697 IE]
German version: Angew. Chem. *84*, 956 (1972)

[1] *A. Kjær* in *N. Kharasch:* Organic Sulfur Compounds. Pergamon Press, Oxford 1961, Vol. 1, p. 418.

[2] Previous methods of preparation start from β-hydroxyamines or 2-hydroxyalkyl isothiocyanates that correspond to stage *(4)*.

[3] *F. Sachs* and *H. Loevy*, Ber. Dtsch. Chem. Ges. *37*, 874 (1904); *D. E. Worrall*, J. Amer. Chem. Soc. *50*, 1456 (1928).

[Bis(dimethylamino)aluminoxy]dimethylamino-carbene as a Complex Ligand[**]

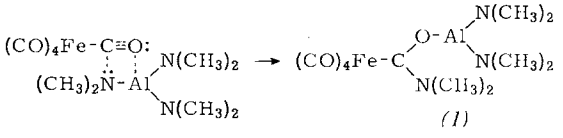
By *Wolfgang Petz* and *Günter Schmid*[*]

During investigations of the behavior of carbonylmetal complexes towards elements of the third main group[1, 2] we have studied the reaction of pentacarbonyliron with dimeric tris(dimethylamino)alane. Whereas some alanes form addition or cluster compounds with octacarbonyldicobalt[2], we observed in this case the surprising formation of a carbene complex:

$$2\,Fe(CO)_5 + \{[(CH_3)N_2]_3Al\}_2 \rightarrow \{(CO)_4FeC[N(CH_3)_2]OAl[N(CH_3)_2]_2\}_2$$
(1)

This complex, whose composition corresponds to the results of elemental analysis, is obtained in almost quantitative yield as yellow crystals that are extremely sensitive to air. Its dimeric nature follows from the ^{1}H-NMR spectrum and is to be ascribed to bridge building by the dimethylamino groups attached to the aluminum.

The unexpected formation of a carbene complex can be interpreted as due to nucleophilic attack by one amino group of the alane on a carbonyl-carbon atom of $Fe(CO)_5$.



(1)

An Al—O bond is presumably formed at the same time as the Al—N bond is broken. Many examples are known of reactions that are caused by nucleophilic attack of amines on the C atom of carbonyl groups[3–6].

In Table 1 are collected the proton signals of *(1)*, the $C_{carbene}N(CH_3)_2$ group of the comparable carbene complex $(CO)_4FeC[N(CH_3)_2]C_6H_5$ *(2)* and dimeric tris(dimethylamino)alane *(3)*.

Table 1. ^{1}H-NMR signals of $\{(CO)_4FeC[N(CH_3)_2]OAl[N(CH_3)_2]_2\}_2$ *(1)*, $(CO)_4FeC[N(CH_3)_2]C_6H_5$ *(2)* and $\{Al[N(CH_3)_2]_3\}_2$ *(3)* (τ values referred to TMS as internal standard; relative intensities in parentheses).

	$C_{carbene}N(CH_3)_2$	Terminal $AlN(CH_3)_2$	Bridging $AlN(CH_3)_2$	Solvent
(1)	6.37(1), 6.88(1)	7.22(2)	7.33(2)	CH_2Cl_2
(2)	5.96(1), 6.78(1)	—	—	[D_6]Acetone
	(trans) *(cis)*			
(3)	—	7.26(2)	7.63(1)	Benzene

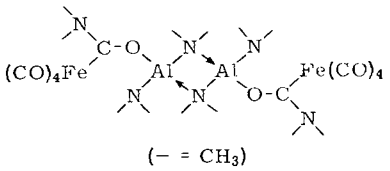
The Table shows clearly that the proton signals of *(1)* can be derived formally by combining the corresponding signals of *(2)* and *(3)*. The two signals found for $CN(CH_3)_2$ of *(1)* and *(2)* can be ascribed to the *cis*- and *trans*-*N*-methyl groups[7]. The terminal and bridging amino groups bound to the Al of *(1)* can be distinguished, as already found in the case of *(3)*, the proton signals of the bridging $N(CH_3)_2$ groups appearing at higher field[8]. If a monomeric structure had been assumed for *(1)* only one kind of $AlN(CH_3)_2$ proton would have been observed. Thus the annexed structure is suggested for *(1)*.

The IR spectrum also accords with this structure. If trigonal-bipyramidal surroundings are assumed for the iron, three ν(CO) vibrations are to be expected for the carbene ligand in the axial position (C_{3v}), and these were found at 2031 (m), 1949 (vs) and 1912 (vs) (measurements in THF

[*] Prof. Dr. G. Schmid and Dr. W. Petz
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Dr. *J. Pebler* for measuring the Mössbauer spectrum and for contributions to the discussions.

solution); if the carbene ligand had been in the equatorial position it should lead to four ν(CO) vibrations. The large separation of the two $(CO)_4Fe$ groups prevents coupling, so that, as far as CO vibrations are concerned, the molecule behaves as a monomeric substance of type $(CO)_4FeL$.



(– = CH_3)

We assign a band at 1512 cm^{-1} of medium intensity provisionally to the C—O—Al vibration. The relatively high position of this frequency may be connected with the four-fold coordination of the aluminum, which could lead to a relatively large C=O double bond character. The remainder of the IR spectrum is dominated mainly by the amino groups.

The trigonal-bipyramidal arrangement of the ligands attached to the iron in *(1)*, as indicated by the number of ν(CO) vibrations, is confirmed by the Mössbauer spectrum: The isomeric shift (IS) is at +0.154 mm s^{-1} [referred to $Na_2Fe(CN)_5NO \cdot 2H_2O$], and the quadrupole splitting amounts to 1.96 mm s^{-1}. The compound thus fits well into the series of trigonal-bipyramidal iron(0) complexes; for comparison: $Fe(CO)_5$: IS = +0.160, QS = 2.57[9]; $(CO)_4FeP(C_6H_5)_3$: IS = +0.135, QS = 2.42 mm s^{-1}[10]. Six-fold coordinated iron(0) complexes show appreciably smaller quadrupole splittings, *e.g.* $Fe_2(CO)_9$: IS = +0.360, QS = 0.54 mm s^{-1}[10].

Experimental:

A solution of *(3)* (5.32 g, 16.8 mmol) in benzene/pentane (1:1; 150 ml) is cooled to 0 °C with rigorous exclusion of air and then mixed by stirring with $Fe(CO)_5$ (6.59 g, 33.6 mmol). Lemon-yellow crystals of *(1)* separate from the orange-red solution after *ca.* 3—5 min. The whole is stirred at 0 °C in the dark for a further 30 min and the precipitate is collected, washed twice with pentane, and dried in a vacuum. A further amount of *(1)* separates if the mother liquor is kept in a refrigerator. The united precipitates are recrystallized from tetrahydrofuran. Yield: 10 g, 84%.

Received: July 31, 1972 [Z 703 IE]
German version: Angew. Chem. *84*, 997 (1972)

[1] *G. Schmid* and *B. Stutte*, J. Organometal. Chem. *37*, 375 (1972).

[2] *G. Schmid* and *V. Bätzel*, J. Organometal. Chem., in press.

[3] *L. Busetto* and *R. J. Angelici*, Inorg. Chim. Acta *2*, 391 (1968).

[4] *A. E. Kruse* and *R. J. Angelici*, J. Organometal. Chem. *24*, 231 (1970).

[5] *R. J. Angelici* and *D. L. Denton*, Inorg. Chim. Acta *2*, 3 (1968).

[6] *R. J. Angelici* and *A. E. Kruse*, J. Organometal. Chem. *22*, 461 (1970).

[7] *E. O. Fischer, H.-J. Beck, C. G. Kreiter, J. Lynch, J. Müller*, and *E. Winkler*, Chem. Ber. *105*, 162 (1972).

[8] *J. K. Ruff* in *Ch. B. Colburn*: Developments in Inorganic Nitrogen Chemistry. Elsevier, London 1966, Vol. I, p. 470.

[9] *R. H. Herber, W. R. Kingston*, and *G. K. Wertheim*, Inorg. Chem. *2*, 153 (1963).

[10] *R. H. Herber, R. B. King*, and *G. K. Wertheim*, Inorg. Chem. *3*, 101 (1964).

1,4-Dioxocin

By *Emanuel Vogel, Hans-Josef Altenbach*, and *Dieter Cremer*[*]

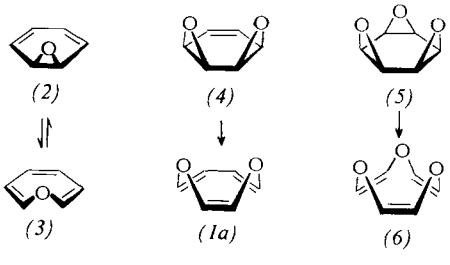
Dedicated to Professor R. Criegee in Honor of his 70th Birthday

The existence and aromaticity of the cyclooctatetraene dianion[1] has stimulated many attempts in recent years to synthesize the 10π-heterocycles *(1a)—(1c)*, the 1,4-diheterocins (1,4-dihetero[8]annulenes[2]), which are isoelectronic with that dianion. Although these investigations have led to the preparation of some non-aromatic benzo derivatives of the 1,4-diheterocins[3], no one has yet succeeded in obtaining the parent compounds[4].



(1a), X = O
(1b), X = NH
(1c), X = S

Our interest in such 10π-heterocycles, and especially in 1,4-dioxocin *(1a)*, arose naturally from further development of experiments begun some time ago on the synthesis and valence isomerizations of arene oxides[5, 6]. While benzene monoxide *(2)* exists at room temperature in rapid, energetically balanced equilibrium with oxepin *(3)*[5], it is to be expected that the hitherto unknown *syn*-benzene dioxide *(4)* would fairly readily undergo an orbital-symmetry allowed $[_\pi 2_s + _\sigma 2_s + _\sigma 2_s]$-cycloreversion (retro-Diels-Alder reaction) to 1,4-dioxocin *(1a)*. Finally, the also still hypothetical *syn*-benzene trioxide *(5)* can be anticipated to experience a $[_\sigma 2_s + _\sigma 2_s + _\sigma 2_s]$-cycloreversion (retro-homo-Diels-Alder reaction) to yield the interesting heterocycle *all-cis*-1,4,7-trioxonin *(6)*[7, 8].



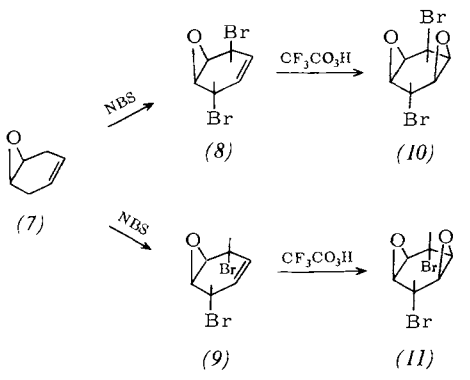
(2) *(4)* *(5)*
(3) *(1a)* *(6)*

We are now able to report the synthesis of the 1,4-dioxocin *(1a)* by way of a thermal *syn*-benzene dioxide valence isomerization.

The starting point of the route to *(1a)* is the monoepoxide of 1,4-cyclohexadiene *(7)*[9]. If *(7)* is treated in boiling carbon tetrachloride with *N*-bromosuccinimide (NBS) (molar ratio 1:2), a mixture of bromination products is formed from which it is possible to isolate, by fractional crystallization from ether/methylene chloride (1:1), *trans*-3,6-dibromo-4,5-epoxycyclohexene *(8)* [m. p. 117 °C; yield 18%; NMR ($CDCl_3$): broad multiplets at τ = 4.25 (2 olefinic protons), 4.95 and 5.10 (2 CHBr protons) as well as 6.09 and 6.30 ppm (2 epoxidic protons)] together with

[*] Prof. Dr. E. Vogel, Dipl.-Chem. H.-J. Altenbach, and Dipl.-Chem. D. Cremer
Institut für Organische Chemie der Universität
5 Köln 1, Zülpicher Strasse 47 (Germany)

one of the two *cis*-3,6-dibromo isomers, very probably the *cis*-3,6-dibromo-*anti*-4,5-epoxycyclohexene *(9)* [m. p. 97 °C; yield 5%; NMR ($CDCl_3$): narrow multiplets at $\tau = 4.17$ (2 olefinic protons), 5.12 (2 CHBr protons) and 6.28 ppm (2 epoxidic protons)].

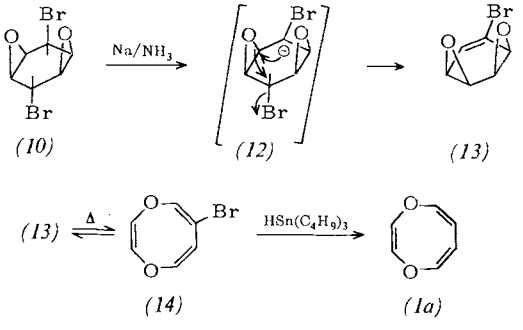


(7) *(8)* *(10)* *(9)* *(11)*

The configurations assigned to these epoxy dibromides follow from comparison of their NMR spectra. For the compound of m. p. 117 °C the epoxy and CHBr protons each give rise to different chemical shifts, from which the presence of *(8)* can be concluded, whereas for the isomer of m. p. 97 °C, in accord with the symmetry of a configuration containing the Br atoms in *cis*-relationship, these types of protons each give rise to a narrow multiplet. The configuration *(9)* for the isomer of m. p. 97 °C can be deduced from the NMR finding[10] that with cyclohexene epoxides having *syn*- and *anti*-substituents (OH or OAc groups) respectively next to the epoxide ring the resonances of the epoxide protons always occur at the higher field strength if an *anti*-relationship of the substituents obtains. Finally, the occurrence of *(9)* is supported by the argument that formation of this epoxy dibromide rather than its *syn-cis*-3,6-dibromo isomer should be favored on steric grounds[11].

The epoxy dibromides *(8)* and *(9)* could be epoxidized by trifluoroperacetic acid—but not by other peracids—in Na_2HPO_4-buffered methylene chloride solution, whereby each afforded a sterically homogeneous diepoxy dibromide in almost quantitative yield. The diepoxy dibromide formed from *(9)* must have structure *(11)* since its NMR spectrum [($CDCl_3$): narrow multiplets at $\tau = 5.13$ (2 CHBr protons) and 6.44 ppm (4 epoxidic protons)] shows the four epoxidic protons to be equivalent. The *syn*-stereospecificity of the epoxidation of *(9)* is apparently due to the tendency of the pre-existing epoxide function to stabilize the transition state of the reaction by hydrogen-bridge formation[12]. For the diepoxy dibromide derived from *(8)*, assignment of configuration from the NMR spectrum [($CDCl_3$): triplets at $\tau = 5.15$ and 5.31 (2 CHBr protons) as well as multiplets at $\tau = 6.27$ and 6.49 ppm (4 epoxidic protons)] is problematical, but *syn*-arrangement of the two epoxide rings in accord with structure *(10)* can be regarded as certain also for this compound both by analogy and as a result of its subsequent reactions[11].

The diepoxy dibromide *(10)* undergoes a remarkable rearrangement when treated with 1 g-atom of sodium per mol of *(10)* in liquid ammonia at −78 °C: by elimination of one mol of hydrogen bromide, presumably by way of the anionic intermediate *(12)*, this affords 1-bromo-*syn*-benzene dioxide *(13)*, m. p. 73 °C (dec), in 63% yield [NMR ($CDCl_3$): doublet of doublets at $\tau = 3.21$ (1 olefinic proton) and multiplet at $\tau = 6.41$ ppm (4 epoxidic protons). The *syn*-configuration of this benzene dioxide follows with considerable certainty from the relatively small activation energy of 28.5 kcal/mol ($A = 3.8 \times 10^{13}$) for thermal rearrangement of the compound in carbon tetrachloride to achieve equilibrium with 6-bromo-1,4-dioxocin *(14)* [composition at 77 °C (in CCl_4), 35% of *(13)* and 65% of *(14)* (activation parameters of the reverse reaction: $E_a = 25.6$ kcal/mol and $A = 3.2 \times 10^{12}$)]. The equilibrium can be set up from both sides. Isolation of *(14)* [b. p. 35 °C/0.5 torr; NMR (CCl_4): singlet at $\tau = 3.15$ (H-5), AB system at $\tau = 4.06$ and 4.20 with $J = 4.2$ Hz (H-2, H-3), and a further AB system at $\tau = 3.72$ and 4.63 ppm with $J = 7.5$ Hz (H-7, H-8)] was achieved by careful distillation below the isomerization temperature. *(14)* can be converted readily into the 1,4-dioxocin *(1a)*, a colorless liquid of b. p. 39 °C/14 torr, $n_D^{20} = 1.5215$, in 32% yield by reductive elimination of the bromine atom by means of tri-*n*-butyltin hydride at room temperature.



(10) *(12)* *(13)* *(13)* *(14)* *(1a)*

The 1,4-dioxocin *(1a)* is unambiguously shown to be an olefinic compound both by its spectra and by its chemical behavior. In accord with the structure assumed, the NMR spectrum (100 MHz, CCl_4) of this compound only consists of a singlet at $\tau = 4.0$ (H-2, H-3) and an AA'XX' system at $\tau_A = 3.41$ and $\tau_X = 4.88$ ppm (H-5, H-8, and H-6, H-7, respectively). Analysis of the AA'XX' system showed that the protons of the diene portion of the molecule have the following coupling constants: $J_{5,6} = 8.00$ $J_{5,7} = -0.17$, $J_{5,8} = 0.76$, and $J_{6,7} = 9.22$ Hz. In view of the absorption of all the protons in the olefinic region the fact that the vicinal couplings J_{AX} and $J_{XX'}$ are of the same order of magnitude is certainly not an expression of any considerable bonding equalization in *(1a)*[3b] but may be ascribed to the different influences of the oxygen atoms on the two couplings[13] as well as to a coplanar arrangement of the conjugated double bonds[14]. The NMR spectrum does not permit any statement about the favored conformation of the whole molecule.

The shape of the UV spectrum of *(1a)* [λ_{max} (in cyclohexane) = 238 ($\varepsilon = 7400$) and 285 nm (320, shoulder)] shows a relation to that of 1,3,6-cyclooctatriene[16].

Chemically, the olefinic nature of the 1,4-dioxocin is manifested particularly in the tendency of the compound to polymerize on standing for even a short time. The new heterocycle is also readily hydrogenated over palladium/charcoal, yielding a compound [95%; b. p. 149 °C: NMR (CCl_4): multiplets at $\tau = 6.22$ (4 protons) and 8.27 (4 protons) and a singlet at $\tau = 6.43$ ppm (4 protons)] considered to be 1,4-dioxacyclooctane, as well as a further, unidentified hydrogenation product (5%).

The experience with *(14)* indicates that a thermal equilibrium between the 1,4-dioxocin *(1a)* and the valence-isomeric *syn*-benzene dioxide *(4)* might be established above *ca.* 60 °C, but this could not as yet be realized experimentally. If such an equilibrium exists, the amount of the *syn*-benzene dioxide component in CCl_4 solution below 100 °C is certainly less than 5% (NMR limit of detection). The same follows from the thermal and spectroscopic properties of *syn*-benzene dioxide *(4)* which has meanwhile been synthesized by an independent route[17].

Received: March 13, 1972 [Z 607 IE]
German version: Angew. Chem. *84*, 983 (1972)

[1] *T. J. Katz*, J. Amer. Chem. Soc. *82*, 3784, 3785 (1960).

[2] For nomenclature see: *P. J. Garratt, A. B. Holmes, F. Sondheimer,* and *K. P. C. Vollhardt*, Chem. Commun. *1971*, 947.

[3] a) *W. Schroth* and *B. Werner*, Angew. Chem. *79*, 684 (1967); Angew. Chem. internat. Edit. *6*, 697 (1967); *W. Schroth, F. Billig,* and *A. Zschunke*, Z. Chem. *9*, 184 (1969); b) *H.-J. Shue* and *F. W. Fowler*, Tetrahedron Lett. *1971*, 2437; c) *D. L. Coffen, Y. C. Poon,* and *M. L. Lee*, J. Amer. Chem. Soc. *93*, 4627 (1971).

[4] According to *D. L. Coffen et al.* [3c], 1,4-dithiocin *(1c)*, which is more likely to exhibit aromatic character than the other 1,4-diheterocins, fragments under the conditions of formation to benzene and sulfur, presumably by way of *syn*-benzene bisepisulfide; a multiply substituted, stable 1,4-dithiocin has, however, been reported by *M. O. Riley* and *J. D. Park*, Tetrahedron Lett. *1971*, 2871.

[5] Review: *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967).

[6] The study of arene oxide-oxepin chemistry initiated in this laboratory mainly from theoretical aspects gained an unexpected new dimension when arene oxides were very recently recognized by *B. Witkop et al.* as labile intermediates of the metabolism of aromatic compounds; see *B. Witkop*, 13th Paul Karrer Lecture, Experientia *27*, 1121 (1971).

[7] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[8] Compare the thermal behavior of bis- and tris-homobenzenes and their monohetero derivatives: a) *W. R. Roth* and *B. Peltzer*, Liebigs Ann. Chem. *685*, 56 (1965); b) *H. Prinzbach* and *D. Stusche*, Angew. Chem. *82*, 836 (1970); Angew. Chem. internat. Edit. *9*, 799 (1970); Helv. Chim. Acta *54*, 755 (1971); c) *A. de Meijere, D. Kaufmann*, and *O. Schallner*, Angew. Chem. *83*, 404 (1971); Angew. Chem. internat. Edit. *10*, 417 (1971); d) *H. W. Whitlock, Jr.* and *P. F. Schatz*, J. Amer. Chem. Soc. *93*, 3837 (1971); e) *D. L. Dalrymple* and *S. P. B. Taylor, ibid. 93*, 7098 (1971).

[9] *M. Tiffeneau* and *B. Tschoubar*, C. R. Acad. Sci. Paris *212*, 581 (1941).

[10] *K. Jankowski* and *J.-Y. Daigle*, Can. J. Chem. *49*, 2594 (1971).

[11] To support the configurations [*(8)* and *(9)*, *(10)* and *(11)*, respectively] assigned to the epoxy dibromides and diepoxy dibromides we are in process of studying the signal shifts in the NMR spectra of the four compounds caused by additions of paramagnetic lanthanoid complexes.

[12] *H. B. Henbest*, Tilden Lecture of the Chemical Society, London 1962.

[13] *L. M. Jackman* and *S. Sternhell*: Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry. Pergamon Press, Oxford 1969.

[14] In view of the dependence of vicinal coupling constants on dihedral angles [15] studied by *Karplus* and *Conroy* [15], a twisted arrangement would be expected to reverse the relation of the coupling constants to give $J_{5,6} > J_{6,7}$.

[15] *M. Karplus*, J. Amer. Chem. Soc. *85*, 2870 (1963); *H. Conroy*, Advan. Org. Chem. *2*, 265 (1960).

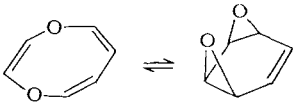
[16] *A. C. Cope* and *F. A. Hochstein*, J. Amer. Chem. Soc. *72*, 2515 (1950).

[17] Starting from *(9)*, *H.-J. Altenbach* (unpublished work) has prepared *syn*-benzene dioxide as a stable colorless compound of m. p. 93 °C.

Valence Tautomerism of 1,4-Dioxocin with *syn*-Benzene Dioxide[**]

By *Hans-Josef Altenbach* and *Emanuel Vogel*[*]

Oxepin and its valence tautomer, benzene oxide, exist in rapid equilibration at room temperature, the two components being present in comparable amounts[1]. In the conversion of oxepin into benzene oxide the removal of a C=C double bond and the formation of an epoxide-C—C bond must thus be energetically in approximate balance[2]. This finding implies the at first sight surprising possibility that 1,4-dioxocin *(1)* and *all-cis*-1,4,7-trioxonin might also be in equilibrium with detectable amounts of their benzene oxide-type valence tautomers, *i.e. syn*-benzene dioxide *(2)* and *syn*-benzene trioxide[3], respectively, for the isomerization of the two oxaannulenes also involves loss of a double bond and gain of an epoxide ring. We provide below proof of existence of valence tautomerism, mobile above *ca.* 50 °C, between 1,4-dioxocin and *syn*-benzene dioxide[4, 5].



(1) *(2)*

In benzene (but not in CCl_4) at 50—80 °C, the 1,4-dioxocin *(1)* described in the preceding communication[4] undergoes slight isomerization, that can be followed readily by NMR spectroscopy (Figs. 1a and 1b) and whose amount is not notably increased by continued heating. The isomerization product is homogeneous and can be isolated as a crystalline compound of m. p. 93 °C (from ether/pentane) after removal of the relatively volatile *(1)* by distillation in a vacuum. Spectral comparison and a mixed melting point determination proved the identity of this isomer with *syn*-benzene dioxide *(2)* obtained by an independent synthesis.

Availability of *cis*-3,6-dibromo-*anti*-4,5-epoxycyclohexene *(3)*[4, 6] encouraged us to attempt the preparation of *syn*-benzene dioxide in a conventional manner by way of benzene bis(bromohydrins), *e.g. (5)*, having a configuration suitable for a double epoxide ring closure.

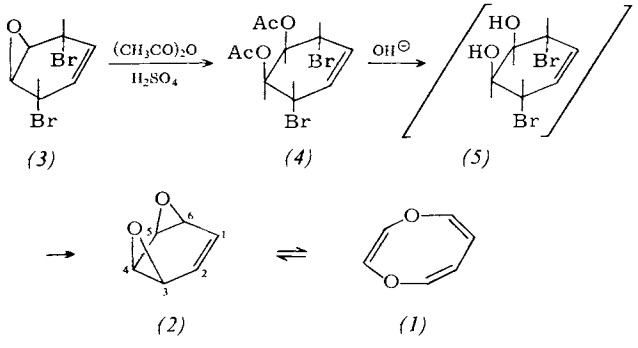
If it were possible to open the epoxide ring of *(3)* in a *cis* fashion with formation of *(5)* or an ester of *(5)*, this would place in our hands a benzene bis(bromohydrin) that should yield *(2)* under the influence of bases.

Treatment of *(3)* with acetic anhydride and sulfuric acid at room temperature—a procedure that could be considered the most likely to lead to *cis*-opening of the epoxide ring (formation of a diacetate)[7]—gave a homogeneous diacetate of m. p. 98 °C in 90% yield. This product is, however, clearly not the expected *(4)* since its NMR spectrum showed the presence of two different acetyl groups; it seems probable that it is the *trans*-diacetate corresponding to *(4)*. Neglecting the structural and configurational un-

[*] Dipl.-Chem. H.-J. Altenbach and Prof. Dr. E. Vogel
Institut für Organische Chemie der Universität
5 Köln 1, Zülpicher Strasse 47 (Germany)

[**] *Note added in proof* (September 22, 1972): *anti*-Benzene dioxide, the only still unknown oxide of benzene, has now also been synthesized [m. p. 58—59 °C; NMR ($CDCl_3$): triplet at $\tau = 3.9$ and multiplets at $\tau = 6.2$ and 6.9]. The compound is formed from *trans*-3,6-dibromo-4,5-epoxycyclohexene by reaction with acetic anhydride/sulfuric acid and treatment of the diacetate (m. p. 101 °C) thus obtained with sodium hydroxide in ether.

certainty[8] of the compound of m. p. 98 °C we treated it at room temperature with methanolic potassium hydroxide; there was formed, in 60% yield, a non-phenolic



substance of m. p. 93 °C having the molecular formula $C_6H_6O_2$ and identified by means of its NMR and IR spectra as one of the stereoisomeric benzene dioxides.

Its NMR spectrum (100 MHz, $CDCl_3$) shows a triplet at $\tau = 3.53$ (H^1, H^2) and multiplets at $\tau = 6.29$ (H^4, H^5) and 6.61 (H^3, H^6). Assignment to the epoxide protons, according to which the multiplet at higher field refers to the allylic protons H^3 and H^6, was based on double resonance experiments, as follows. Irradiation at $\tau = 6.61$ reduces the other two signals each to a singlet, while irradiation at $\tau = 6.29$ only converts the multiplet at 6.61 into a triplet. On irradiation at $\tau = 3.53$ the multiplet at higher field is simplified in such a way that together with the multiplet at lower field it now forms an AA'BB' system; analysis of the AA'BB' system affords the following coupling constants for the epoxide protons: $J_{3,4} = 3.52$, $J_{3,5} = 0.43$, $J_{4,5} = 2.83$, and $J_{3,6} = 0.01$ Hz[9]. The NMR-spectrum in C_6D_6 is reproduced in Fig. 1c.

The IR spectrum shows two relatively strong bands in the region 750 to 950 cm^{-1} where numerous epoxides absorb. There is no UV absorption above 220 nm.

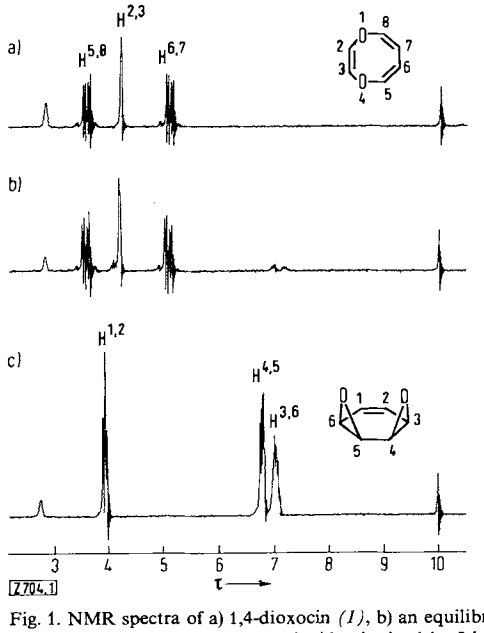
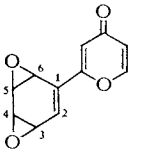


Fig. 1. NMR spectra of a) 1,4-dioxocin *(1)*, b) an equilibrium mixture of 1,4-dioxocin and *syn*-benzene dioxide obtained by 8 hours' heating of *(1)* in C_6D_6 at 70 °C, and c) *syn*-benzene dioxide *(2)* in C_6D_6 (60 MHz, TMS as internal standard).

The *syn*-configuration of this benzene dioxide follows from the chemical finding that catalytic hydrogenation of the compound over Pd/C in ethyl acetate affords the known *cis*-1,2:3,4-diepoxycyclohexane[10].

In the crystalline state *syn*-benzene dioxide *(2)* is stable for some time at room temperature. However, as expected from the thermal behavior of 1,4-dioxocin, *(2)* rearranges in solution, relatively rapidly above 50 °C, until equilibrium is reached with its valence tautomer containing an eight-membered ring. At 60 °C in benzene, the relative amounts of *(2)* and *(1)* are 5:95, independently of from which side equilibrium is approached. Kinetic evaluation, by NMR spectroscopy, of the valence tautomerism between *syn*-benzene dioxide and 1,4-dioxocin gave, for the forward reaction *(2)* → *(1)* $E_a = 27.0$ kcal/mol and $A = 7.1 \times 10^{13}$ and for the back reaction *(1)* → *(2)* $E_a = 25.4$ kcal/mol and $A = 3.2 \times 10^{11}$.

Since soon after their synthesis[1] arene oxides were recognized as metabolites of aromatic compounds[11], and have even been connected with carcinogenesis[12], it is hardly remarkable that nature can also produce arene dioxides. Recently *Borders, Shu,* and *Lancaster*[13] isolated, as a metabolite from an unspecified type of fungus, an antibiotic whose structure was determined by spectroscopic and chemical investigation as *(6)* which contains a benzene dioxide ring system. The *anti*-configuration



(6)

proposed by these authors for the two epoxide rings was based solely on the relatively low $J_{4,5}$ coupling constant of 2.8 Hz (dihedral angle between the appropriate protons in the *syn*- and *anti*-configuration = 0° and 50°, respectively). Since, according to the analysis given above, the corresponding protons in *(2)* also have an unusually low coupling constant (2.83 Hz)[14], the question whether the benzene dioxide moiety of *(6)* has the *syn*- or the *anti*-configuration seems to us to be still open.

Received: July 28, 1972 [Z 704 IE]
German version: Angew. Chem. *84*, 985 (1972)

[1] *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967).

[2] There is as yet no satisfactory explanation for the fact that the equilibria between oxepin and benzene oxide and between cycloheptatriene and norcaradiene lie at very different positions, although, according to *A. S. Pell* and *G. Pilcher*, Trans. Faraday Soc. *61*, 71 (1965), an epoxide ring possesses about the same strain as the cyclopropane ring.

[3] The stereoisomeric benzene trioxides have recently been synthesized in our laboratories. The *syn*-isomer [m. p. 242 °C; NMR (CD_3CN): singlet at $\tau = 6.62$] is formed from *(3)* by hydroxylation with potassium permanganate and treatment of the diol (m. p. 69 °C) thus obtained with methanolic potassium hydroxide; the *trans*-isomer [m. p. 88 °C; NMR (C_6D_6): narrow multiplets at $\tau = 6.96$ and 7.17] is obtained among several other products on thermolysis of the adduct of singlet oxygen to benzene oxide-oxepin.

[4] Cf. the valence tautomerism between 1-bromo-*syn*-benzene dioxide and 6-bromo-1,4-dioxocin previously described by *E. Vogel, H.-J. Altenbach,* and *D. Cremer*, Angew. Chem. *84*, 983 (1972); Angew. Chem. Internat. Edit. *11*, 935 (1972).

[5] Analogous thermal equilibria were recently observed by *D. Stusche, M. Breuninger,* and *H. Prinzbach* (Helv. Chim. Acta, in the press) be-

tween *cis*-monooxa-σ-bishomobenzene derivatives and the corresponding oxa-π-bishomobenzene compounds (oxacyclooctatrienes). We thank Prof. *Prinzbach* for this information.

[6] The structural assignment of this *cis*-3,6-dibromo-4,5-epoxycyclohexene has meanwhile been strengthened by the evaluation of the shifts of the proton resonance signals in the presence of $Eu(fod)_3$.

[7] Cf. *A. S. Y. Chau* and *W. P. Cochrane*, Chem. Ind. (London), *1970*, 1568, who cite further literature on *cis*-opening of epoxides.

[8] Owing to the number of reactive centers in *(3)* an anomalous course for the reaction with acetic anhydride/sulfuric acid cannot be excluded. A further investigation is in progress.

[9] We thank *H. Schmickler* for analysis of the AA'BB' system.

[10] *K. K. Maheshwari, P. de Mayo*, and *D. Wiegand*, Can. J. Chem. *48*, 3265 (1970).

[11] *B. Witkop*, 13th Paul Karrer Lecture, Experientia *27*, 1121 (1971).

[12] *P. L. Grover, P. Sims, E. Huberman, H. Marquardt, T. Kuroki*, and *C. Heidelberger*, Proc. Nat. Acad. Sci. USA, *68*, 1098 (1971).

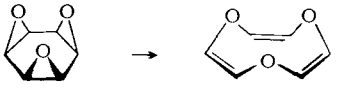
[13] *D. B. Borders, P. Shu*, and *J. E. Lancaster*, J. Amer. Chem. Soc. *94*, 2540 (1972).

[14] As shown by *K. Tori, T. Komeno*, and *T. Nakagawa* [J. Org. Chem. *29*, 1136 (1964)], in the 1,2-epoxycyclohexane system the value of $J_{vicinal}$ between an epoxide proton and a proton on the neighboring carbon atom is appreciably smaller for dihedral angles of 0° to *ca.* 50° than would be expected from the Karplus equation. These authors cite the electronegativity of the oxygen atom as the cause of this deviation. In the light of this, the coupling of 2.83 Hz found for $J_{4,5}$ in *(2)* seems reasonable.

Valence Isomerization of *syn*-Benzene Trioxide to *cis,cis,cis*-1,4,7-Trioxacyclononatriene; *anti*-Benzene Trioxide[**]

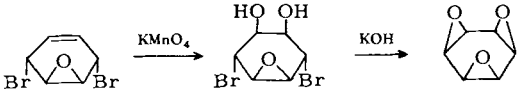
By *Emanuel Vogel, Hans-Josef Altenbach*, and *Claus-Dieter Sommerfeld*[*]

Simple consideration of energetics[1] indicates that *syn*-benzene dioxide and *syn*-benzene trioxide *(1)*—by analogy with the valence tautomerism between benzene oxide and oxepin[2]—would be in equilibrium with comparable or at least detectable amounts of their monocyclic valence tautomers, *i.e.* 1,4-dioxocin and *cis,cis,cis*-1,4,7-trioxacyclononatriene *(2)*, respectively. We have already reported[1] that valence tautomerism does exist between *syn*-benzene dioxide and 1,4-dioxocin, becoming mobile only above 50 °C, and that the benzene oxide component can just be identified both chemically and spectroscopically. We have now succeeded in realising the thermal valence isomerization of the *syn*-benzene trioxide to *cis,cis,cis*-1,4,7-trioxacyclononatriene, but have so far found no evidence of reversibility of this rearrangement.



(1) *(2)*

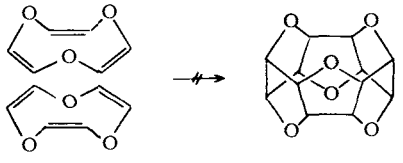
After our experience with the systems named above it seemed to us that a synthetic approach to the *syn*-benzene trioxide-*cis,cis,cis*-1,4,7-trioxacyclononatriene system was most likely to be realizable from the benzene oxide side. The obvious epoxidation of *syn*-benzene dioxide *(8)* by trifluoroperacetic acid, where there was the possibility that both stereoisomeric benzene trioxides might be obtained, gave in fact the *anti*-isomer with high stereoselectivity (see below). Our attempts to prepare *(1)* therefore concentrated on dehydrohalogenation, by bases, of benzene monoxide bis(bromohydrins) and benzene tris(bromohydrins) having configurations suitable, respectively, for a double and a treble epoxide ring-closure.



(3) *(4)* *(1)*

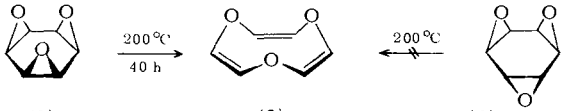
When treated with potassium permanganate in ethanol/water, the known *cis*-3,6-dibromo-*anti*-4,5-epoxycyclohexene *(3)*[3] afforded a homogeneous *cis*-glycol (m. p. 69 °C; yield 60%), which must have structure *(4)* since hydroxylation on the side remote from the bromine atoms is sterically favored. In agreement with this assumed configuration, *(4)* can be converted by treatment with methanolic potassium hydroxide at room temperature into the desired *syn*-benzene trioxide *(1)* (yield 35—40%); this melts at 242 °C (long needles from acetonitrile), which is remarkably high for a compound of this structure.

The NMR spectrum (CD_3CN) of *(1)* shows only one sharp signal at $\tau = 6.62$, corresponding to the symmetry and the epoxide structure of the compound (Fig. 1a). In the IR spectrum it is indicative that there are fewer bands than in that for the *anti*-isomer *(6)*.



(2) *(5)*

The high melting point of *(1)* at first caused us to speculate whether we had the dimer *(5)* derived from *(2)* rather than the trioxide, for this would also have been in accord with the NMR spectrum. This speculation, moreover, was entertained by the experiments of *Woodward, Fukunaga*, and *Kelley*[4] to dimerize triquinacene[5] to dodecahedrane. However, the molecular weight determined by mass spectrometry and osmometry proved the formula $C_6H_6O_3$.



(1) *(2)* *(6)*

The orbital-symmetry allowed $[_\sigma 2_s + _\sigma 2_s + _\sigma 2_s]$ cycloreversion[6] of *syn*-benzene trioxide *(1)* to *cis,cis,cis*-1,4,7-trioxacyclononatriene *(2)* occurs only on heating to 200 °C (40 h) in acetonitrile (quartz ampoule) (yield 70% on 80% reaction). For preparative purposes it is preferable, because of the shorter reaction time, to carry out the isomerization in the gas phase (Pyrex tube) at 400 to 500 °C (yield 75—80%). *(2)* is obtained as a relatively stable, colorless compound

[*] Prof. Dr. E. Vogel, Dipl.-Chem. H.-J. Altenbach, and C.-D. Sommerfeld
Institut für Organische Chemie der Universität
5 Köln 1, Zülpicher Strasse 47 (Germany)

[**] The first report of our syntheses of *syn*- and *anti*-benzene trioxide *(1)* and *(6)* was made by *E. Vogel* at a seminar in Freiburg arranged by Professor *H. Prinzbach* on July 11, 1972. The synthetic methods, melting points and NMR spectra of the two compounds were included in a previous paper [1] received on July 28, 1972.

of b. p. 90 °C. In agreement with the postulated structure, the NMR spectrum (CD_3CN) consists of a singlet at $\tau = 4.13$ (Fig. 1b), and in the IR spectrum (in substance) a C=C stretching band occurs at 1650 cm^{-1}. The UV spectrum (cyclohexane) shows end absorption that finally vanishes only at *ca.* 290 nm (ε between 240 and 290 nm: 260→0).

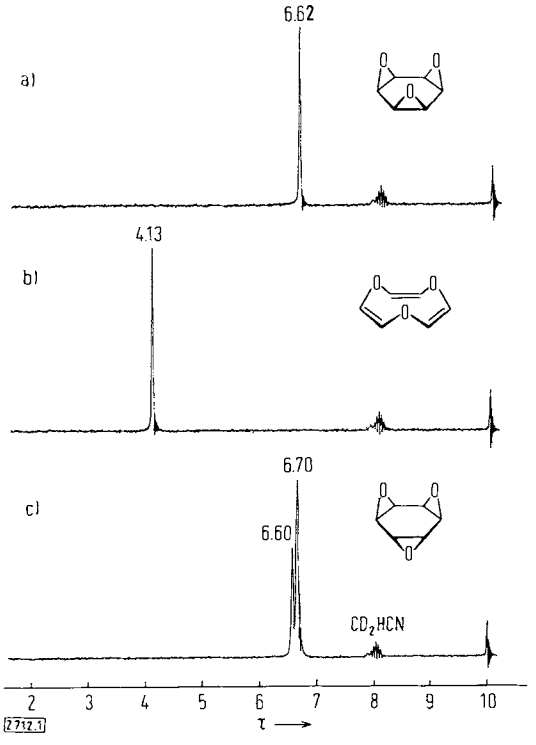
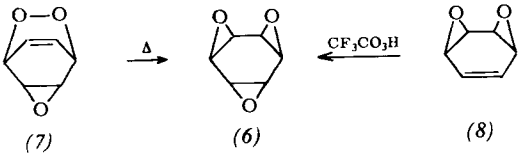


Fig. 1. NMR spectra of a) *syn*-benzene trioxide *(1)*, b) *cis,cis,cis*-1,4,7-trioxacyclononatriene *(2)* and c) *anti*-benzene trioxide *(6)* in CD_3CN (60 MHz; TMS as internal standard).

The *anti*-benzene trioxide was included in the present investigation to obtain a comparison of its thermal stability with that of its *syn*-isomer, in view of the interest in cycloreversions of *syn-anti*-isomers of bis- and tris-homobenzene compounds[7]. According to the *Woodward-Hoffmann* rules[6], *(6)* should also be susceptible to symmetry-allowed cycloreversion to give *(2)*, although in this case it would be a $[_\sigma 2_s + _\sigma 2_a + _\sigma 2_a]$ process, which for steric reasons would certainly require a relatively high activation energy. *(6)* should therefore be considerably more stable than *(1)* if there were no interference by side reactions.



(7) *(6)* *(8)*

anti-Benzene trioxide *(6)*[8] can be obtained by thermolysis of the *endo*-peroxide *(7)*[9] that in turn is formed on methylene blue-sensitized photooxygenation of benzene oxide-oxepin in acetone[10, 11]. The peroxide is not isolated in this process; instead, after the irradiation, the solution is boiled under reflux for 3 h, which causes the rearrangement. *(1)* is not obtained by this reaction, which permits the conclusion that addition of singlet oxygen to benzene monoxide affords *(7)* with high stereoselectivity. Working up by chromatography on silica gel with methylene dichloride as eluant yields *(6)* as a crystalline substance of m. p. 88 °C (needles from ether/pentane; yield 11%). *(6)* is also obtained, in 10% yield, by epoxidation of *(8)* with trifluoroperacetic acid.

Structural proof for *(6)* rests mainly on the NMR spectrum (CD_3CN), in which two narrow multiplets appear, at $\tau = 6.60$ and 6.70 (Fig. 1c).

(6) is very stable thermally, as expected; heating for several hours at 200 °C, and even gas-phase pyrolysis at 400 to 500 °C [as described for *(1)*], do not change the compound.

As crown ethers, compounds *(1)*, *(2)*, and the hydrogenation product of the latter, 1,4,7-trioxacyclononane, may be expected to yield interesting metal complexes[12], and investigations of this aspect are in progress.

Received: August 24, 1972 [Z 712 IE]
German version: Angew. Chem. *84*, 986 (1972)

[1] *H.-J. Altenbach* and *E. Vogel*, Angew. Chem. *84*, 985 (1972); Angew. Chem. internat. Edit. *11*, 937 (1972).

[2] Review: *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967).

[3] *E. Vogel, H.-J. Altenbach*, and *D. Cremer*, Angew. Chem. *84*, 983 (1972); Angew. Chem. internat. Edit. *11*, 935 (1972).

[4] *R. B. Woodward, T. Fukunaga*, and *R. C. Kelley*, J. Amer. Chem. Soc. *86*, 3162 (1964).

[5] For the synthesis of triquinacene see also: *A. de Meijere, D. Kaufmann*, and *O. Schallner*, Angew. Chem. *83*, 404 (1971); Angew. Chem. internat. Edit. *10*, 417 (1971).

[6] *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry, Verlag Chemie, Weinheim 1970, p. 101.

[7] *H. Prinzbach* and *D. Stusche*, Angew. Chem. *82*, 836 (1970); Angew. Chem. internat. Edit. *9*, 799 (1970); *H. Prinzbach* and *D. Stusche*, Helv. Chim. Acta *54*, 755 (1971); *H. W. Whitlock, Jr.* and *P. F. Schatz*, J. Amer. Chem. Soc. *93*, 3837 (1971); *D. L. Dalrymple* and *S. P. B. Taylor, ibid. 93*, 7098 (1971).

[8] The *anti*-trishomobenzene corresponding to *(6)* was very recently described by *M. Engelhard* and *W. Lüttke*, Angew. Chem. *84*, 346 (1972); Angew. Chem. internat. Edit. *11*, 310 (1972).

[9] Examples of thermal rearrangements of *endo*-peroxides to *syn*-diepoxides have been provided by *K. H. Schulte-Elte, B. Willhalm*, and *G. Ohloff*, Angew. Chem. *81*, 1045 (1969); Angew. Chem. internat. Edit. *8*, 985 (1969); also *K. K. Maheshwari, P. de Mayo*, and *D. Wiegand*, Can. J. Chem. *48*, 3265 (1970).

[10] *K. Gollnick* and *G. O. Schenck* in *J. Hamer*: 1,4-Cycloaddition Reactions. Academic Press, New York 1967, p. 286.

[11] Irradiation was effected with a sodium vapor lamp (Philips 57016 P 50 I, 60 W) in order to avoid the photoisomerization of oxepin to 2-oxabicyclo[3.2.0]hepta-3,6-diene caused by UV light.

[12] *C. J. Pedersen* and *H. K. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972).

trans-σ-Bis- and -Tris-homobenzene Derivatives; Synthesis of Cycloheptatriene-3,4-dicarboxylic Acid Derivatives[**]

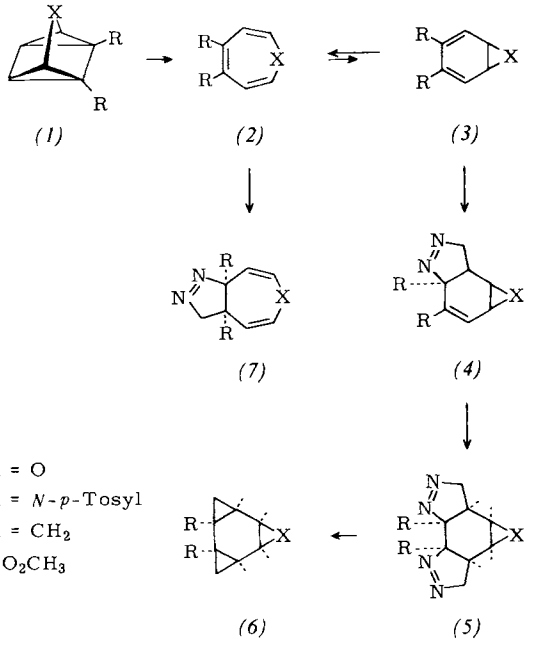
By *Horst Prinzbach* and *Reinhard Schwesinger*[*]

The first unbridged *cis*-σ-trishomobenzene derivatives *(6a)* and *(6b)* were synthesized by the reaction sequence *(1)* → *(2)* → *(3)* → *(4)* → *(5)* → *(6)*[1]. Here the methoxy-

[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. R. Schwesinger
Lehrstuhl für Organische Chemie der Universität
78 Freiburg, Albertstr. 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

carbonyl substituents have a decisive influence; they act favorably on the addition of diazomethane to the bicyclic components *(3a)* and *(3b)* of the equilibrium mixture to give *(4a)* and *(4b)* which is in general disfavored thermodynamically[2] in comparison with the addition to *(2a)* and *(2b)* which gives *(7a)* and *(7b)*.



(a), X = O
(b), X = *N*-*p*-Tosyl
(c), X = CH_2
R = CO_2CH_3

The utility of this procedure for preparation of carbocyclic trishomobenzene compounds has been studied for the example *(2c)*⇌*(3c)*. Particular attention was paid to whether the notably high *cis*-selectivity was preserved in the stages *(3)*→*(4)* and *(4)*→*(5)* when X = CH_2.

In contrast to *(2a)*⇌*(3a)* and *(2b)*⇌*(3b)*, the system *(2c)*⇌*(3c)* could not be prepared by thermolysis of the tetracycle *(1c)*[3]. We have now obtained *(2c)*⇌*(3c)* in 60% yield by thermal fission of the adduct *(10)* obtained from the homobarrelene diester *(8)*[4] and the cyclopentadienone *(9)*[5]. According to ^{1}H-NMR measurements so far made on *(2c)* and its anhydride *(2d)* the proportion of the bicyclic valence tautomer in the equilibrium mixture at −120 °C is below the limit of detection by this method[6].

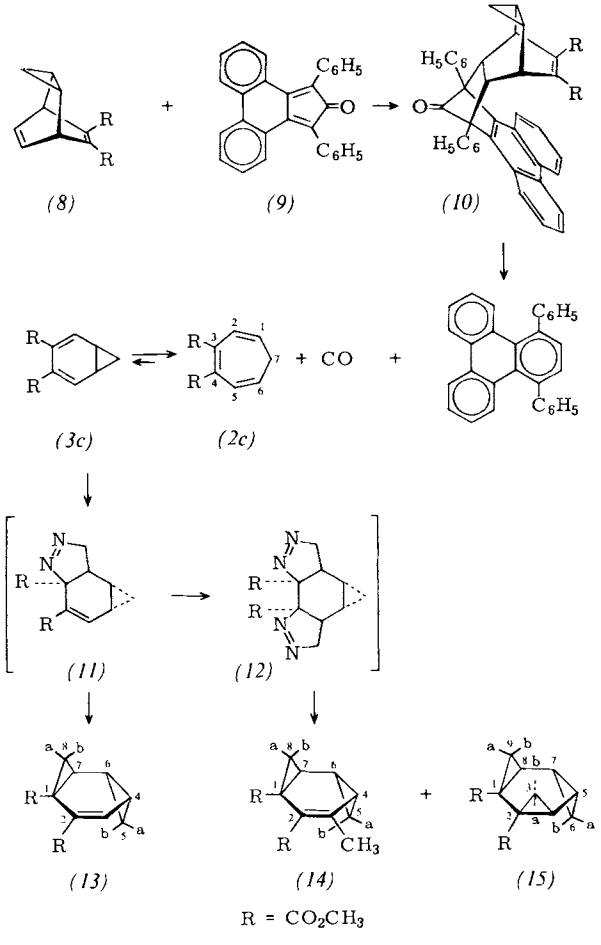
On reaction of *(2c)* with an excess (*ca.* 4 equivalents) of diazomethane in ether, which was stopped after 5 days, a complex mixture of pyrazolines is formed that, according to NMR analysis, contained about 20% of the dipyrazoline compound *(12)* which, however, could not be separated in spite of many modifications of the conditions. The crude mixture was therefore photolyzed directly, chromatographed and treated with permanganate, and the products separated, with much loss, by thin-layer and gas chromatography; the *trans*-σ-bis- *(13)* and *(14)* and *trans*-σ-trishomobenzene derivatives *(15)* were isolated in *ca.* 2% yield. Unlike the *cis*-compounds, they are thermally very stable and up to *ca.* 250 °C do not undergo the 2σ→2π or 3σ→3π isomerizations which, as synchronous reactions, are symmetry-allowed but sterically unfavorable (*cis,trans,trans*-geometry in the products). Thus, as judged

Table 1. UV and NMR data for compounds *(2c)*, *(2d)*, *(2e)*, *(2f)*, *(10)*, *(12)*, *(13)*, *(14)*, and *(15)*.

Cpd.	UV [a] λ_{max} (nm), (ε)	NMR (τ-values, coupling constants *J* in Hz)		
(2c)	276 207	3.58 (2(5)-H); 4.42 (1(6)-H); 6.24 (OCH_3); 6.69 (7-H)	$J_{1,7}=J_{6,7}=9.4$ $J_{1,2}=J_{5,6}=6.8$	[b]
(2d) [f]	293 (3500) 212 (19600)	3.17 (2(5)-H); 4.14 (1(6)-H); 6.29 (7-H)	$J_{1,7}=J_{6,7}=9.2$ $J_{1,2}=J_{5,6}=6.8$	[c]
(2e)	275 (4800) 211 (17400)	2.76 (2-H); 3.27 (4-H); 3.42 (3-H); 3.71 (5-H); 4.18 (6-H); 6.13 (7-H); 6.28 (OCH_3); 6.47 (OCH_3)	$J_{2,7}=5.8$; $J_{3,4}=11.1$; $J_{4,5}=5.4$; $J_{5,6}=9.6$; $J_{6,7}=8.2$	[b]
(2f)	268 (4800) 208 (14700)	2.46 (4-H); 3.59 (1-H); 3.73 (5-H); 4.18 (6-H); 6.34 (OCH_3); 6.42 (OCH_3); 7.62 (7-H)	$J_{1,7}=7.5$; $J_{4,5}=5.5$; $J_{5,6}=9.4$; $J_{6,7}=6.4$	[b]
(10)	284 (11300) 252 (9700) 211 (52000)	1.3–1.7 (M, 3H); 1.9–2.3 (M, 1H); 2.83 (S, 6H); 3.4 (br. S, 2H); 3.9–4.1 (M; 2H); 6.8–8.0 (M, 18H)		[c]
(12) [e]		5.06 (3a(9a)-H); 5.73 (3b(9b)-H); 6.30 (OCH_3); 7.13 (4(8)-H); 8.9–9.5 (5(7)-H; 6a-H); 9.78 (6b-H)	$J_{3a,4}=J_{8,9a}=\left.\begin{matrix}7.5\\6.3\end{matrix}\right\}$ $J_{3b,4}=J_{8,9b}=$ $J_{3a,b}=J_{9a,b}=17.3$	[c]
(13)		3.14 (3-H); 6.55 (OCH_3); 6.65 (OCH_3); 7.93 (8a-H); 8.23 (7-H); 8.89 (6-H); 9.12 (8b-H); 9.2–9.5 (4-H; 5a,b-H)	$J_{3,4}=3.8$; $J_{6,7}=0.5$; $J_{7,8a}=9.0$; $J_{7,8b}=6.5$; $J_{8a,b}=3.6$	[c]
(14)	245 (6600)	6.51 (OCH_3); 6.65 (OCH_3); 7.85 (CH_3); 7.94 (8a-H); 8.13 (7-H); 8.75 (6-H); 9.03 (8b-H); 9.18 (5a-H); 9.32 (4-H); 9.47 (5b-H)	$J_{4,5a}=8.1$; $J_{4,5b}=4.1$; $J_{4,6}=7.6$; $J_{5a,6}=8.2$; $J_{5b,6}=5.4$; $J_{5a,b}=2.1$; $J_{6,7}=1.1$; $J_{7,8a}=5.8$; $J_{7,8b}=6.4$; $J_{8a,b}=3.1$	[d]
(15)	230 end absorpt.	6.35 (OCH_3); 8.44 (3a(9a)-H); 8.77 (4(8)-H); 8.94 (5(7)-H); 9.2 (6a-H); 9.44 (3b(9b)-H); 9.79 (6b-H)	$J_{3a,b}=J_{9a,b}=4.9$; $J_{3a,4}=J_{8,9a}=8.8$; $J_{3b,4}=J_{8,9b}=6.1$; $J_{4,5}=J_{7,8}\approx 0.7$; $J_{5,6a}=J_{6a,7}=8.1$; $J_{5,6b}=J_{6b,7}=5.4$; $J_{6a,b}=4.1$	[c]

[a] In cyclohexane, with the exception of *(10)* (acetonitrile).
[b] In CCl_4.
[c] In $CDCl_3$.
[d] In C_6D_6.
[e] Numbering of the protons as in *(15)*.
[f] Anhydride of *(2c)*.

by the formation of *(11)* and *(12)*, the norcaradiene diester *(3c)* which is not directly detectable can be trapped by diazomethane in the carbocyclic system *(2c)* $\rightleftharpoons$ *(3c)*. However, it appears that addition of CH_2N_2 to *(3c)* and to *(11)* occurs, even if not exclusively, in a manner with high selectivity *trans* to the cyclopropane ring. The *cis*-selectivity found for *(3a)*, *(3b)*, *(4a)*, and *(4b)* must consequently be ascribed to a *cis*-directing effect of the hetero ring members[7]. Carbocyclic *cis*-σ-trishomobenzene derivatives thus seem to be inaccessible by the *(1)* → *(6)* route[8]. The structures of the new compounds have been proved by subsequent reactions, elemental analyses and spectroscopic data (Table 1). The coupling constants determined



for *(13)*, *(14)*, and *(15)* accord particularly well with values obtained for model compounds.

Received: August 9, 1972 [Z 711 a IE]
German version: Angew. Chem. *84*, 988 (1972)

[1] *H. Prinzbach* and *D. Stusche*, Angew. Chem. *82*, 836 (1970); Angew. Chem. internat. Edit. *9*, 799 (1970); Helv. Chim. Acta *54*, 755 (1971); cf. *H. W. Whitlock, Jr.*, and *P. F. Schatz*, J. Amer. Chem. Soc. *93*, 3837 (1971). – For stable *cis*-σ-bishomobenzene derivatives see: *D. Stusche*, *M. Breuninger*, and *H. Prinzbach*, Helv. Chim. Acta, in the press.

[2] It has not yet been determined if, or how far, the equilibrium *(2)* $\rightleftharpoons$ *(3)* is shifted in favor of the bicyclic structures by the ester groups.

[3] *H. Prinzbach*, Pure Appl. Chem. *16*, 17 (1968).

[4] *K. Alder* and *G. Jakobs*, Chem. Ber. *86*, 1528 (1953); *M. J. Goldstein* and *A. H. Gevirtz*, Tetrahedron Lett. *1965*, 4413.

[5] The adduct *(10)* proved superior to the adducts of phenyl azide, diphenylnitrile imine or dimethyl tetrazinedicarboxylate to *(8)* for elimination of the C_2H_2 bridge from *(8)*. At a lower thermolysis temperature of *ca.* 200 °C a partial isomerization of *(2c)* by 1,5-hydrogen shift could not be avoided; after hydrolysis of the ester mixture [*ca.* 60% of *(2c)* with *ca.* 30% of dimethyl cycloheptatriene-1,7-dicarboxylate *(2e)* and 8% of dimethyl cycloheptatriene-2,3-dicarboxylate *(2f)*], *(2c)* was isolated by way of its pure, crystalline anhydride *(2d)*.

[6] *H. Günther*, *R. Schwesinger*, and *H. Prinzbach*, unpublished work.

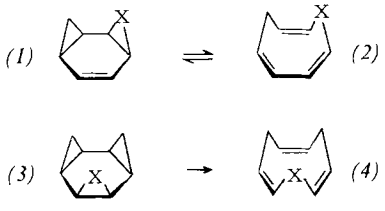
[7] Cf. *S. Winstein* and *J. Sonnenberg*, J. Amer. Chem. Soc. *83*, 3235 (1961); *W. G. Dauben* and *G. H. Berezin*, *ibid. 85*, 468 (1963).

[8] For further preparations of *trans*-σ-trishomobenzene derivatives see *M. Engelhard* and *W. Lüttke*, Angew. Chem. *84*, 346 (1972); Angew. Chem. internat. Edit. *11*, 310 (1972); *D. L. Dalrymple* and *S. P. Taylor*, J. Amer. Chem. Soc. *93*, 7098 (1971).

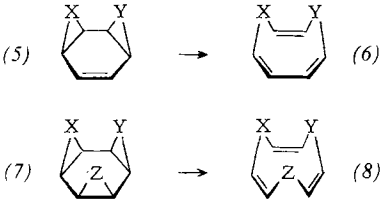
cis-Trioxatris-σ-homobenzene (*cis*-"Benzene Trioxide")[**]

By *Reinhard Schwesinger* and *Horst Prinzbach*[*]

The preparation of *cis*-monohetero-bis- and -tris-homobenzene derivatives, *(1)* and *(3)*, respectively, has been reported several times[1]. These systems are not of the least preparative importance because of the σ→π isomerization to *(2)* and *(4)*, respectively.



We have extended these studies to the σ/π-bis- and -tris-homobenzene compounds *(5)* to *(8)* with, respectively, two and three three-membered hetero rings in which the hetero atoms may be the same or different[2].

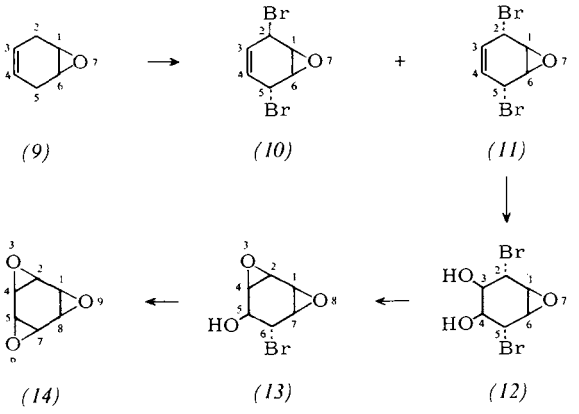


We have succeeded in synthesizing the particularly attractive *cis*-trioxatris-σ-homobenzene (*cis*-"benzene trioxide"; 3,6,9-trioxatetracyclo[6.1.0.$0^{2,4}$.$0^{5,7}$]nonane by the reaction sequence *(9)*→*(11)*→*(12)*→*(13)*→*(14)*[3]. The *cis*- and *trans*-dibromides obtained on allylic halogenation (CCl_4; *N*-bromosuccinimide + azodiisobutyronitrile) of *(9)*[5] can be separated by crystallization [isolated yields: *ca.* 25% of *(10)*, 20% of *(11)*]. As expected, *cis*-hydroxylation of *(11)* by potassium permanganate to yield *(12)* is much faster than that of *(10)*. Epoxide formation by sodium glycolate is almost quantitative, and larger or smaller amounts of the intermediate *(13)* can be isolated along with *(14)* according to the experimental conditions. The trioxide *(14)* crystallizes in colorless columns from

[*] Prof. Dr. H. Prinzbach and Dipl.-Chem. R. Schwesinger
Lehrstuhl für Organische Chemie der Universität
78 Freiburg, Albertstr. 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

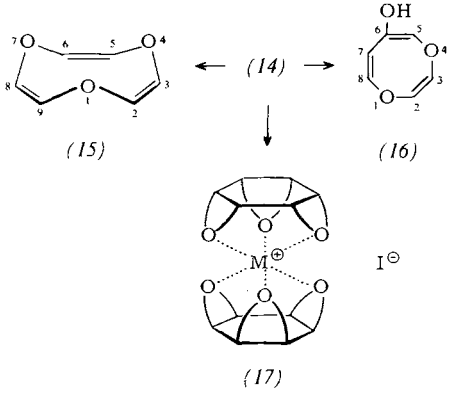
acetone, has a very high melting point [240 °C (dec)], and is thermally very stable. In solution in hexamethylphosphoric triamide or benzonitrile, there is no $3\sigma \rightarrow 3\pi$ conversion into 1,4,7-trioxonin *(15)* before decomposition sets in at *ca.* 220 °C.



(9) *(10)* *(11)*

(14) *(13)* *(12)*

The hitherto unknown heterocycle *(15)* [NMR (CCl_4; 30 °C): singlet at $\tau = 4.3$; temperature-independent between +20 and −85 °C] can, however, be obtained on a preparative scale in 80% yield by gas-phase pyrolysis at 400 °C[6]. The stability of *(14)* provides an impressive confirmation of the effect of the oxygen as a ring member in stabilizing the σ-structures, as already found for the analogs *(1)* and *(3)*. We have temporarily assigned the 1,4-dioxocin-6-ol structure *(16)* [NMR ($CDCl_3$; 30 °C): $\tau = 4.8$ (1 H; $J = 7.5$; 2.0 Hz); 5.7 (1 H, $J = 7.5$; 2.5 Hz); 6.1—6.6 (3 H; M); 6.6 to 6.8 (1 H; M)] to the product selectively formed from *(14)* by acid catalysis (CF_3CO_2H) at 30 °C[7]. Because of its geometrical properties the crown ether *(14)* seemed to us predestined for complex formation with metal ions[8]. In fact more or less stable complexes were obtained with a number of metal salts: for example, with KI in acetone, *(14)* affords a crystalline 2:1 complex as colorless needles that decompose from 180 °C to a brown melt (not the starting materials) (molecular weight: =418.2; Calc.: C 34.46; H 2.89; Found: C 34.26; H 3.08; IR (KI): 3226, 1376, 1280, 1238, 1099, 1071, 999, 896, 843, 746 cm^{-1}]; a structure with octahedral coordination to the central atom [*e.g. (17)* with $M^+ = K^+$] seems likely[9].



(15) *(14)* *(16)*

(17)

Table 1. NMR data for compounds *(9)*, *(10)*, *(11)*, *(12)*, and *(13)*.

Cpd.	1-H (6-H)	2-H (5-H)	3-H (4-H)	7-H (OH)
(9)	6.8 (2, M)	7.5 (4, M)	4.5 (2, M)	
(10) M. p. 118 °C	6.1 (6.3) (1, M) (1, M)	5.0 (5.1) (1, M) (1, M)	4.1–4.4 (2, M)	
(11) M. p. 98 °C	6.3 (2, M)	5.1 (2, M)	4.2 (2, M)	
(12) M. p. 93 °C	6.2 (2, br. S)	5.5 (2, M)	5.8 (2, M)	(7.4) (2, br. S)
(13) M. p. 84 °C	(5.5–5.8) (1, M)	(5.5–5.8) (1, M)		(6.8–7.3) (1, M)
	6.2–6.8 (4, M)			

The structures of all new compounds were proved by elemental analyses as well as by UV, IR, MS[10] and NMR data (Table 1)[11].

Compound (14):

UV (water): 215 nm end-absorption.

IR: The spectrum obtained in KI is almost identical with that of the KI complex, indicating complex formation in the KI disk. (Perchlorobutadiene): 3021, 1447, 1426, 1410, 1383, 1282, 1253 cm^{-1}; (Nujol): 1064, 1054, 1001, 995, 894, 779, 769 cm^{-1}.

MS: $m/e = 126$ (M^+); 125; 97(−HCO); 84, 81, 71, 69, 68 (100%); metastable peaks at 49 (97−CO), 37 (126−$C_2H_2O_2$); 24.5 (69−CO).

NMR: $CDCl_3$ (30 °C): $\tau = 6.5$ (S); CD_3CN (30 °C): $\tau = 6.6$ (S). The ^{13}C-H coupling constant of 186 Hz (CD_3CN; 80 °C) differs only very slightly from the known values for simple oxiranes[12].

Received: August 9, 1972 [Z 711b IE]
German version: Angew. Chem. *84*, 990 (1972)

[1] *H. Prinzbach* and *R. Schwesinger*, Angew. Chem. *84*, 988 (1972); Angew. Chem. internat. Edit. *11*, 940 (1972), where earlier literature is cited.

[2] *D. Stusche*, *M. Breuninger*, and *H. Prinzbach*, Helv. Chim. Acta, in the press.

[3] According to a personal communication (July 11, 1972) from Prof. *E. Vogel* of Köln, *(14)* has been obtained in the same way. Intensive attempts to obtain *(14)* from benzene oxide [4], utilizing a *cis*-directing effect of the epoxide oxygen [2], have so far not given any decisive result (*H. Prinzbach* and *D. Forster*, unpublished work).

[4] *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967).

[5] *M. Tiffeneau* and *R. Tschoubar*, C. R. Acad. Sci. *212*, 581 (1941).

[6] *R. Schwesinger* and *H. Prinzbach*, unpublished work.

[7] *R. Schwesinger*, *L. Knothe*, and *H. Prinzbach*, unpublished work; see *E. Vogel*, *H.-J. Altenbach*, and *D. Cremer*, Angew. Chem. *84*, 983 (1972); Angew. Chem. internat. Edit. *11*, 935 (1972). *(14)* shows the expected reactivity towards nucleophilic reagents (RO^-, $RR'NH$, RS^-, and $RR'CH^-$). Attempts to prepare the "benzene triimine", "benzene trisulfide" or carbocyclic "*cis*-tris-σ-homobenzene compounds" by using suitable substitution products of *(14)* are in progress.

[8] *C. J. Pedersen* and *K. H. Frensdorff*, Angew. Chem. *84*, 16 (1972); Angew. Chem. internat. Edit. *11*, 16 (1972).

[9] X-ray structure analysis of this and other complexes is being undertaken.

[10] We thank Dr. *H. Achenbach* for measuring the mass spectra.

[11] PES investigations will be reported in a joint paper with Prof. *Heilbronner* of Basel and Prof. *Vogel* of Köln.

[12] Ethylene oxide: 175.2 Hz [*N. Sheppard* and *J. J. Turner*, Proc. Roy. Soc. *A 254*, 506 (1951)]; *trans*-1,4-cyclohexadiene dioxide: 183 Hz (*R. Schwesinger*, *L. Knothe*, and *H. Prinzbach*, unpublished work).

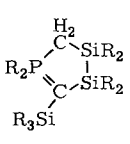
Silicon as a Carbanion Substituent in Ylides[**]

By *Hubert Schmidbaur*[*]

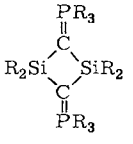
From numerous recent publications[1] it appears that silicon atoms as substituents can stabilize an ylide group very considerably. The consequence is a much diminished basicity or nucleophilicity of silylated ylides. Investigations of silyl ylides of phosphorus, arsenic, and sulfur containing various ligands on the silicon atom have shown that this "silicon effect" is founded in the properties of the silicon itself and is not caused by inductive, mesomeric, or steric effects of the ligands.

Possible explanations are concerned with a d-orbital-π-interaction or an altered charge distribution in the σ-skeleton. Photoelectron spectra and mass-spectroscopic determination of ionization potentials[2] do not provide unambiguous differentiation since the data for the free ylides and their silyl derivatives show hardly any stepwise progression.

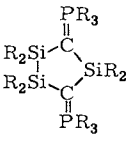
Extension of the substituents to *disilanyl* groups, which would potentially permit a *(d-d)*π-interaction, did not lead to appreciable further stabilization; on the contrary, considerable steric hindrance occurred, which made syntheses much more difficult. Investigations were made, not only with open-chain mono- and di-silanyl ylides, but also especially with cyclic ylides *(1)*—*(4)*, in which the steric



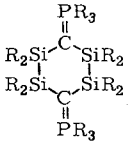
(1)



(2)



(3)



(4)

factors would be largely eliminated. The tendency for formation of the latter and their stability were surprisingly high.

Among the reactions of silyl ylides, *trans-* and *de*-silylation processes are particularly important. The former permit simple introduction of other substituents, including functional ones, such as $SiCl_3$, $SiHCl_2$, $Si(CH_3)Cl_2$, $Si(CH_3)_2Cl$, $Ge(CH_3)_3$, $Sn(CH_3)_3$, PCl_2, and $As(CH_3)_2$ groups. Desilylation leads to salt-free pure ylides whose preparation by other routes is often difficult or impossible. Addition of reagents such as HF, CH_3OH, or CH_3SH *in situ* in connection with desilylations has led to the first syntheses of pentacoordinated tetraorganofluoro-, -alkoxy-, and -mercaptophosphoranes (R_4PF, R_4POR, and R_4PSR)[3]. By use of an excess of the reagent, products of the type $R_4PF \cdot HF$, $R_4POR' \cdot R'OH$, *etc.*, are obtained, in which the anions contain strong hydrogen bonds.

Lecture at München on May 9, 1972 [VB 345 IE]
German version: Angew. Chem. *84*, 957 (1972)

[*] Prof. Dr. H. Schmidbaur
Institut für Anorganische Chemie der Universität
87 Würzburg, Landwehr (Germany)

[**] Work performed in collaboration with *G. Kammel, W. Kapp, W. Malisch, K.-H. Mitschke, H. Stühler, W. Tronich, W. Vornberger* (deceased), and *J. Weidlein*.

[1] *H. Schmidbaur* and *W. Tronich*, Chem. Ber. *100*, 1032 (1967); *101*, 595, 604, 3556, 3545 (1968); *H. Schmidbaur* and *W. Malisch, ibid. 102*, 83 (1969); *103*, 97, 3007, 3448 (1970); *104*, 150 (1971); *H. Schmidbaur* and *G. Kammel, ibid. 104*, 3252 (1971); *H. Schmidbaur* and *W. Kapp, ibid. 105*, 1203 (1972); *H. Schmidbaur, H. Stühler*, and *W. Vornberger, ibid. 105*, 1084 (1972).

[2] Unpublished work in collaboration with *H. Bock* and *S. Elbel*, Frankfurt.

[3] *H. Schmidbaur* and *H. Stühler*, Angew. Chem. *84*, 166 (1972); Angew. Chem. internat. Edit. *11*, 145 (1972); *H. Schmidbaur, K.-H. Mitschke*, and *J. Weidlein*, Angew. Chem. *84*, 165 (1972); Angew. Chem. internat. Edit. *11*, 144 (1972).

Crystalline Transition-Metal Complexes with Strongly Anisotropic Physical Properties

By *H. J. Keller*[*]

Square coordination compounds of the transition metals, which crystallize in columnar stacks, *i.e.* with formation of infinite linear metal chains, exhibit strongly anisotropic physical properties in the solid state. Among these solid substances there are a few representatives—such as Magnus salt or the glyoximato complexes of the d^8-ions Ni(II), Pd(II), and Pt(II)—with only weak intermolecular interactions along the metal chain, which can, however, be enhanced in various ways:

a) By oxidation of $[Pt(NH_3)_4]$ $[PtCl_4]$ or bis(benzildioximato)palladium(II) an originally fully occupied d_{z^2} band (valence band) can become partly emptied (conduction band). This results in the partly oxidized complexes having a metallic luster and increased electrical conductivity.

b) By coordination of d^8 metal ions with ligands which make an overlapping of the energetically higher and empty $d_{x^2-y^2}$ band with the fully occupied d_{z^2} band possible. Among these may be mentioned the isonotriles in complexes of the type $PtCl_2(CNR)_2$ (R = phenyl, *p*-toluyl, naphthyl, *etc.*). A half-occupied conduction band results, which explains the one-dimensional metallic properties of these compounds.

c) By use of d^7 central metal ions, *e.g.* cobalt(II). α-Modifications of diiodotetrakis(arylisonitrile)cobalt(II) exhibit, depending on the type of isonitrile, greatly reduced magnetic moments (one-dimensional antiferromagnetic behavior) and remarkable metallic surface luster.

Since lattice defects hinder metallic dc conductivity, for the identification of strong one-dimensional interactions in such compounds, resort must be made to either optical methods, ESR investigations of doped single crystals, or NMR investigations of the central metal ion.

Compounds of this type are—as suggested by *W. A. Little*—suitable as high-temperature superconductors. For this purpose it is necessary to link the one-dimensional metallic chain with easily polarizable organic groups. Hence, in the synthesis of columnar complexes of platinum(II), iridium(I), rhodium(I) or (II), and cobalt(II) with one-dimensional metallic properties readily variable organic molecules (glyoximes or isonitriles) were chosen as ligands in order to verify *Little's* model experimentally.

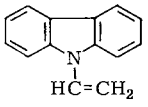
Lecture at Ludwigshafen, June 14, 1972 [VB 353 IE]
German version: Angew. Chem. *84*, 998 (1972)

[*] Prof. Dr. H. J. Keller
Anorganisch-Chemisches Institut der Universität
69 Heidelberg 1, Im Neuenheimer Feld 7 (Germany)

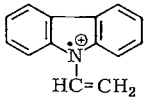
Reviews

Abstracts of selected progress reports and review articles

The polymerization of *N*-vinylcarbazole with metal salts is reviewed by *M. Biswas* and *D. Chakravarty*. Depending on their nature, metal salts can either convert *N*-vinylcarbazole *(1)* into a radical cation *(2)*, in which the positive charge



(1)



(2)

subsequently migrates to the vinyl double bond thus initiating polymerization, or they can attack the vinyl double bond directly and there generate a cationic, polymerization-active center. While the mode of action of oxidizing metal salts regarding the formation of *(2)* is well known, the way in which compounds of the BF_3 type (aprotic acids) initiate the polymerization of *(1)* is still unclear. [Polymerization of *N*-Vinylcarbazoles. Rev. Macromol. Chem. *8*, 189—208 (1972); 40 References]

[Rd 528 IE—G]

Polymer compatibility is the subject of a report by *Sonja Krause*. By compatibility is understood the miscibility of homopolymers and of random copolymers in the amorphous, non-crystalline state. The review is divided, in effect, into two parts, the first of which gives detailed experimental data on the miscibility of polymer pairs including that in the literature up to March 1971 under the heading "polymer compatibility". The second part deals with the theory of miscibility of polymers and a step-by-step account is given of how one can predict the miscibility of two particular polymers. [Polymer Compatibility. Rev. Macromol. Chem. *8*, 251—314 (1972); 135 References]

[Rd 530 IE—G]

Transition-metal complexes of olefins and acetylenes are dealt with by *L. D. Pettit* and *D. S. Barnes* in a review which is mainly devoted to the stability, structures, and bond characteristics of these compounds. Both σ- as well as π-complexes of the metals silver, copper, platinum, palladium, and rhodium are discussed and thermodynamic data and results of X-ray or neutron diffraction analysis are quoted. [The Stability and Structures of Olefin and Acetylene Complexes of Transition Metals. Fortschr. Chem. Forsch. *28*, 85—139 (1972); 153 References]

[Rd 533 IE—G]

Ring ligand substitution reactions of aromatic-metal complexes form the theme of a progress report by *H. Werner*. Reactions of this type, for instance

$$Ni(C_5H_5)_2 + 4KCN \rightarrow K_2[Ni(CN)_4] + 2KC_5H_5$$

often require a relatively high activation energy, so they are generally not so characteristic of the complexes of the type C_nH_n—M. However, they form an important part of the chemistry of aromatic-metal complexes, which has earned attention not only from the preparative point of view but also from the point of view of bond theory and reaction kinetics. Substitution reactions of complexes of the type C_5H_5—M and C_6H_6—M are discussed. Cyclobutadiene complexes are also dealt with; the analogous reactions of C_7H_7—M and C_8H_8—M are, as yet, unknown. [Fortschr. Chem. Forsch. *28*, 141—181 (1972); 166 References]

[Rd 534 IE—G]

Enzymes containing molybdenum are the subject of a review by *R. C. Bray* and *J. C. Swann*. The dynamics of reactions catalyzed by enzymes of this group are described extensively using xanthine oxidase from cow's milk as an example. The role of molybdenum in other oxidases as well as in reductases, dehydrogenases, and nitrogenases is outlined. [Molybdenum-Containing Enzymes. Structure and Bonding *11*, 107—144 (1972); 115 references]

[Rd 543 IE—H]

The occurrence of iron in living nature is reviewed by *J. B. Neilands*. Iron compounds found in microorganisms, in plants, and in animals are specified and, if known, their physiological role and mode of action are explained. The present state of knowledge suggests that the primordial type of iron complexation was with sulfur; coordination with sulfur and nitrogen, sulfur and oxygen, and exclusively with oxygen developed stepwise. [Evolution of Biological Iron Binding Centers. Structure and Bonding *11*, 145—170 (1972); 112 references]

[Rd 544 IE—H]

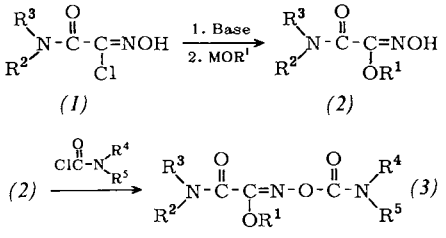
The synthesis of hydroxy-deuterated alcohols, R-OD, is summarized by *L. Verbit* in an article giving procedures for large-scale preparations of substances having high isotopic purities. D_2O is mostly used as deuterium source. Sufficient methods are available to permit deuteration of almost any desired hydroxyl group: Simple exchange reactions and hydrolysis of alkoxides, trialkyl borates, dialkyl carbonates, dialkyl sulfites, silicone derivatives, carboxylates, ortho esters, and ketals. Countercurrent exchange in the gaseous phase between D_2O and alcohols having b.p. < 200 °C (isotopic purity > 98%) appears of special interest. [The Synthesis of Alcohols-OD. Synthesis *1972*, 254—258; 38 references]

[Rd 540 IE—M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

New 1-carbamoyl-*N*-carbamoyloxyformimidates *(3)*, methods for their preparation, and pesticides containing *(3)* are claimed. The 1-carbamoyl-*N*-hydroxyformimidates *(2)*, which are obtainable as intermediates in accordance with the reaction scheme, are also claimed. Depending on R^4



(1) *(2)*

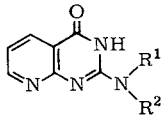
(3)

Preferred compounds:
R^1 = (substituted) alkyl, allyl, or alkenyl
R^2 = H, alkyl, or methoxy
R^3 = H, or alkyl
R^4,R^5 = H or CH_3
M = alkali metal

and/or R^5, the compounds *(2)* are treated with sodium cyanate and hydrogen chloride or with substituted isocyanates or with sodium hydride with subsequent treatment of the resulting salts with a substituted carbamoyl chloride. The new formimidates *(3)*, possibly with the addition of surface active agents and/or other biologically active compounds, can be made into pesticides for use *e. g.* against insects, ticks, mites, and nematodes. [DOS 2135251; E.I. du Pont de Nemours and Co., Wilmington]

[PR 13 –N IE]

2-Aminopyrido[2,3-*d*]pyrimidine-4(3*H*)-one derivatives have a diuretic and natriuretic effect. The compounds, which can be prepared by known methods, cause increased



R^1,R^2 = (substituted) alkyl, alkenyl, cycloalkyl, aralkyl, furylalkyl, thienylalkyl, tetrahydrofurylalkyl
R^1 or R^2 = H

excretion of sodium ions without affecting the excretion of potassium ions. [DOS 2038035; Boehringer Mannheim GmbH, Mannheim-Waldhof]

[PR 15 –N IE]

New aminoethanesulfonyl derivatives *(1)* are used medicinally as analgesics, antihistamines, and hypocholesterolemic and anti-inflammatory agents. The compounds can be prepared by known methods. Compounds with X = NH_2 are preferably obtained by amination of the halides or by deacylation of the acylamino (or acylimino) compounds.



(1)

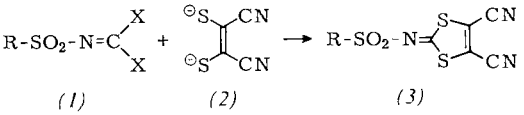
R = 2-thiazolylamino, 1-pyrrolyl, 4-methylpiperazyl, or 1-indolyl; X = NH_2. If R is 2-thiazolylamino, X may also be nicotinoylamino. [DOS 2139288; Naito Shinichi, Kyoto]

[PR 20 –K IE]

Branched amide-imide-ester polymers for non-hygroscopic electrical insulating varnishes with unlimited storage life are obtained from four or five components: a) 2-amino-2-ethyl-1,3-propanediol, 2-amino-2-methyl-1,3-propanediol, tris-(2-hydroxyethyl) isocyanurate, or 2-hydroxymethyl-2-methyl-1,3-propanediol, b) an aromatic or alicyclic diamine, *e.g.* bis(aminophenyl)methane, c) trimellitic anhydride or mixtures thereof with up to 20% of isophthalic acid, phenylindanedicarboxylic acid, benzophenone-4,4′-dicarboxylic acid, adipic acid, or sebacic acid, or with up to 15% of pyromellitic anhydride, benzophenone-2,3;2′,3′-tetracarboxylic dianhydride, 2,3; 6,7-naphthalenetetracarboxylic dianhydride, or 3,4; 3′,4′-biphenyltetracarboxylic anhydride, and d) a crosslinking agent containing titanium, *e.g.* triethanolamine titanate or glycol titanate, and possibly e) a phenol-blocked polyisocyanate, *e.g.* trimeric toluene diisocyanate or 4,4′-diphenylmethane diisocyanate blocked with cresol. The polymers, which are used as solutions in cresol or in mixtures of cresol with up to 40% of hydrocarbons, give coatings having very good flexibility at high temperatures and on aging. [DOS 2134479; Schenectady Chemicals Inc., Schenectady, N. J.]

[PR 31 IE—C]

Fungicidal and bactericidal 4,5-dicyano-2-sulfonylimido-1,3-dithiacyclopentenes *(3)* can be obtained by reaction of the sulfonyl compounds *(1)* with the dicyanodithiolates *(2)* (alkali metal or alkaline earth metal salts) in inert organic solvents. The dithiacyclopentenes *(3)* exhibit very



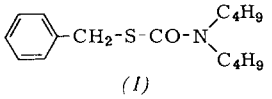
(1) *(2)* *(3)*

R = lower alkyl group (up to C_6), (substituted) aryl group (up to C_{10});
X = halogen

low toxicity for mammals. [DOS 2120666; Nippon Soda Co., Ltd., Tokyo]

[PR 33 IE—N]

***S*-Benzyl *N*,*N*-di-*sec*-butylthiocarbamate** *(1)* is an effective herbicide against weeds in rice fields, and also stimulates the growth of the rice. The compound can be prepared by conventional methods.



(1)

[DOS 2144700; Montecatini Edision S.p.A., Milan]

[PR 34 IE—N]

Nucleinsäuren (Nucleic acids). By *D. Beyersmann*. Chemische Taschenbücher Band 16 (Chemical Pocketbooks Vol. 16). Verlag Chemie GmbH, Weinheim/Bergstr. 1971. 1st edit., viii, 192 pp., numerous figs, and tables, bound, DM 24.—.

This book is the latest in the "Chemical Pocketbooks" series, which have already won a name for themselves by their good presentations of interesting specialist topics; it deals with the topical subject of nucleic acids in six chapters.

A discussion on nomenclature, the fundamental monomer building blocks, and the chemistry of the high-molecular nucleic acids is followed by a detailed exposition on the molecular weight and conformation of these compounds. The remaining four chapters include the essential facts on the biosynthesis of nucleotides and a comprehensive treatment of the metabolism of nucleic acids, tables helping to present the wealth of information in a clear and easily comprehensible manner. After the role of nucleic acids in the transmission of genetic information has been clearly shown and a number of regulation mechanisms have been discussed, the last chapter indicates some possible ways of attacking the problems of the metabolism and function of the nucleic acids.

The author has succeeded in presenting the most important aspects of this very extensive field in a clear, detailed, and attractive manner. The reader is familiarized with the current position on the chemical and biochemical viewpoints on the nucleic acids, and can go into the subject more deeply by means of the literature references (there could have been more of these in one or two chapters). The book is recommended to anyone requiring information on nucleic acids.

Herbert Schott [NB 71 IE]

Kunststoff-Handbuch (Plastics Handbook). Vol. 11. Polyacetals, Epoxy Resins, Polymers Containing Fluorine, Silicones, *etc.*, Production, Properties, Processing, and Use. Edited by *R. Vieweg*, *M. Reiher* and *H. Scheurlen*. Carl Hanser Verlag, München, 1971, 1st ed., xxii, 616 pp., 362 figures, 176 tables, bound DM 220.—.

Volume 11, the latest volume of the collective work[1], deals with plastics that do not fit into the rigorous classification of the earlier volumes. The polyacetals, epoxy resins, polymers containing fluorine, and silicones are discussed in detail, while polyvinylalcohols, polyvinylacetals, polyvinyl ethers, polyvinylpyrrolidone, and poly-*N*-vinylcarbazole are described relatively briefly. The first group of products mentioned above, like the major plastics described in earlier volumes (polyethylene, polyvinyl chloride, polystyrene, *etc.*), are discussed in sections dealing with production, properties, processing, and use, after an introduction presenting a historical survey and some economic data.

The sections on epoxy resins and polymers containing fluorine are particularly successful. A rather more comprehensive discussion would have been justified in the chapter on polyvinyl acetals, polyvinyl ethers, *etc.* Lacquer raw materials should also find a place in a plastics handbook. It is a pity that the book contains no contributions on high-temperature plastics, such as diphenyl oxides, polyimides, and poly-*p*-xylylenes, though sufficient literature for such contributions has existed for a number of years. The polysulfones should also belong to this volume.

Nevertheless, the book provides users and processors with a good, concise source of quickly retrievable information on polyacetals, epoxy resins, *etc.* Since the relevant literature is abundantly cited, chemists and applications technologists who wish to delve deeper into the subject can do so with the aid of this book. The volume can be wholeheartedly recommended to all who wish to obtain fairly detailed information on the plastics mentioned in the title.

Otto Horn [NB 72 IE]

Römpps Chemie Lexikon (Römpp's Chemical Lexicon). By *O.-A. Neumüller*. Franck'sche Verlagshandlung, W. Keller & Co., Stuttgart, 1972, 7th ed., vol. 1; xiv, 734 pp., numerous figs., bound, DM 110.—.

Twenty-five years have elapsed since the first edition of this work appeared. The first volume of the seventh edition is now out, covering the entries from A to C. The new editor is *O.-A. Neumüller*, who took over when *E. Ühlein* died.

On thumbing through the new first volume, one first notices that it is now the pages and not the columns that are numbered, the head words stand out, and the material must have been subjected to very careful editing and proofreading. The number of entries has not yet been specified, but comparison with the sixth edition[1] points to a roughly 10% increase in volume. Almost all the entries have been revised or rewritten; in particular those coming under organic chemistry, physical chemistry, biochemistry, and nuclear chemistry have been extended. This amplification has not been entirely successful in the case of named reactions, because some of them are still missing. The key words are also given in English and French, and, as mentioned in the Preface, they will be listed alphabetically at the end of the last volume. However, this list is likely to be incomplete, because the terms are not always given after the head words. Compounds are named according to IUPAC rules. One or more sources of supply are usually specified for each substance, which will certainly be found most useful. The literature references have been increased in number and are now fully up to date. The listing of tradenames in entries on drugs has been mostly abandoned.

This volume deserves a good reception, as do the further volumes of Römpps Chemie Lexikon, which are to be published at intervals of six months.

Christian Weiske [NB 74 IE]

[1] Cf. Angew. Chem. Internat. Edit. *6*, 893 (1967).

Transition Metal Carbides and Nitrides. By *L. E. Toth*, Academic Press New York—London 1971. 1st ed., xiii, 279 pp., numerous figures and tables, bound $ 16.50.

The carbides and the nitrides of groups 4 to 6 of the periodic system have found steadily growing importance in research

[1] Cf. Angew. Chem. Internat. Edit. *9*, 817 (1970).

and in industry because of their high melting points (up to 4100 °C), their very low creep rates at high temperatures and their particularly good wear resistance, as well as other favorable thermal and electrical properties. Whereas the tungsten-based hard metals have been of world-wide importance for many years, it is only during the past few years that in particular the carbides of titanium, zirconium, and tantalum, as well as their nitrides, have come into industrial use. Thus, because of their low tendency to wear, thin coatings of titanium carbide and titanium nitride with lower-melting metals lead to a considerable improvement in the service life of cutting metals, and solid solutions of the carbides and nitrides of titanium have yielded valuable materials for special uses in electrical engineering. For the further development of these carbide and nitride materials, however, a thorough knowledge of their crystal-chemical, thermodynamic, and electrical properties as well as of their superconductivity will be necessary in order to improve above all their mechanical properties.

The fundamental knowledge about the properties of these substances is presented comprehensively in this book, which therefore offers the investigator in this field valuable support, in connection both with the preparation of these materials and with their possible uses.

W. Dawihl [NB 80 IE]

The Periodic System of Chemical Elements. By *J. van Spronsen*. Elsevier Publ. Comp., Amsterdam-London-New York 1969. 1st ed., xv, 368 pp., numerous figures and tables, bound Dfl. 50.—.

For more than ten years now *van Spronsen* has been intermittently publishing interesting material on the history and prehistory of the periodic system of chemical elements, and the profession was aware that a larger work from his pen was to be published in 1969, 100 years after *Dimitri Ivanovich Mendeleev's* publication. The hopes and expectations of a new standard work on the history of chemistry were fulfilled, and it was surprising how much additional material the author had to relate.

By dividing the book into two parts (Part I: General Aspects pp. 7 to 211; Part II: Specific Aspects, pp. 213—355, followed by a personal index and a subject index), he has managed to present this material without overwhelming the reader with details, since the first part gives a systematic survey, into which everything else fits automatically because of the cross references in the second part. Moreover, because of the great scientific importance of the search for a system of elements and the construction of the periodic system, the book also constitutes a history of the chemistry of the past 200 years, and in particular a history of ideas and problems.

Not surprisingly to a science historian, it emerged that the idea of a "natural" system of the chemical elements was already very old, and that the stimulus by no means always arose exclusively from chemistry or was chemically oriented from the outset. There was a series of affinity tables in the 18th century, which are not discussed in any detail by *van Spronsen* (but cf. *A. M. Duncan*: Some theoretical aspects of eighteenth-century Tables of Affinity I. Annals of Science *18*, 177—194 (1962)), but comprehensive tables of a "natural" system were possible only after the acceptance of *Lavoisier's* antiphlogistic chemistry; the first appeared soon after this (*Döbereiner's* triads, *Berzelius's* electrochemical system, *etc.*). A periodic system was possible only after terms such as atom and atomic weight had been clarified at the Chemist's Conference at Karlsruhe in 1860. A whole series of such systems immediately appeared, and the well-known systems of *Lothar Meyer* (1864/1870) and *Mendeleev* (1869) were by no means the first; *A. E. Béguyer de Chancourtois* (1862), *J. A. R. Newlands* (1863), *W. Odling* (1864), and *G. D. Hinrichs* (1867) had preceded them in part. However, the various workers knew little or nothing about one another, and *van Spronsen* rightly states (p. 135): "It should be clearly understood that Mendeleev's work was so brilliant precisely because he knew nothing of the studies of his contemporaries... If he had known of them, Mendeleev's work could only be considered as a useful summary and continuation of that of his predecessors". (It was only on the presentation of his results to the meeting of the Russian Chemical Society in March 1869 that *Olding's* work was brought to his notice.)

On the basis of *van Spronsen's* definition of the periodic system (p. 338: "The periodic system of elements is a sequence of all [known] elements arranged according to increasing atomic weight in which the elements with analogous properties are arranged in the same group or column"), all six investigators mentioned above should be referred to as "discoverers", and this is confirmed by the many other attempts that were subsequently made to find an arrangement. (The author lists and discusses them with their reasons and their consequences up to and including 1949; *E. G. Mazur* [Types of graphic representation of the Periodic System of Chemical Elements, 1957] carried them on up to 1955, but mainly only bibliographically.)

The book is a goldmine for those who are interested in the history of chemistry, and contains an abundance of interesting information and ideas from the recent history of chemistry, which would offer stimulation and orientation even to the non-historically minded chemist.

Fritz Krafft [NB 73 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1972. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 40 36/40 37, Telex 46 55 16 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (06201) 40 31, Telex 46 55 16 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 11
November 1972
Pages 949–1040

International Edition in English

New Reactions with Cyanic Esters

By Ernst Grigat[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

The reactions of cyanic esters with acylating agents and the reactions of the resulting *N*-acyliminocarbonic ester halides are surveyed, and syntheses of heterocycles with cyanic esters and their reaction products are then reported.

1. Introduction

Since the appearance of the review "Synthesis and Reactions of Cyanic Esters" in 1967[1,2], the chemistry of these esters has expanded further. In addition to the preparation methods, the basic reaction types that had been investigated until then were described, *viz.*:

A) Nucleophilic reactants H—X add under mild conditions to the nitrile group of ArO—C≡N to form derivatives of iminocarbonic esters ArO—C(=NH)X.

B) Under more forcing conditions, these decompose into ArOH and N≡C—X, *i.e.* esters of cyanic acid can be used to transfer a nitrile group to nucleophilic reactants.

C) C—C bonds are formed by addition of compounds having a nucleophilic C atom to the nitrile group of the cyanates.

D) The readiness with which esters of cyanic acid add water and hydrogen sulfide can be used for the intramolecular and intermolecular elimination of organically bonded H_2O and H_2S.

E) The tendency to trimerize, even with the inclusion of nitrile groups from other sources, offers possibilities for the direct synthesis of *s*-triazine derivatives.

F) As very reactive dipolarophiles, cyanic esters enter into 1,3-dipolar cycloadditions under mild conditions.

G) Ring closure to form benzoxazinones occurs on reaction of aryl cyanates having carboxylic ester functions *ortho* to the OCN group with nucleophiles.

H) The addition of electrophiles to the —O—C≡N group occurs only in a few special cases

In the meantime, extensions have been found mainly in two areas:

1. With acid chlorides in the widest sense, cyanic esters are smoothly acylated to form *N*-acyliminocarbonic ester halides[3]. These new classes of extremely reactive compounds open up many synthetic possibilities, particularly in the fields of heterocycles and carbonic acid derivatives. This work is discussed in the first part of the present article.

2. Syntheses of heterocycles are not confined to reaction types E), F), and G). With suitable reactants, reaction types A) to D) can also be used for direct syntheses of heterocycles. Hitherto unpublished syntheses of this type form the subject of the second part of the article.

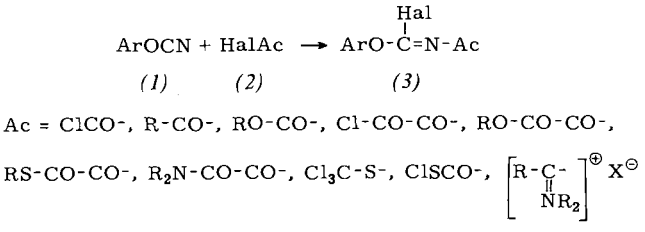
[*] Dr. E. Grigat
Present address:
Bayer AG, PU Forschung 2
4047 Dormagen (Germany)

New individual results obtained by reactions of types A) to G) are not reported here. Where possible, they are incorporated into the tables at the end of the article.

1. Reaction of Cyanic Esters with Acylating Agents

1.1. Reaction with Acid Halides

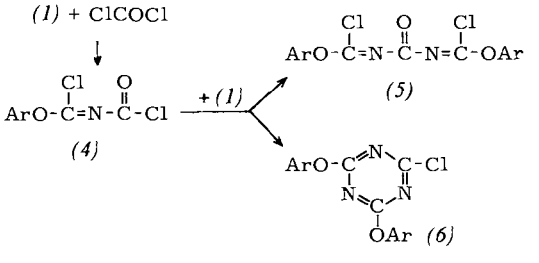
Since cyanic esters *(1)* had proved to be very inert toward electrophilic reagents[1, 2, 4], it was surprising to find that they can be *N*-acylated under very mild conditions in some cases, and in good yields, with various types of acyl halides *(2)*[3]. The resulting *N*-acyliminocarbonic ester halides *(3)* are surprisingly stable, but extremely reactive.



The versatility of these previously undescribed classes of substances for further syntheses is illustrated below.

1.1.1. Addition of Phosgene to Cyanic Esters

When equimolar quantities of phosgene and *(1)* are mixed in an inert solvent, reaction to form *(4)* takes place even at 0 °C without addition of a catalyst. The reaction products are formed in good yields and can be distilled[5].

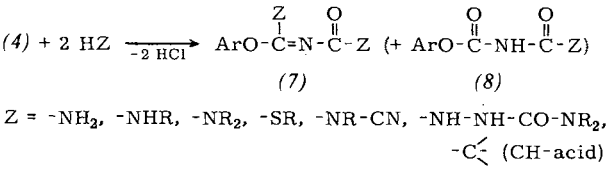


Further reaction with an excess of cyanate *(1)* leads to two products, which are formed in various proportions. In the case of R = α-naphthyl, *(5)* predominates, whereas *(6)* predominates for R = C_6H_5 or 4-CH_3—C_6H_4.

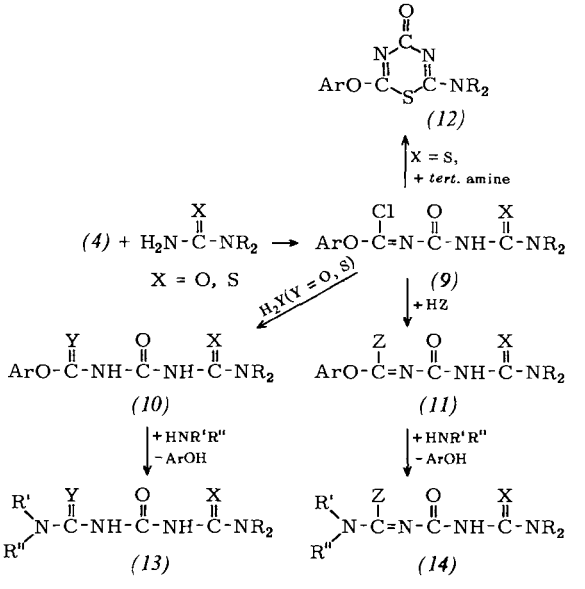
Further reactions:

On hydrolysis, *(4)* decomposes into ArOCO—NH_2, HCl, and CO_2; ArO—CS—NH_2 is isolated after reaction with H_2S, and ArO—CO—NH—CO—OAlk on alcoholysis. Strong nucleophiles immediately substitute both Cl atoms to form *(7)*[6], a C—C bond being formed if the group Z exhibits C—H acidity. If moisture is present during the reaction, *(8)* is observed as a by-product.

With less nucleophilic reagents, it is possible to make use of the difference in the reactivities of the two Cl atoms in *(4)*. Thus with ureas or thioureas, reaction initially occurs only with the Cl atom adjacent to the CO group,

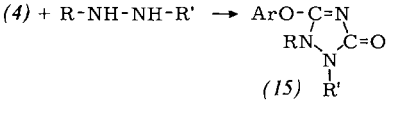


with formation of *(9)*[7]. This intermediate product, which can be isolated, can then be hydrolyzed in a second step to *(10)*[8], reacted with other nucleophilic reactants to form *(11)*, or cyclized intramolecularly to form *(12)*[9].



The exchangeability of the aryloxy residue in *(10)* and *(11)* against amines, hydrazines, semicarbazides, *etc.* offers possibilities for the synthesis of compounds of the types *(13)* and *(14)*.

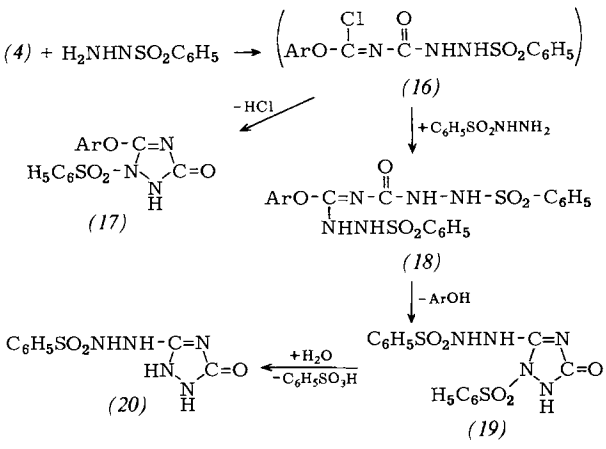
Direct ring closure reactions of *(4)* can also be carried out with suitable reactants. Examples of the formation of five-membered heterocycles are the reactions of *(4)* with hydrazine and its derivatives. Whereas reaction with hydrazines themselves lead exclusively to the triazolones *(15)*[10], sulfonohydrazides lead to a whole range of



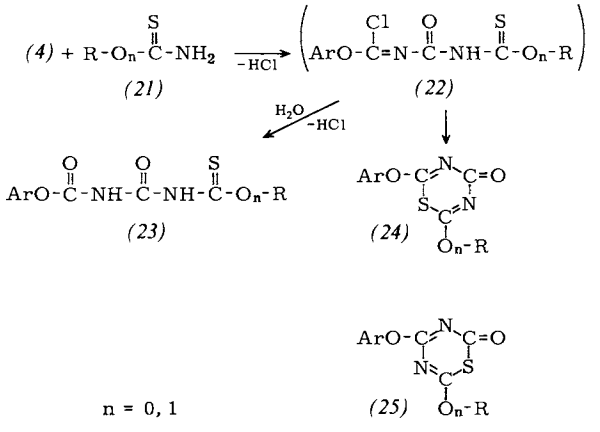
substances *(16)* to *(20)*, which, with the exception of *(16)*, have all been isolated and identified.

Examples of the formation of six-membered heterocycles are the reactions of *(4)* with amides or thiocarboxylic or thiocarbamic acids *(21)* to form thiadiazinones *(24)*[11].

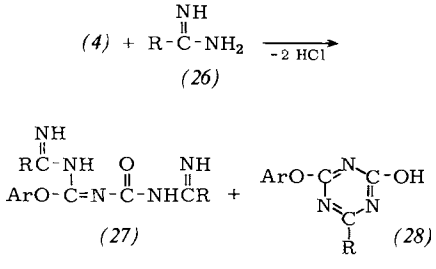
Whereas reaction at room temperature leads only to *(22)*, whose hydrolysis product *(23)* can be isolated by working up with water, ring closure to form *(24)* occurs at moderately higher temperatures (40 to 80°C).



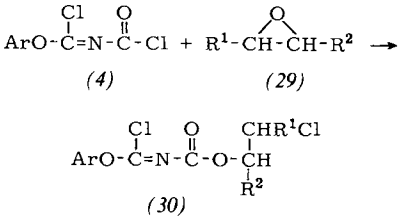
The isomeric thiadiazinone *(25)* has been isolated as a by-product in one case (R = 4-H_3C—C_6H_4—).



Amidines *(26)* add less uniformly to *(4)* than thioamides or thiocarbamates. The compounds *(27)* and *(28)* are both formed; the less basic trichloroacetamidine gives mainly *(27)* (with R = Cl_3C), while more of *(28)* (with R = C_6H_5) is formed with benzamidine.



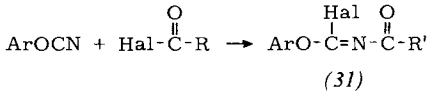
A smooth route to *(28)* (also with R = CCl_3) without formation of *(27)* as a by-product involves the addition compounds of *(4)* with epoxides. Like the α-chloroalkylidenecarbamoyl chlorides[12], the *N*-chlorocarbonyliminocarbonic ester halides *(4)* add to epoxides *(29)* in such a way that the oxirane ring is opened. The epoxide



molecule is formally inserted between the CO group and the Cl atom of the —CO—Cl grouping, and the alkoxycarbonyliminocarbonic ester chlorides *(30)* are formed[13]. They belong to the same class of substances as the products of the addition of carbonic ester halides to ArOCN. Their further reactions are described in Section 1.1.3. It will merely be mentioned here that *(30)* cyclizes smoothly with amidines *(26)* to form *(28)*, with elimination of HCl and HO—CHR^2—CHR^1—Cl.

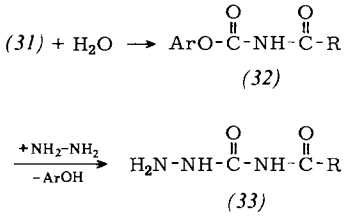
1.1.2. Addition of Halides of Carboxylic Acids to Cyanic Esters

Higher temperatures are required for the reaction of carboxylic acid halides with cyanic esters than for the addition of phosgene. The undiluted components are heated to temperatures of up to 200 °C (depending on the acyl chloride), and the very stable *N*-acyliminocarbonic ester halides *(31)*, which are formed in good yields, are purified by vacuum distillation[3,14].

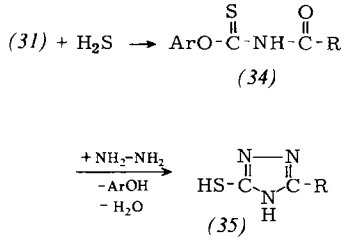


Further reactions:

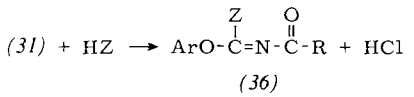
Hydrolysis leads to *N*-acylated carbamates *(32)*[15]. Of the reactions of these products (exchange of ArO for nucleophiles), only that with hydrazine will be mentioned, since this provides a simple route to the acylsemicarbazides *(33)* with a free hydrazino group and an acylated amino group[16].



The reaction of H_2S or H_2S donors (R—CS—NH_2; H_2N—CS—NH_2) yields *N*-acylthiocarbamates *(34)*[17]. However, further reaction of these products with hydrazine leads not to the acylthiosemicarbazides analogous with *(33)* but directly to the mercaptotriazoles *(35)* with cyclization. No similar spontaneous ring closure has been observed with *(33)*.



The halogen atom in *(31)* is easily exchanged for other nucleophiles. Compounds of the type *(36)* are formed[18].



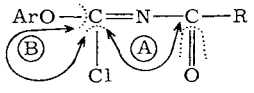
(36)

Z = $-NH_2$, $-NHR$, $-NR_2$, $-SR$, $-OR$, $-NHNR-CO-NH_2$, $-C\langle$ (CH-acid)

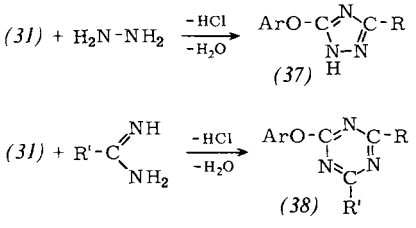
Direct syntheses of heterocycles with *(31)* are possible by two types of reactions:

Type A: Substitution of the halogen atom, followed by ring closure to the carbonyl group of the *N*-acyl residue, with removal of water.

Type B: Substitution of the halogen atom, followed by ring closure to the same C atom, with removal of the ArO residue and retention of the *N*-acyl grouping.



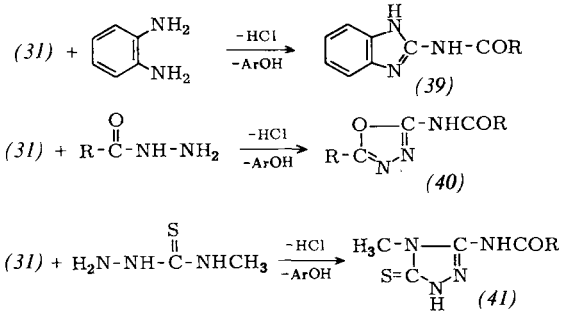
An example of a five-membered ring synthesis of type A is the reaction of *(31)* with hydrazine to form the triazole *(37)*[19], while an example of a six-membered ring synthesis is the reaction with amidines to form the *s*-triazines *(38)*[20].



(37)

(38)

As examples of type B, *(31)* reacts with *o*-phenylenediamine to form 2-(*N*-acylamino)benzimidazoles *(39)*, with acylhydrazides to form the oxadiazoles *(40)*[21], and with thiosemicarbazides to form the triazoles *(41)*[22].

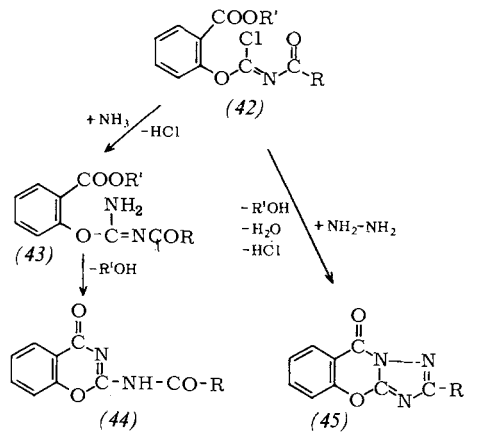


(39)

(40)

(41)

N-Acyliminocarbonic ester halides having a carboxylic ester function in the *ortho* position *(42)*, like the cyanic esters from which they are derived, also exhibit special cyclization reactions. The reaction with NH_3 leads *via (43)* to the 2-acylaminobenzoxazinones *(44)*[23], while the reaction with hydrazine leads directly to the triazolobenzoxazinones *(45)*[24].



(42)

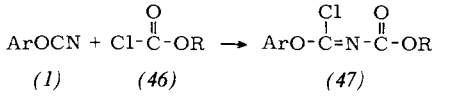
(43)

(44)

(45)

1.1.3. Addition of Carbonic Ester Halides to Cyanic Esters

Carbonic ester halides *(46)* can also add to cyanic esters *(1)* in good yields to give the *N*-aryloxy- or alkyloxycarbonyliminocarbonic ester halides *(47)*[25].



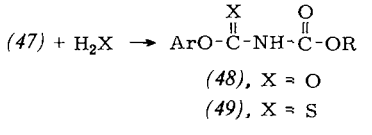
(1) *(46)* *(47)*

A limitation is that *alkyl* carbonate halides *(46)* with R = lower alkyl decompose in the presence of ArOCN into CO_2 and RCl.

Reference should again be made to the possibility of synthesizing some substances of the class *(47)* from the addition compound *(4)* with epoxides (cf. Section 1.1.1).

Further reactions:

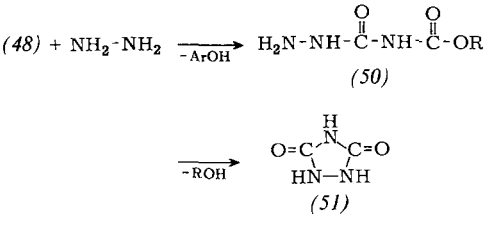
Hydrolysis and reaction with H_2S (or H_2S donors such as R—CS—NH_2, H_2N—CS—NH_2) lead to the products *(48)* and *(49)* respectively[17].



(48), X = O

(49), X = S

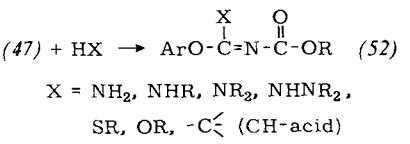
The replaceability of the aryloxy residue in the hydrolysis product *(48)* by nucleophiles is again illustrated by the reaction with hydrazine. Unlike in the same reaction with *(37)*, the ring closure product *(51)* is formed here by further reaction (particularly in the case of R = aryl), as well as *(50)*[16].



(50)

(51)

The reaction of *(47)* with nucleophiles (HX) leads, with elimination of HCl, to the compounds *(52)*[18].



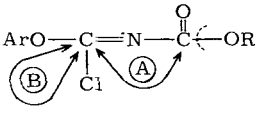
(47) + HX → ArO-C(X)=N-C(=O)-OR *(52)*

X = NH_2, NHR, NR_2, $NHNR_2$, SR, OR, -C< (CH-acid)

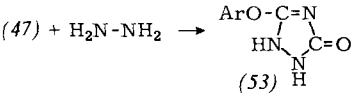
In the case of *(47)*, the direct synthesis of heterocycles is again possible by two types of reactions:

Type A: Substitution of the halogen atom, followed by ring closure to the aryloxycarbonyl group, with elimination of ROH.

Type B: Substitution of the halogen atom, followed by ring closure to the same C atom with removal of the ArO residue and retention of the *N*-alkyloxycarbonyl or *N*-aryloxycarbonyl grouping [strictly analogous to *(31)*].

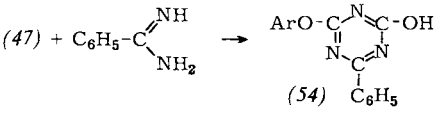


Five-membered ring synthesis of type A[26]:



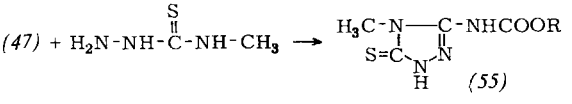
(47) + H_2N-NH_2 → ArO-C(=N)-HN-N(H)-C=O *(53)*

Six-membered ring synthesis of type A:

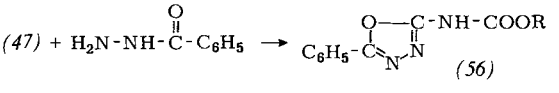


(47) + C_6H_5-C(=NH)-NH_2 → ArO-C(=N)-N=C-OH *(54)* C_6H_5

Heterocycle syntheses of type B[21,22]:



(47) + H_2N-NH-C(=S)-NH-CH_3 → H_3C-N(-C=S)-C(=N)-NHCOOR



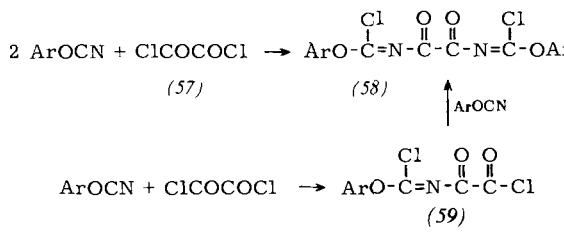
(47) + H_2N-NH-C(=O)-C_6H_5 → O—C(=N)-NH-COOR, C_6H_5 *(56)*

1.1.4. Addition of Oxalyl Chloride to Cyanic Esters

Oxalyl chloride *(57)* can be converted into two products with cyanic esters[3].

With 0.5 mole of *(57)* per mole of ArOCN, only the 2:1 addition product *(58)* is formed[27], whereas with an excess of *(57)* (2.5 moles) with respect to ArOCN only the 1:1 addition product *(59)* is formed[28]. An advantageous point here is that if the correct molar ratios are used, each of the two products can be prepared in good yields without contamination by the other.

As expected, *(59)* can be converted into *(58)* by reaction with further ArOCN, and it is thus possible to synthesize unsymmetrical compounds *(58)*[29].

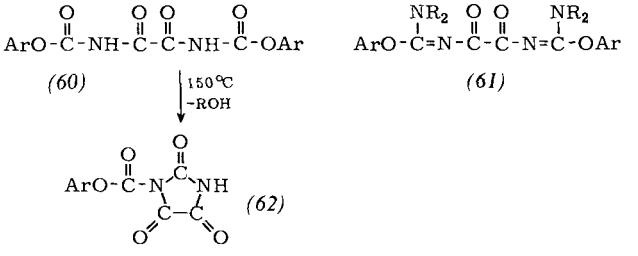


2 ArOCN + ClCOCOCl → ArO-C(Cl)=N-C(=O)-C(=O)-N=C(Cl)-OAr *(58)* (*(57)*)

(58) + ArOCN → ArO-C(Cl)=N-C(=O)-C(=O)-N=C(Cl)-OAr *(59)*

Some reactions with (58):

Hydrolysis and reaction with secondary amines lead to the products *(60)* and *(61)* respectively[30].



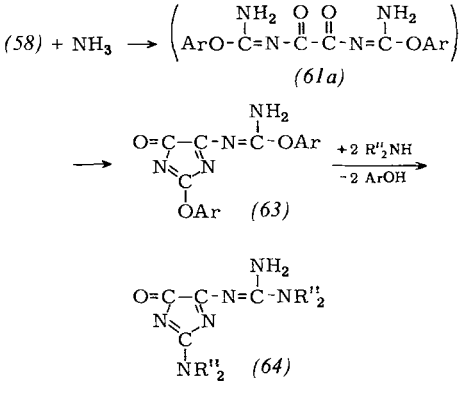
ArO-C(=O)-NH-C(=O)-C(=O)-NH-C(=O)-OAr *(60)*

(60) —150°C, -ROH→ *(62)*

ArO-C(=O)-N(-C(=O)-C(=O)-)-NH *(62)*

$(NR_2)_2$-C=N-C(=O)-C(=O)-N=C-OAr *(61)*

When heated, *(60)* cyclizes with elimination of phenol to form *(62)*. On reaction with NH_3, instead of *(61a)*, its cyclized further reaction product *(63)* is formed immediately; both ArO groups in this product can be replaced *e.g.* by amine [to form *(64)*][30].



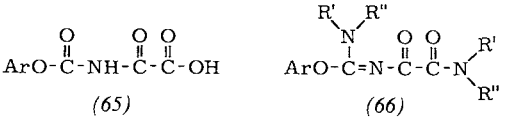
(58) + NH_3 → $(NH_2)_2$-C=N-C(=O)-C(=O)-N=C-OAr *(61a)*

(61a) → *(63)* (+2 R''_2NH, -2 ArOH)

(63) → *(64)* (+2 R''_2NH, -2 ArOH)

Some reactions with (59):

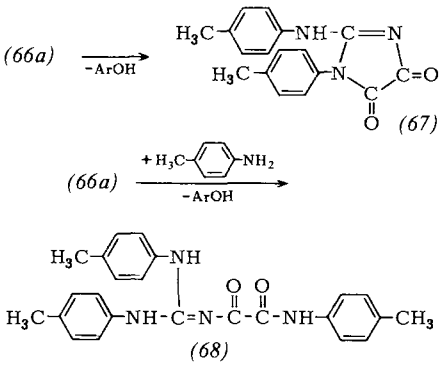
Hydrolysis and reaction with amines lead to the products *(65)* and *(66)* respectively[30,31].



ArO-C(=O)-NH-C(=O)-C(=O)-OH *(65)*

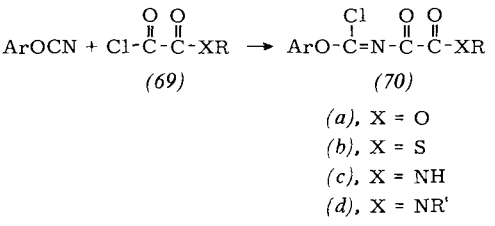
ArO-C(=N-C(=O)-C(=O)-N(R')R'')-C=N *(66)*

Here we have another example of a follow-on reaction that proceeds immediately: With primary amines (*e.g. p*-toluidine), in addition to *(66a)* [=*(66)* with R′=H, R″=4-CH_3—C_6H_4—], products are also formed in which the ArO residue is immediately displaced, either by cyclization to form *(67)* or by exchange with a further mole of amine to form *(68)*[30].



1.1.5. Addition of Oxalic Ester Chlorides, Oxalic Thioester Chlorides, and Oxalic Amide Chlorides to Cyanic Esters

The addition of *(69)* to ArOCN proceeds smoothly when the components are admixed in an inert solvent at temperatures of up to 40 °C[32].

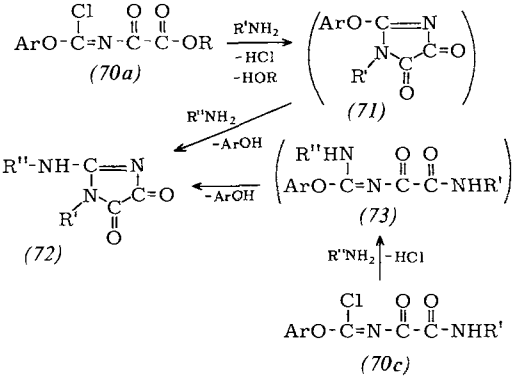


The halogen atom in *(70)*, as in the analogous compounds *(4)*, *(31)*, *(47)*, *(58)*, and *(59)*, is readily hydrolyzed, thiolyzed, and replaced by nucleophiles (amines, hydrazines, mercaptans, thiophenols, CH-acid compounds such as malodinitrile, *etc.*)[33]. Special mention will be made here only of a few direct ring closure reactions:

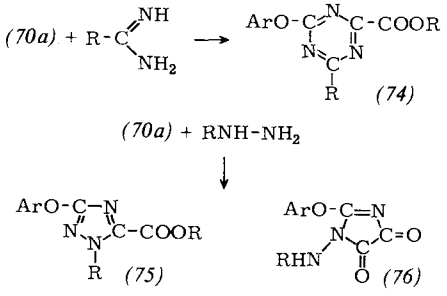
The imidazolinediones *(72)* are formed

a) from *(70a)* by replacement of the Cl with primary amine, cyclization with elimination of the ester alcohol ROH and displacement of the ArO residue by a further mole of amine [*(71)* not isolable, so R′=R″ in every case];

b) from *(70c)* by substitution of the halogen with amine followed by cyclization with removal of ArOH (in this case R′≠R″ is possible).

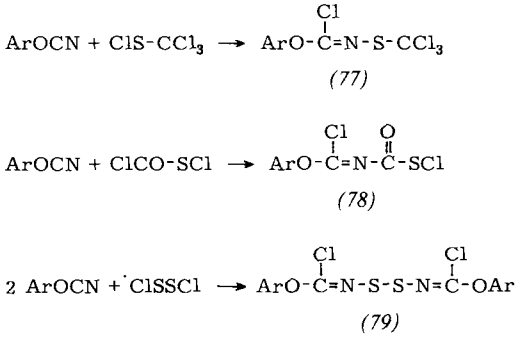


Amidines react with *(70a)* to give only the *s*-triazinecarboxylic esters *(74)*[20], whereas with hydrazines *(70a)* is converted in moderate yields partly with elimination of HCl and H_2O into the triazolecarboxylic acids *(75)*, and partly with elimination of HCl and ROH into the *N*-aminoimidazoledione derivatives *(76)*.



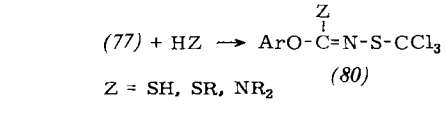
1.1.6. Addition of Sulfenyl Halide Derivatives to Cyanic Esters[34-36]

ClCO—SCl does not add to the OCN group *via* the sulfenyl chloride grouping [to form *(78)*][37], but it is mentioned here because of its similarity to the other compounds. The three classes of compounds *(77)* to *(79)* are formed in very good yields when the components are heated in inert solvents to temperatures of 30 to 80 °C. The compounds *(77)* can generally be distilled under vacuum, whereas *(78)* and *(79)* decompose on distillation. When they are oily they are subjected to further reaction as crude products; the crystalline products *(78)* and *(79)* can be purified by recrystallization. The storage life of both classes of substances is limited as they slowly decompose on standing.



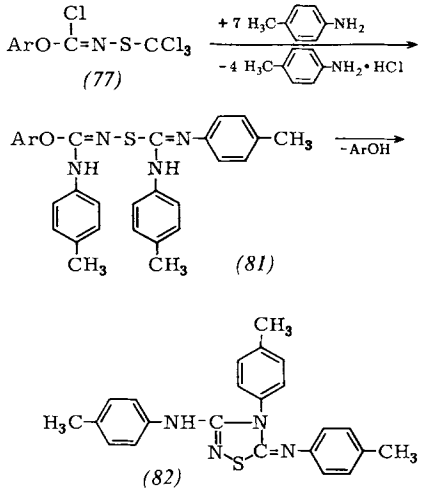
Reactions with (77)[37]:

The —S—CCl_3 residue is removed on hydrolysis. The carbamate ArO—CO—NH_2 is obtained. On the other hand, the molecular structure remains intact on replacement of the imidoyl chloride halogen by a number of other nucleophiles [to form *(80)*]:



With primary aromatic amine (*p*-toluidine), even the CCl_3 halogens are replaced. The reaction leads in good yields

to *(81)*, which cyclizes even on slight heating in solution to form the thiadiazole derivative *(82)*.



Two comments are in place with regard to Sections 1.1.1 to 1.1.6:

1. The foregoing summary is intended to give a general picture of the possible reactions of cyanic esters with acyl halides and of the wide uses of the resulting products, particularly for the synthesis of heterocycles. For this reason it included neither all the acylating agents that have been added to cyanic esters nor all the further reactions of the various *N*-acylation products.

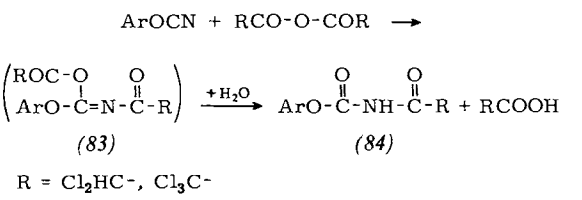
2. Disubstituted cyanamides can be *N*-acylated in the same way as the cyanic esters. The classes of substances analogous to the compounds *(31)*[38], *(47)*[39], *(59)*[40], *(70)*[41], *(77)*[42], and *(78)* with the R_2N residue instead of ArO have been obtained in good yields. The description of the further reactions of these *N*-acyliminocarbonic amide chlorides would take as much space as the above. It will therefore merely by pointed out that in nearly every instance the reactions proceed in the same manner as in the case of the Ar—O analog, including the observed heterocycle syntheses. As far as possible the reaction products are included in the tables at the end.

The *N*-acylation of the thiocyanic esters is more difficult, but has been achieved in some cases ($ClCOCH_3$, ClCOCOCl).

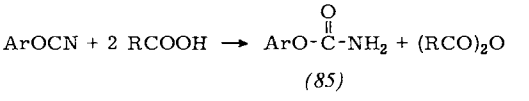
1.2. Reaction with Acid Anhydrides

1.2.1. Anhydrides of Unsubstituted Aliphatic or Aromatic Monocarboxylic Acids

Cyanic esters do not react with these compounds[43]. On the other hand, anhydrides of particularly acidic carboxylic acids (Cl_2HC—COOH; CCl_3COOH) add in the same way as the acyl chlorides to the nitrile group of the cyanic esters. It was not possible to obtain the primary adducts *(83)* in the pure state, since they are strong acylating agents, and as such they immediately acylate traces of water to form the carboxylic acid and decompose on distillation. The *N*-acylated carbamates *(84)* were isolated in good yields.

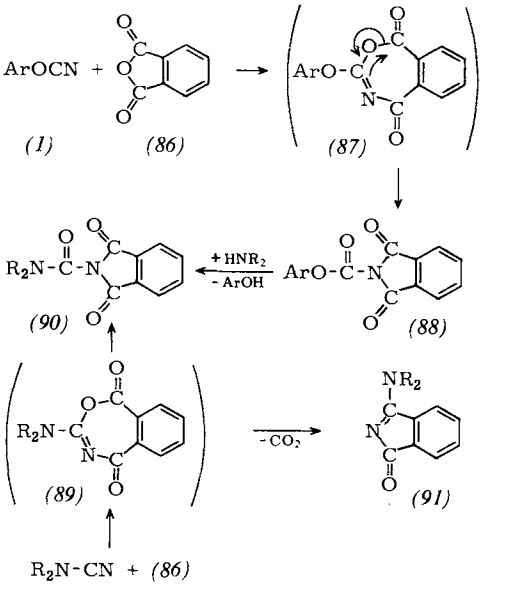


With cyanic esters, the carboxylic acids formed are converted back into their anhydride with simultaneous carbamate formation *(85)*[43].



1.2.2. Anhydrides of Aromatic and Cycloaliphatic *o*-Dicarboxylic Acids

These compounds react directly with cyanic esters to form cyclic *N*-aryloxycarbonyldicarboximides. The reaction probably again proceeds *via* a primary *N*-acylation of the —O—C≡N group. The intermediate *(87)*, which cannot be isolated, is stabilized by intramolecular transacylation to form *(88)*[44,45]. Evidence pointing to the seven-membered ring as an intermediate is the isolation of the by-product *(91)* in the reaction of cyanamides with *(86)* to form *(90)*, which proceeds in an exactly analogous manner[46]. The formation of *(91)* is easily explained by elimination of CO_2 from *(89)*. *(88)* can react with amine, with displacement of the ArO residue, to form *(90)*.



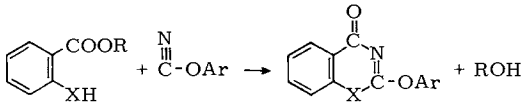
2. Further Heterocycle Syntheses with Cyanic Esters

2.1. *o*-Bifunctional Benzene Derivatives as Reactants

2.1.1. Aromatic *o*-Hydroxy-, *o*-Mercapto-, and *o*-Aminocarboxylic Acid Derivatives

As was reported earlier[47], the reactions of *o*-hydroxy-, *o*-mercapto-, and *o*-aminocarboxylic *esters (92)* with

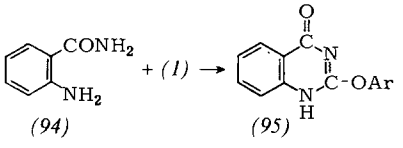
cyanic esters proceed in the same manner with elimination of the ester alcohol to form the 2-aryloxy-4*H*-1,3-benzoxazinones, -benzothiazinones, and -quinazolones *(93)*.



(92) *(1)* *(93)*

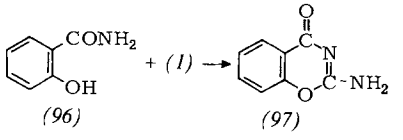
X = O, S, NH

The amides, on the other hand, react differently. Only anthranilamide *(94)* reacts in the same way as the esters, with loss of NH_3 to form the 2-aryloxyquinazolone *(95)*.



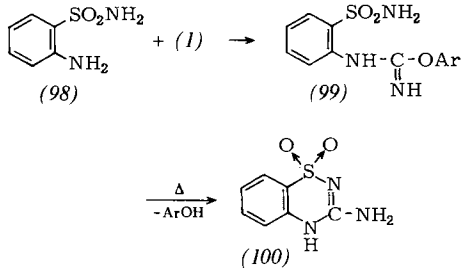
(94) *(95)*

In the case of salicylamide *(96)*, on the other hand, ring closure takes place with loss of the aryloxy residue and incorporation of the amide NH_2 group into the ring. The product is *(97)*.



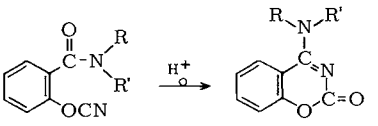
(96) *(97)*

Similar behavior is observed for *o*-aminobenzenesulfonamide *(98)*, which forms the amino heterocycle *(100)* *via* the isolable primary addition product *(99)*[48]. In both cases the cyanic ester functions only as a C≡N group donor.



(98) *(99)* *(100)*

Mention should also be made of the rearrangement of the salicylamide cyanates *(101)*, derived from secondary amines in nonaqueous solvents under the catalytic influence of protons and Lewis acids, which leads to the 4-amino-1,3-benzoxazin-2-ones *(102)*[49].

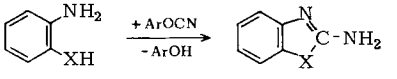


R, R' ≠ H

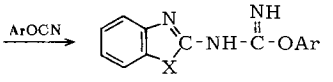
(101) *(102)*

2.1.2. *o*-Hydroxy-, *o*-Mercapto-, and *o*-Aminoanilines

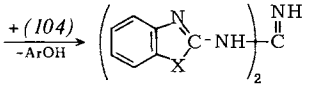
The aminoheterocycles *(104)* are obtained from *(103)* and ArOCN in an exhothermic reaction even at room temperature. *(105)* and *(106)* sometimes occur as further reaction products. As in the formation of *(97)* and *(100)*, the cyanic esters function here as CN group donors (cf. Introduction, basic reaction type B). The transferred cyano group is incorporated in such a way that it is found in the $\geq C-NH_2$ grouping of the ring closure product. If the group $\geq C-NH_2$ is lacking for the formation of a heterocycle, the use of cyanic esters for its introduction can generally be recommended (cf. Section 2.1.3.).



(103), X = O, S, NH *(104)*

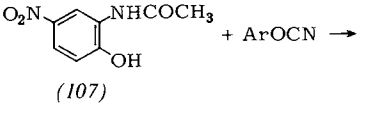


(105)

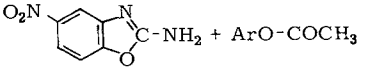


(106)

The influence of acylation of the NH_2 group on the course of the reaction has been investigated for *(107)*. The *N*-acyl group does not prevent the ring closure to form *(108)*; it is eliminated. In anhydrous media it acylates the liberated phenol.



(107)

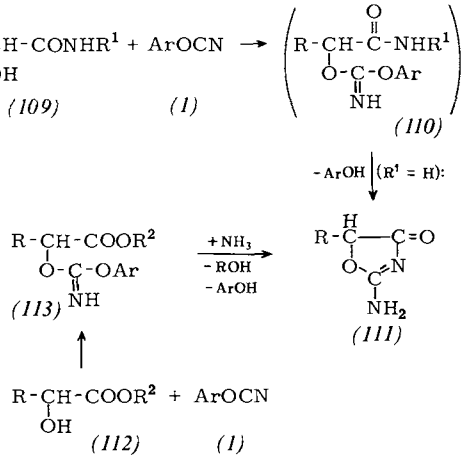


(108)

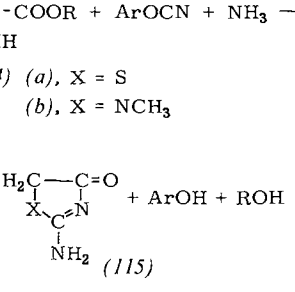
2.2. Aliphatic Carboxylic Acid Derivatives with a Functional Group in the α-Position as Reactants

2.2.1. α-Hydroxy-, α-Mercapto-, and α-Aminocarboxylic Esters and Amides

At room temperature, mandelamide *(109)*, $R=C_6H_5$, $R^1=H$, reacts immediately with cyanic esters in the presence of NaOH to form the aminooxazolone *(111)*, $R=C_6H_5$[50]. The reaction probably proceeds *via* the unisolated intermediate *(110)*, since the addition of cyanate to carboxamides under such mild conditions has not so far been observed in any other case. With *N*-ethylmandelamide *(109)*, $R=C_6H_5$, $R^1=C_2H_5$, the final product of the reaction is *(110)*, $R=C_6H_5$, $R^1=C_2H_5$. It was not possible to force a ring closure.

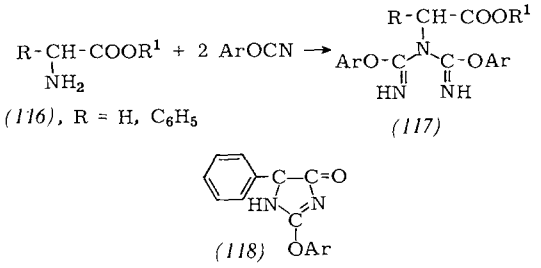


(111) is also formed in good yields when the reaction solution from the ester *(112)* and *(1)* is poured into ammonia water[50]. With mercaptoacetic esters *(114a)*, cyanic esters, and ammonia, on the other hand, the corresponding thiazole *(115a)* is formed only in very low yield.



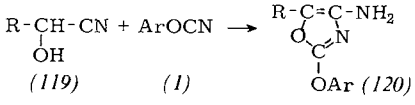
When subjected to the same procedure α-(methylamino)-acetic esters *(114b)* also undergo ring closure in satisfactory yields to give *(115b)*.

On the other hand, the NH_2 group in α-aminocarboxylic esters *(116)* behaves as a primary amine and immediately adds 2 moles of cyanate to form *(117)*. In the case of $R=C_6H_5$, *(118)* was also isolated with alcohol as the solvent.

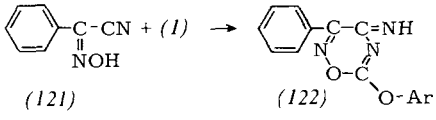


2.2.2. α-Hydroxybenzonitrile and α-Hydroxyiminobenzonitrile

Mandelonitrile *(119)* and cyanic esters *(1)* react directly in the presence of triethylamine to form the aminooxazole *(120)*, a surprisingly unstable compound, which rapidly yellows and decomposes even after immediate purification by recrystallization.

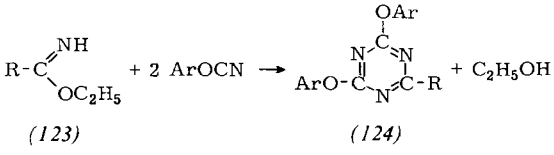


α-Hydroxyiminobenzonitrile *(121)* and *(1)*, again in the presence of triethylamine, react quantitatively to give the oxadiazine derivative *(122)*, which slowly decomposes on standing.

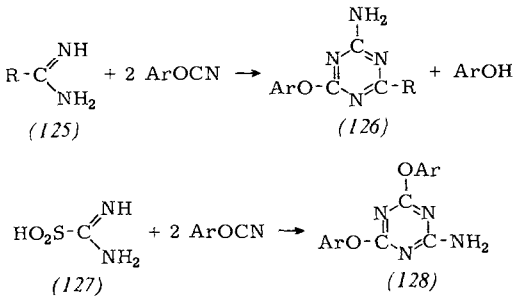


2.3. Iminocarboxylic Acid Derivatives and Reactants

Imino ethers *(123)* react immediately with 2 moles of ArOCN *(1)*, in all mixing ratios, to give the *s*-triazines *(124)*. Both molecules of *(1)* are incorporated, while the C_2H_5O group of the imino ether is removed[51].



In the reaction of the amidines *(125)* to form *(126)*, on the other hand, 1 mole of ArOCN is incorporated, while the second mole merely transfers its CN group[52]. An exception is the special "amidine" *(127)*, which loses its SO_2H group on ring closure to form *(128)*.

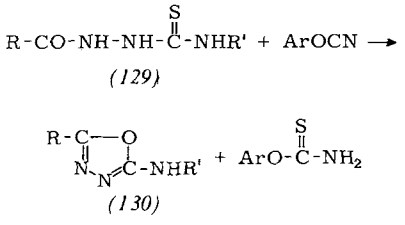


(125) (126)

(127) (128)

2.4. Ring Closure by Removal of H_2S with ArOCN

Cyanic esters function only as H_2S acceptors in the reaction with *N*-acylthiosemicarbazides *(129)*. After the removal of H_2S, the residual molecule is stabilized by ring closure to form the aminooxadiazole *(130)*[53].



(129)

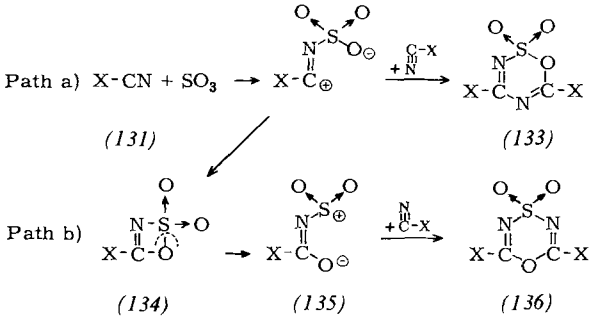
(130)

2.5. Ring Closure by 1,4-Dipolar Cycloaddition

The possibilities of using cyanic esters as dipolarophiles in 1,3-dipolar cycloadditions have already been exhaustively described[1, 2a].

An example showing the ability of cyanic esters to react as in a 1,4-dipolar cycloaddition is the reaction with SO_3. The dipole is first formed by addition of SO_3 to 1 mole of ArOCN, and it then reacts with a second mole of ArOCN as the dipolarophile. There are two possibilities for the structure of the final product:

In the reaction of benzonitrile *(131)*, X=C_6H_5, with SO_3, the unsymmetrical oxathiadiazine *(133)* is formed by path a)[54], whereas cyanogen chloride *(131)*, X=Cl, and SO_3 react by path b), which was formulated by *Huisgen*, to give the symmetrical isomer *(136)*[55].



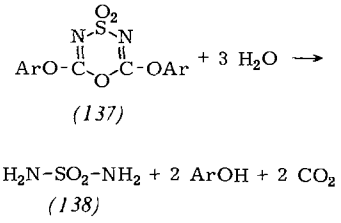
(131) (133)

(134) (135) (136)

The following findings[57] confirm that the reaction of cyanic esters with SO_3 proceeds *via* path b) and leads to the symmetrical compounds *(137)*, X=ArO[56]:

a) In the reaction of cyanamides *(131)*, X=NR_2, with SO_3[58], both isomers *(133)* and *(136)* were formed in one case [X=$N(CH_3)_2$][59]. It was thus possible to assign the products to the alternative structures (substance giving fewer IR bands has the symmetrical structure). An oxathiadiazine obtained on replacement of the two ArO residues in the product from ArOCN and SO_3 by —$N(CH_3)_2$ was identical with the symmetrical one *(136)*, X=$N(CH_3)_2$, of the two cyanamide reaction products.

b) Mild alkaline hydrolysis (milk of lime, 40 °C) led quantitatively to *(138)*.

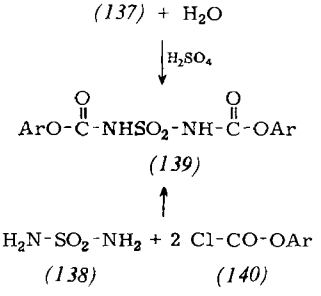


(137)

$H_2N-SO_2-NH_2$ + 2 ArOH + 2 CO_2

(138)

c) Acid hydrolysis (96% H_2SO_4) leads to *(139)*, the structure of which was verified by independent synthesis from *(138)* and *(140)*.

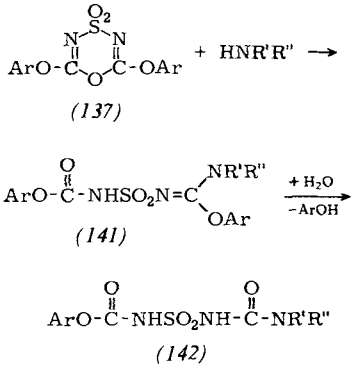


(138) (140)

(139)

Further reactions with (137):

Replacement of the aryloxy groups by —$N(CH_3)_2$ with retention of the ring structure in the reaction of *(137)* with dimethylamine [cf. a) above] is an exception. Amines generally add to one of the C atoms in *(137)*, and ring cleavage occurs to give *(141)*[60], which can be hydrolyzed to *(142)*. One of the aryloxy residues of *(141)* is exchanged against a second mole of amine only at higher temperatures.

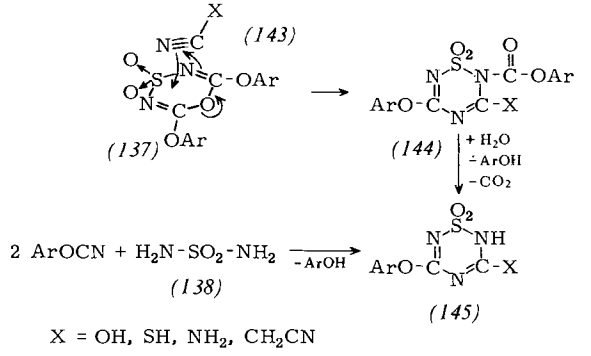


(137)

(141)

(142)

Compounds *(143)*, X=OH, SH, NH_2, CH_2CN, containing a nitrile group react in the form of their alkali metal salts with *(137)* in very good yields even at room temperature. They are formally inserted between C and N of the oxathiadiazine ring, in such a way that a new thiatriazine system *(144)* is formed on ring cleavage[59]. With X=OH, NH_2, and CH_2CN the reaction stops at compound *(144)*, while with X=SH the hydrolysis product *(145)* is formed immediately[59]. Another route to *(145)* with X=NH_2 is the reaction of ArOCN with sulfodiamide *(138)*[61].

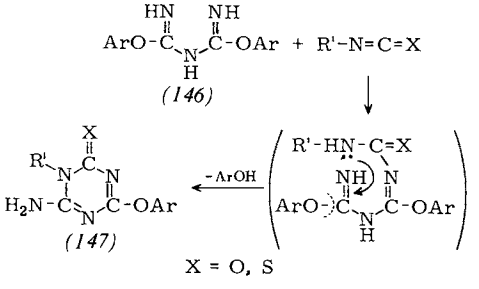


2.6. Heterocycle Syntheses with Further Reaction Products of Cyanic Esters

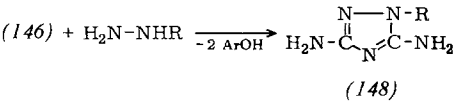
A number of heterocycle syntheses that became available through further reaction products from cyanic ester chemistry will be mentioned in conclusion.

2.6.1. From the 2:1 Addition Product *(146)* of ArOCN with NH_3

Even at room temperature the *s*-triazine derivatives *(147)* are formed directly in an exothermic reaction from *(146)* and isocyanates or isothiocyanates[62,63]

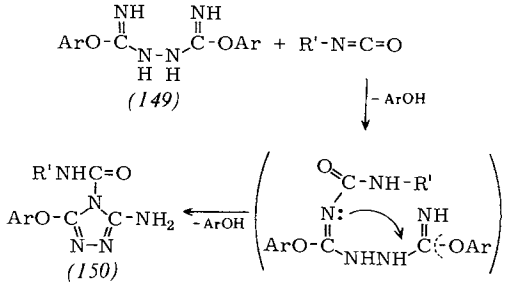


With hydrazines, again at room temperature, both ArO residues are exchanged to form *(148)*.



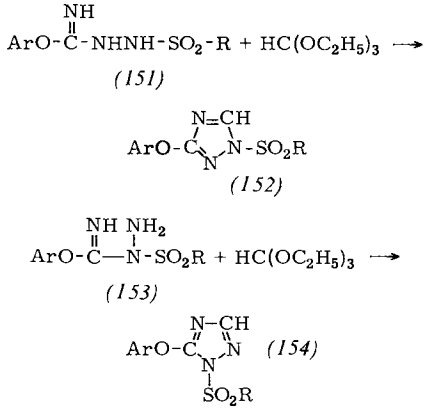
2.6.2. From the 2:1 Addition Product *(149)* of ArOCN with NH_2—NH_2

The triazoles *(150)* are obtained from the components only at temperatures above 100 °C. The yields are good[64].



2.6.3. From the Addition Products *(151)* and *(153)* of ArOCN with Sulfonohydrazide[65]

When *(151)* or *(153)* is heated in boiling ethyl orthoformate, the triazole *(152)* or *(154)* is formed. The yields are best if the alcohol formed is distilled off during the reaction[66].



2.6.4. From the Addition Product *(155)* of ArOCN with Cyanamide

As in most iminocarboxylic acid derivatives (cf. Section 2.6.1), the aryloxy residue in *(155)* can be replaced by nucleophiles. Stirring with hydrazines at room temperature leads smoothly to the cyanoaminoguanidines *(156)*, which cyclize to form *(157)*, in some cases on prolonged standing (R=H) and in others when heated (R=alkyl, aryl).

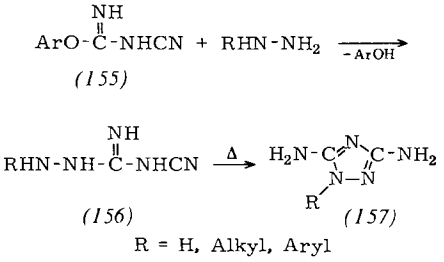
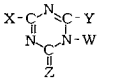


Table 1. *s*-Triazines.



X	Y	Z	Preparation route	Ref. [67]
—OAr	—OAr	—OAr	3 ArOCN	[A]
—OAr	—OAr	—OH	2 ArOCN + HOCN	[A]
—OAr	—OAr	—NH_2	a) 3 ArOCN + NH_3	[A]
			b) 2 ArOCN + H_2N—CN	[A]
—OAr	—OAr	—NR_2	3 ArOCN + HNR_2	[A]
—OAr	—OAr	—Cl	2 ArOCN + $COCl_2$	[B]
—OAr	—OAr	—R	a) 2 ArOCN + R—C(=NH)—OR	[B]
			b) 2 ArOCN + NH_3, then + R—COCl	[68]
—OAr	—OAr	—H	2 ArOCN + NH_3, then + $HC(OR)_3$	[B]
—OAr	—OH	—OH	ArOCN + 2 HOCN	[A]
—OAr	—SH	—SH	ArOCN + 2 HSCN	[A]
—OAr	—NH_2	—NH_2	a) ArOCN + H_2N—C(=NH)—NHCN	[A]
			b) 2 ArOCN + H_2N—C(=NH)—NH_2	[A]
—OAr	—NH_2	—SR	ArOCN + H_2N—C(=NH)—SR	[A]
—OAr	—SH	—OH	ArOCN + $COCl_2$, then + H_2N—CS—NH_2	[B]
—OAr	—OH	—R	ArOCN + $COCl_2$ (or ClCOOR), then + amidine	[B]
—OAr	—R	—R′	ArOCN + RCOCl, then + amidine	[B]
—OAr	—R	—COOR	ArOCN + ClCOCOOR, then + amidine	[B]
—OAr	—R	—NH_2	2 ArOCN + amidine	[B]
—NR_2	—R	—COOR	R_2N—CN + ClCOCOOR, then + amidine	[20]
—NR_2	—R′	—R″	R_2N—CN + RCOCl, then + amidine	[20]
—NR_2	—OH	—R	R_2N—CN + ClCOOR, then + amidine	[69]

Table 2. Six-membered heterocycles with three and four hetero atoms.



Type A



Type B



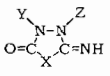
Type C

W	X	Y	Z	Preparation route	Ref. [67]
Type A:					
—R	—OH	—OAr	=S	ArOCN + $COCl_2$, then + RNH—CS—NH_2	[B]
—R, —H	—OH	—NR_2	=S	ArOCN + $COCl_2$, then + RNH—CS—NH_2, then + HNR_2	[B]
—R	—OAr	—NH_2	=O	2 ArOCN + NH_3, then + R—N=C=O	[B]
—R	—OAr	—NH_2	=S	2 ArOCN + NH_3, then + R—N=C=S	[B]
Type B:					
>NH	>CRR′	—OAr	—SH	ArOCN + NH_4SCN + R—CO—R′	[A]
>O	>SO_2	—OAr	—OAr	2 ArOCN + SO_3	[B]
>S	>C=O	—OAr	—OAr′	ArOCN + $COCl_2$, then + Ar′O—CS—NH_2	[B]
>S	>C=O	—OAr	—R	ArOCN + $COCl_2$, then + R—CS—NH_2	[B]
>NH	>SO_2	—OAr	—NH_2	ArOCN + $H_2NSO_2NH_2$	[B]
>NH	>SO_2	—OAr	—SH	2 ArOCN + SO_3, then + HSCN	[B]
Type C:					
>N—COOAr	>SO_2	—OAr	—OH	2 ArOCN + SO_3, then + HOCN	[B]
>N—COOAr	>SO_2	—OAr	—NH_2	2 ArOCN + SO_3, then + H_2N—CN	[B]
>N—COOAr	>SO_2	—OAr	—CH_2CN	2 ArOCN + SO_3, then + NC—CH_2—CN	[B]

Table 3. Five-membered heterocycles with three hetero atoms.


Type A

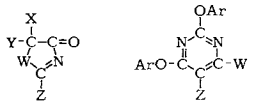

Type B


Type C


Type D

X	Y	Z	Preparation route	Ref. [67]
Type A:				
>O	—NH_2	—R	ArOCN + R—CO—$NHNH_2$	[A]
>O	—NHR′	—R	ArOCN + R—CO—NHNH—CS—NHR′	[B]
>O	—NHCO(O)R	—R′	ArOCN + ClCO(O)R, then + R′CONHNH$_2$	[B]
>S	—NH_2	—R	ArOCN + R—CS—$NHNH_2$	[A]
>NH	—OAr	—R	ArOCN + ClCOR, then + NH_2—NH_2	[B]
>NH	—OAr	—OH	ArOCN + ClCOOR, then + NH_2—NH_2	[B]
>NH	—OH	—OH	ArOCN + ClCOOR, then + H_2O, + NH_2—NH_2	[B]
>NH	—COOR	—OAr	ArOCN + ClCOCOOR, then + NH_2—NH_2	[B]
>NH	—COOR	—NR_2	R_2N—CN + ClCOCOOR, then + NH_2—NH_2	[B]
>NR	—NHCO(O)R′	—SH	ArOCN + ClCO(O)R′, then + H_2N—NH—CS—NHR	[B]
>NCONHR′	—NH_2	—OAr	2 ArOCN + H_2N—NH_2, then + R′—N=C=O	[B]
Type B:				
R	—R	—SH	ArOCN + ClCOR, then + H_2S: + NH_2NH_2	[B]
—R(H)	—OH	—OAr	ArOCN + ClCOCl(ClCOOR), then NH_2—NH_2	[B]
—R(H)	—NH_2	—NH_2	a) 2 ArOCN + NH_3, then + NH_2—NH_2	[B]
			b) ArOCN + NH_2CN, then + NH_2—NH_2	[B]
—R	—NR_2	—OH	R_2N—CN + ClCOOR, then + NH_2—NH_2	[70]
—R(H)	—OH	—COOR	ArOCN + ClCOCOOR, then + H_2N—NHR	[B]
—SO_2R	—NH_2	—OAr	2 ArOCN + H_2N—$NHSO_2$R	[A]
—SO_2R	—OAr	—NH_2	2 ArOCN + H_2N—$NHSO_2$R	[A]
—SO_2R	—H	—OAr	ArOCN + H_3NNHSO_2R + base, then + $HC(OR)_3$	[B]
—SO_2R	—OAr	—H	ArOCN + H_2NNHSO_2R, then + $HC(OR)_3$	[B]
—Ar	—Ar	—OAr	ArOCN + Ar′—CCl=N—NHAr′	[A]
Type C:				
>NR	—R(H)	—H	ArOCN + H_2N—NH—CO—NHR	[A]
>NR	—R(H)	—C(=NH)—OAr	2 ArOCN + H_2N—NH—CO—NHR	[A]
Type D:				
>O	—OAr	=O	ArOCN + NH_2OH, then + ClCOOR	[71]
>S	—OH	=NR	ArOCN + NH_2OH, then + R—S=C=N	[71]
>S	—NHR	=NR	ArOCN + $ClSCCl_3$, then + H_2N—R	[B]

Table 4. Five- and six-membered heterocycles with two hetero atoms.



Type A

Type B

W	X + Y	Z	Preparation route	Ref. [67]
Type A:				
>O	—R + —H	—NH_2	a) ArOCN + R—CHOH—$CONH_2$ b) ArOCN + R—CHOH—COOR + NH_3	[B]
>S	—R + —H	—NH_2	ArOCN + R—CHSH—COOR + NH_3	[B]
>NH	=O	—NR_2	R_2N—CN + ClCOCOCl, then + NH_3	[72]
>N—R	—R + —H	—NH_2	ArOCN + R—CHNHR—COOR + NH_3	[B]
>N—R	=O	—NHR	a) ArOCN + ClCOCOOR, then + H_2N—R b) ArOCN + ClCOCONHR, then + H_2N—R	[B]
>N—R′	=O	—NR_2	R_2N—CN + ClCOCOCl, then + H_2N—R′	[72]
>N—NR_2	=O	—OAr	ArOCN + ClCOCOOR, then + H_2N—NR_2	[B]
>N—NR_2	=O	—NR_2	R_2N—CN + ClCOCOCl, then + H_2N—NR_2	[72]
>N—COOR	=O	—OH	2 ArOCN + ClCOCOCl, then + H_2O	[B]
>N—R′	—Cl + —Cl	—OAr	ArOCN + ClCOCl, then + R′NC	[69]
Type B:				
—OH	—	—CN	2 ArOCN + NC—CH_2—CN	[A]
—NH_2	—	—CN	2 ArOCN + NC—CH_2—COOR	[A]
—C_6H_4—NO_2-(4)	—	—COOR	2 ArOCN + O_2N—C_6H_4—CO—CH_2—COOR	[73]

I am grateful to Dr. R. Pütter for the many suggestions and discussions with which he has helped the progress of this work. I thank G. Rottloff, M. Brockelt, and J. Abraham for their outstanding assistance in the execution of the extensive program of experiments.

Received: February 18, 1972 [A 912 IE]
German version: Angew. Chem. *84*, 1008 (1972)
Translated by Express Translation Service, London

[1] *E. Grigat* and *R. Pütter*, Angew. Chem. *79*, 219 (1967); Angew. Chem. internat. Edit. *6*, 206 (1967).

[2] Other reviews: a) *D. Martin*, Z. Chem. *7*, 123 (1967); b) only *alkyl* cyanates: *K. A. Jensen, M. Due, A. Holm*, and *C. Wentrup*, Acta Chem. Scand. *20*, 2091 (1966). c) After the publication of the reviews mentioned, *M. Hedayatullah*, who prepares individual new cyanic esters by the known methods and subjects them to the further reactions that have been described up to that time, wrote another review in French: Bull. Soc. Chim. France *1968*, 1572.

[3] *E. Grigat*, Angew. Chem. *81*, 623 (1969); Angew. Chem. internat. Edit. *8*, 607 (1969).

[4] *D. Martin* and *A. Weise*, Chem. Ber. *100*, 3736 (1967).

[5] DOS 1668108, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 9, 1968).

[6] DOS 1768228, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Apr. 18, 1968).

[7] DOS 1912227, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 11, 1969).

[8] DOS 1768677, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (June 15, 1968).

[9] DOS 1912226, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 11, 1969).

[10] DOS 1940367, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Aug. 8, 1969).

[11] DOS 1912225, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 11, 1969).

[12] DBPat. 1262260, Farbenfabriken Bayer AG, *G. Oertel* (Nov. 24, 1964).

[13] DOS 1913841, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 19, 1969).

[14] DOS 1768678, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (June 15, 1968).

[15] DOS 1920762, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Apr. 24, 1969).

[16] DOS 2020597, Farbenfabriken Bayer AG, *E. Grigat* (Apr. 28, 1970).

[17] DOS 2017966, Farbenfabriken Bayer AG, *E. Grigat* (Apr. 15, 1970).

[18] DOS 2013786, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 23, 1970).

[19] DOS 1940366, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Aug. 8, 1969).

[20] DOS 2013357, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 20, 1970).

[21] DOS 1956510, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 11, 1969).

[22] DOS 1956508, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 11, 1969).

[23] DOS 1956043, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 7, 1969).

[24] DOS 1956042, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 7, 1969).

[25] DOS 1934227, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (July 5, 1969).

[26] DOS 2042660, Farbenfabriken Bayer AG, *E. Grigat* (Aug. 28, 1970).

[27] DOS 1905562, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Feb. 5, 1969).

[28] DOS 1928130, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (June 3, 1969).

[29] DOS 1932829, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (June 28, 1969).

[30] *O. Schäfer*, Fachhochschule Aachen. Results from the chemical engineering studies carried out in our laboratory.

[31] DOS 2027494, Farbenfabriken Bayer AG, *E. Grigat* (Aug. 4, 1970).

[32] DOS 1817541, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Dec. 31, 1968).

[33] DOS 2020936, Farbenfabriken Bayer AG, *E. Grigat* (Apr. 29, 1970).

[34] DOS 1768420, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (May 11, 1968).

[35] DOS 1793127, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Aug. 7, 1968).

[36] DOS 2042256, Farbenfabriken Bayer AG, *E. Grigat* (Aug. 26, 1970).

[37] *D. Lochner*, Fachhochschule Aachen, Jülich Section. Results from the chemical engineering studies carried out in our laboratory.

[38] DOS 1920498, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Apr. 23, 1969).

[39] DOS 2042255, Farbenfabriken Bayer AG, *E. Grigat* (Aug. 26, 1970).

[40] German Pat. Appl. 2211340, Farbenfabriken Bayer AG, *E. Grigat*. (The reaction with these compounds are the subject of the chemical engineering studies carried out in our laboratory by *G. Schlosser*, Technische Fachhochschule Berlin.)

[41] DOS 1928132, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (June 3, 1969).

[42] German Pat. Appl. 2211339, Farbenfabriken Bayer AG, *E. Grigat*.

[43] *E. Grigat* and *R. Pütter*, Chem. Ber. *98*, 1359 (1965).

[44] *E. Grigat*, Angew. Chem. *82*, 81 (1970); Angew. Chem. internat. Edit. *9*, 68 (1970).

[45] DOS 1940370, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Aug. 8, 1969).

[46] DOS 1936127, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (July 16, 1969).

[47] *E. Grigat*, *R. Pütter*, *K. Schneider*, and *K. F. Wedemeyer*, Chem. Ber. *97*, 3036 (1964).

[48] DOS 1670968, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Jan. 2, 1968).

[49] DOS 1670927, Farbenfabriken Bayer AG, *J. Zirner*, *E. Grigat*, and *R. Pütter* (Sep. 22, 1967).

[50] DOS 1670762, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 2, 1966).

[51] DOS 1937905, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (July 25, 1969).

[52] DOS 2013424, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (March 20, 1970).

[53] DOS 1670702, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (May 25, 1966).

[54] *P. Eitner*, Ber. dtsch. chem. Ges. *25*, 461 (1892).

[55] *R. Graf*, Chem. Ber. *89*, 1071 (1956).

[56] DOS 1670764, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 3, 1966).

[57] *D. Martin* also carried out this reaction, but assigns the unsymmetrical structure *(133)* to the reaction products: Chem. Ber. *100*, 3741 (1967).

[58] DOS 1670769, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Nov. 15, 1966).

[59] *G. Klag*, Farbenfabriken Bayer AG, ZW-Abt. wissenschaftlich. Unpublished results.

[60] DOS 1768285, Farbenfabriken Bayer AG, *E. Grigat* and *R. Pütter* (Apr. 25, 1968).

[61] DOS 2026625, Farbenfabriken Bayer AG, *E. Grigat* (May 30, 1970).

[62] DOS 1670965, Farbenfabriken Bayer AG, *J. Zirner*, *E. Grigat*, and *R. Pütter* (Dec. 21, 1967).

[63] DOS 1670966, Farbenfabriken Bayer AG, *J. Zirner*, *E. Grigat*, and *R. Pütter* (Dec. 21, 1967).

[64] DOS 1670972, Farbenfabriken Bayer AG, *J. Zirner*, *E. Grigat*, and *R. Pütter* (Jan. 18, 1968).

[65] *E. Grigat* and *R. Pütter*, Chem. Ber. *99*, 958 (1966).

[66] *A. Seyberlich*, Farbenfabriken Bayer AG, ZW-Abt. wissenschaftlich. Unpublished experiments.

[67] The original publications for [A] can be found in the reviews [1] and [2a], while those for [B] are given in the present article. The original reference is given here only for reactions that are not mentioned in any of these reviews.

[68] *E. Grigat* and *R. Pütter*, Chem. Ber. *97*, 3027 (1964).

[69] *E. Grigat*, unpublished results.

[70] DOS 2042660, Farbenfabriken Bayer AG, *E. Grigat* (Aug. 28, 1970).

[71] *E. Grigat*, *R. Pütter*, and *C. König*, Chem. Ber. *98*, 144 (1965).

[72] *G. Schlosser*, Technische Fachhochschule Berlin. Results from the chemical engineering studies carried out in our laboratory.

[73] *E. Grigat* and *R. Pütter*, Chem. Ber. *100*, 1385 (1967).

Reactions of Electron-Rich Olefins with Proton-Active Compounds

By Jürgen Hocker and Rudolf Merten[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

Proton-active substances react with certain electron-rich olefins with cleavage of the central C=C double bond to give compounds that can be formally regarded as insertion products of nucleophilic carbenes. If they satisfy certain structural conditions, they isomerize with β elimination to give open-chain compounds. Both CH-acidic compounds and compounds containing NH or OH groups can undergo this reaction. The mechanisms are discussed, and the importance of the intermediate products to biochemistry (thiamine, tetrahydrofolic acid) is indicated.

1. Introduction

The reactivity of the central C=C double bond in tetracyanoethylene *(1)* is determined by the influence of the four electron-attracting groups. The electron-poor double bond exhibits strongly electrophilic character[1,2].

Olefins *(2)* with four electron-donating substituents, on the other hand, react as strong nucleophiles. These compounds are referred to as *electron-rich olefins*[**][3-6].

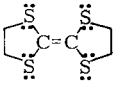


(1) *(2)*

A, B = NR_2, OR, SR.

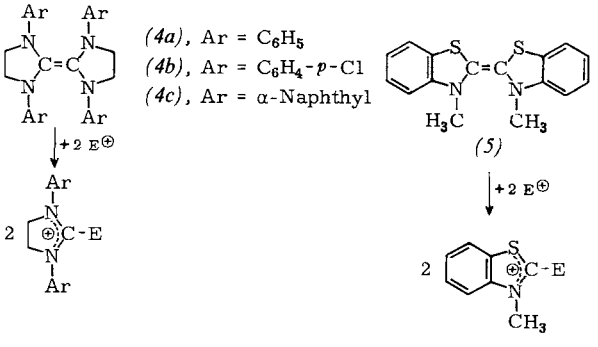
A and B not both SR

The ability of the substituents A and B to supply electrons increases in the order SR < OR < NR_2. Whereas tetraaminoethylenes are very reactive, strongly nucleophilic compounds, tetramercaptoethylenes exhibit only weak reactivity toward electrophiles. For example, they dissolve in concentrated sulfuric acid and are reprecipitated unchanged on dilution[8]. An extended Hückel calculation shows that the charge density on the sulfur in *(3)* is greater than that on the olefinic C atom. Electrophiles are therefore directed to the sulfur and not to the double bond; the chemical behavior of the tetramercaptoethylenes does not agree with that of an electron-rich olefin.



(3)

Electron-rich olefins of the type *(4)* or *(5)* react with electrophiles ($E^{\oplus}$) preferentially with cleavage of the central C=C double bond. The obvious assumption that the olefins dissociate[9,10] into two resonance-stabilized carbenes was not confirmed by crossover experiments[11,12].



(4a), Ar = C_6H_5
(4b), Ar = C_6H_4-*p*-Cl
(4c), Ar = α-Naphthyl

(5)

Nevertheless, electron-rich olefins represent a source of nucleophilic carbenes[*][11,13].

Characteristic reactions of the olefins of types *(4)* and *(5)* with electrophiles that proceed *via* cleavage of the molecule are those with mineral acids to form the azoli(ni)um salts *(6)*[6,13-15], hydrolysis to form *N*-formyl compounds *(7)*[6,16], reactions with diazo compounds to form azines *(8)*[17-20], with azides to form monoaza and/or triaza compounds *(9)*[12,21,22], with iso(thio, seleno)cyanates to form stable dipoles *(10)* or (thio, seleno)hydantoin derivatives *(11)*[22-26], and the reaction of *(4a)* with ketenes, which also gives stable dipoles *(12)*[19,27,28].

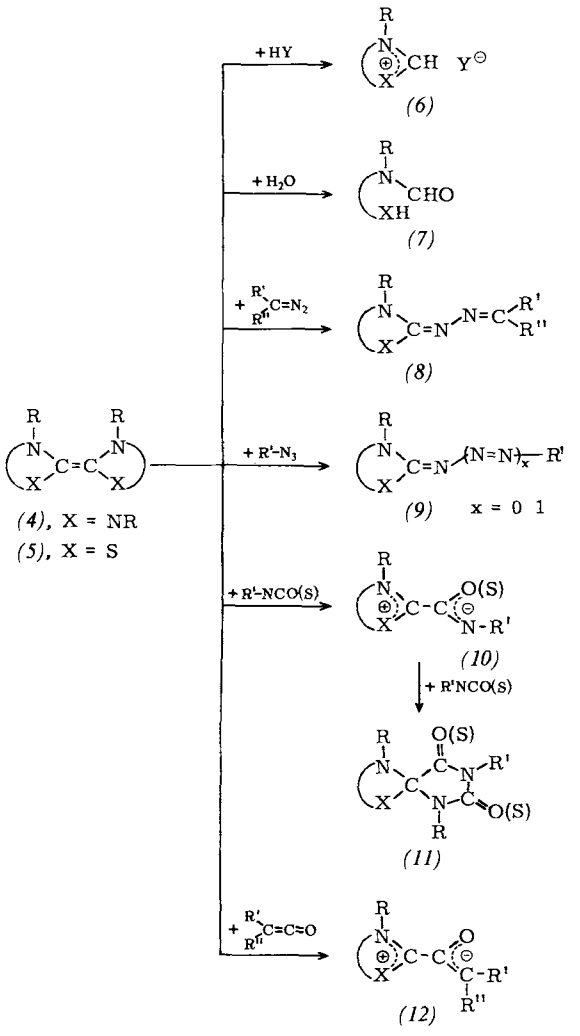
Reactions of olefins of types *(4)* and *(5)* with proton-active compounds are discussed in detail below. The products nearly always contain one "carbene" half of the original ethylene molecule. They are formally products of the insertion[**] of a nucleophilic carbene into an XH bond, possibly with formation of a new C—C, C—N, or C—O bond in addition to a new CH bond.

[*] Dr. J. Hocker and Dr. R. Merten
Wissenschaftliches Hauptlaboratorium der
Bayer AG
509 Leverkusen-Bayerwerk (Germany)

[**] The term "electron-rich olefins" is sometimes also applied to ketene (thio)acetals or aminals, in which the π-electron density of the C=C double bond is also greater than 1.0 [7].

[*] The occurrence of *free* nucleophilic carbenes has not yet been definitely established.

[**] The expression "insertion product" carries no implications regarding the mechanism of the reaction.



2. Reactions with Formation of a New C—C Bond

2.1. With Aliphatic CH-Acidic Compounds (Table 1)

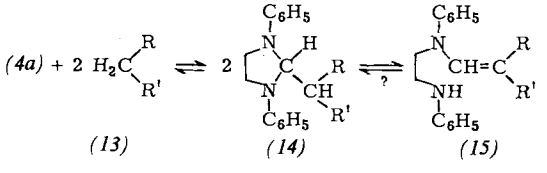
The first reactions of an electron-rich olefin, *i.e.* 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene *(4a)* with CH-acidic compounds *(13)* were described by *H.-W. Wanzlick*. Two types of products can be formed in these reactions:

1. a primary product *(14)*, which may be thought of as resulting from the insertion of a nucleophilic carbene into an activated CH bond, and, in some cases,

2. a further reaction product *(15)*, which is formed from *(14)* by β elimination.

(4a) does not react with α-picoline and valeronitrile at 180 °C[30].

The rate of the reaction of *(4a)* with *(13)* increases with the acidity of the proton-active compound. If a mixture of



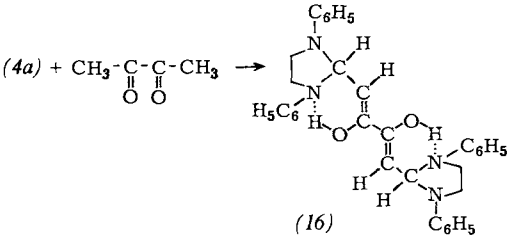
(13) *(14)* *(15)*

Table 1. Reaction of *(4a)* with aliphatic CH-acidic compounds.

(13)	Yield (%) *(14)*	*(15)*	Ref.
(a) $CH_3COOC_2H_5$	57	—	[30]
(b) CH_3CN	83	—	[30]
(c) CH_3NO_2	72	—	[9]
(d) $NC—CH_2—COOC_2H_5$	—	45	[30]
(e) $C_6H_5—CO—CH_3$	little	88.5	[29]
(f) $C_6H_5—CH_2—CO—C_6H_5$	—	55	[30]
(g) $C_6H_5—CH_2—COOC_2H_5$	89	—	[30]
(h) $C_6H_5—CH_2—CN$	92	—	[30]
(i) $C_6H_4—NO_2$-(4)-$CH_2—CN$	—	67	[31]
(k) Cyclopentanone	71	—	[9]
(l) Indan-1-one	little	86.5	[29]
(m) 5,6-Benzomorpholin-3-one	70	—	[31]

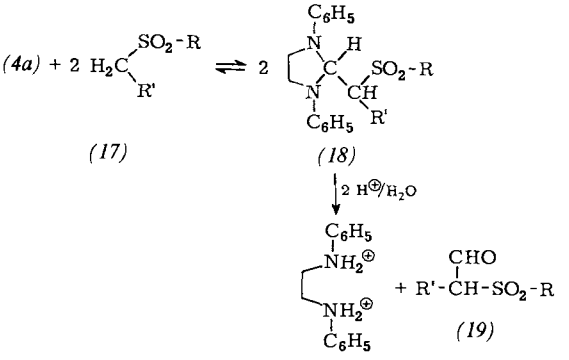
benzyl cyanide *(13h)* and ethyl phenylacetate *(13g)* is allowed to act on *(4a)*, only the benzyl cyanide reacts[30], in agreement with known acidity series.

Biacetyl, which has two activated methyl groups, reacts *via* both to give a yellow compound *(16)*. Spectroscopic data indicate the presence of a double enol chelate. An isolable red-violet complex is obtained with iron(III) chloride[31].



(16)

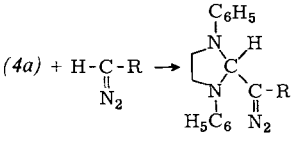
The 2-substituted imidazolidines *(18a)* to *(18f)* were obtained exclusively on reaction of SO_2-activated methylene compounds *(17a)* to *(17f)* with *(4a)*[32]. This reaction can be used for the synthesis of α-sulfonyl aldehydes *(19)*, since acidic hydrolysis of the aminals *(18)* leads to the carbonyl compounds from which they are derived[32].



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

(17)	R	R'
(a)	CH_3	H
(b)	n-C_4H_9	H
(c)	C_6H_5	H
(d)	$C_6H_4CH_3$-(*p*)	H
(e)	C_6H_4Cl-(*p*)	H
(f)	R + R' = —$(CH_2)_3$—	

Diazo compounds *(20)*[33-35] containing mobile diazomethyl hydrogen also give 2-substituted imidazolidines *(21)* on reaction with *(4a)*[19]. Ring cleavage with β



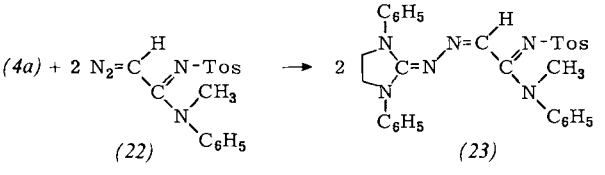
(20) *(21)*

(a), R = $COOC_2H_5$
(b), R = $COOC_4H_9$-*(t)*
(c), R = $CON(C_2H_5)_2$

(d), R = CON⟨ ⟩

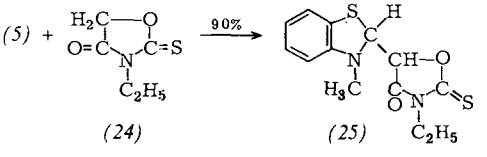
(e), R = $CO—C_6H_5$
(f), R = $PO(C_6H_5)_2$
(g), R = $C_6H_4NO_2$-*(p)*

elimination is ruled out here for structural reasons. Diazo compounds having an immobile diazomethyl proton react in the same way as the disubstituted diazomethanes to give azines[17-20]. An example is the compound *(22)*, in which the acidity of the diazomethyl proton is insufficient for the formation of a diazoaminal *(21)* because of the weak activating effect of the amidine group. Electrophilic attack of the terminal N atom on the double bond of *(4a)* followed by cleavage of the molecule yields the azine *(23)*[19].



(22) *(23)*

Very few reactions of other electron-rich olefins with CH-acidic compounds involving cleavage of the molecule and formation of a new C—C bond have been investigated. The use of *(5)* instead of *(4a)* should merely lead to a change in the reaction rate, but apart from the reaction of *(5)* with 3-ethyl-2-thioxooxazolidin-4-one *(24)* to form

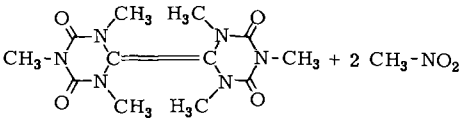


(24) *(25)*

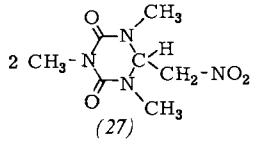
(25)[13], no reactions of this olefin with CH-acidic compounds are known.

1,1',3,3',5,5'-Hexamethyl-6,6'-bi-(1,3,5-triazinylidene)-2,2',4,4'-tetraone *(26)* reacts with nitromethane to give a "CH insertion product" *(27)*[15].

The unbridged electron-rich olefins tetramorpholinoethylene and tetrapiperidinoethylene *(28)* react with nitromethane with elimination of morpholine or piperidine in a

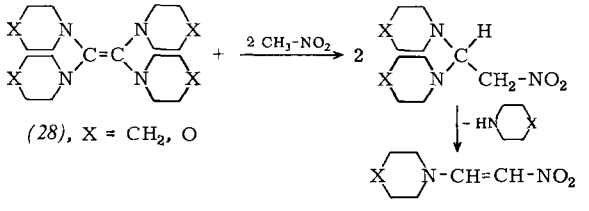


(26)



(27)

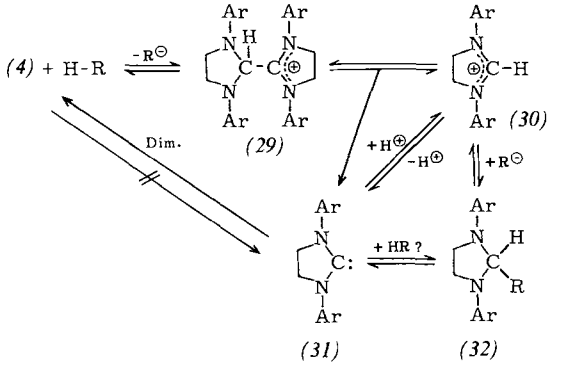
reaction sequence analogous to *(13)*→*(14)*→*(15)* to give enamines[35a].



(28), X = CH_2, O

2.1.1. Mechanistic Considerations

The CH acidity of the proton-active compounds and the fact that electron-rich olefins are strong π bases justify the assumption that the reactions are initiated by protonation of the electron-rich double bond of *(4)* to form *(29)*. Decomposition of *(29)* affords the imidazolinium cation *(30)* and a nucleophilic carbene *(31)*[11]. Direct addition of the anion R^- to *(29)*, as detected by *Hoffmann* and

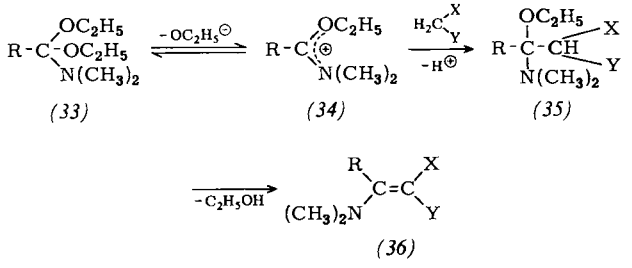


(29) *(30)* *(31)* *(32)*

Gehlhaus[36] in the reaction of tetramethoxyethylene with malodinitrile, has not been observed in the reactions of *(4)*. The cation *(30)* now attacks R^- or RH electrophilically and gives *(32)*. This step is plausible in view of the reactions of azoli(ni)um salts with bases in the presence of CH-acidic compounds, which also yield CH insertion products. For example, 3-methylbenzothiazolium iodide reacts with *(24)* in the presence of Na methoxide to give *(25)* in 71% yield[13].

The mechanism is also supported by the reactions of the amide acetals *(33)*[37] with CH-acidic compounds, which probably proceed *via* carbonium ions *(34)*. The dissociation *(33)*⇌*(34)* is very fast even at −50 °C, as is shown by NMR studies on exchange experiments with *N,N*-dimethyl-

formamide dimethyl acetal[38,39]. The aminomethylene compound *(36)* is obtained with elimination of 2 moles of ethanol.

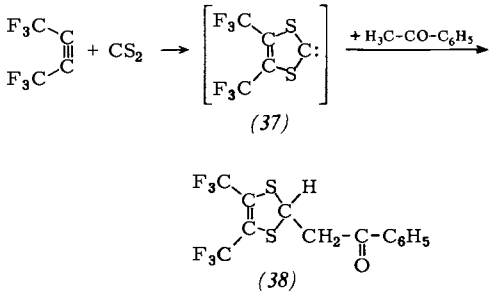


(33) *(34)* *(35)* *(36)*

The nucleophilic carbene *(31)* formed as an intermediate in the reaction *(29)*⇌*(30)* can react in two ways:

1. Dimerization to give the starting olefin *(4)*. This step is irreversible, as is shown by crossover experiments[11,12]. The olefin can take part in the reaction again.

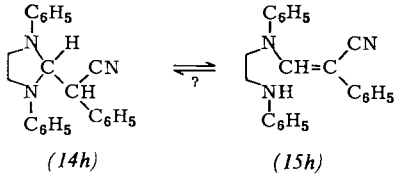
2. Protonation to give the imidazolinium cation *(30)*. This step is reversible, as was shown by H-D exchange experiments on the C-2 atom of imidazoli(ni)um or thiazolium salts[40–49]. *Hartzler*[50] was able to show in the reaction of the dithiocarbene[*] *(37)* with acetophenone to form *(38)* that a carbene formed as an intermediate reacts directly with a CH-acidic compound to give the CH insertion product.



(37) *(38)*

The overall reaction *(4)*⇌*(32)* is reversible, as was shown by *Wanzlick*[30]. Thus when *(14a)* is heated at 130 °C and 14 torr, it is converted back into the starting olefin *(4a)*.

In the reaction of an active methyl or methylene compound with *(4a)*, two products, *(14)* and *(15)*, are possible. The reaction of *e.g. (13h)* with *(4a)* leads to a colorless substance *(14h)*, whose IR spectrum contains no NH absorption[30]. Under certain conditions, however, *(15h)* can be detected as well as *(14h)* in the NMR spectrum[31].



(14h) *(15h)*

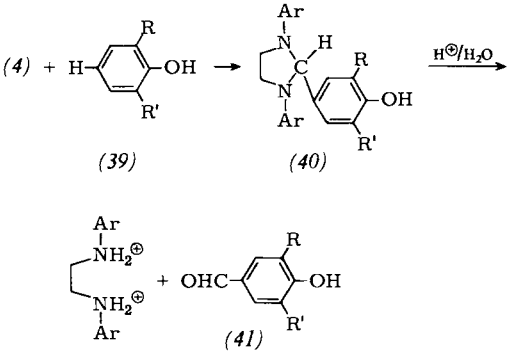
[*] It should be noted, however, that dithiocarbenes react mainly electrophilically [51]. For the reaction of dithiolium salts or dithiocarbenes with CH-acidic compounds, cf. also [52]. For the reaction of an intermediate diaminocarbene with a CH-acidic compound, cf. [26].

This product appears to result from a ring-chain tautomerism, which has not yet been investigated in detail.

The reaction of 4-nitrophenylacetonitrile with *(4a)* leads to a 70% yield of *(15i)*, which shows no tendency to undergo ring closure either in the crystalline state or in solution[31].

2.2. With Aromatic Compounds

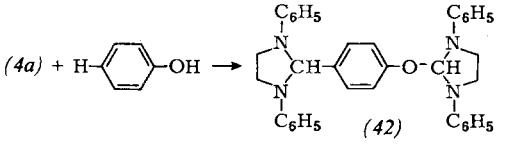
Only preliminary studies have so far been carried out on the reactions of electron-rich olefins with phenols, the examples studied being *(4a)* and *(4b)*. *o,o'*-Disubstituted phenols *(39)* give the compound *(40)* in good yields[31]. These products are cyclic aminals, and they can be hydrolyzed with hydrochloric acid to give high yields of *p*-hydroxybenzaldehydes *(41)*[31]. The introduction of formyl groups with the aid of *Wanzlick*'s olefin *(4)* is thus possible not only for aliphatic CH-acidic compounds (cf. α-sulfonyl aldehydes, Section 2.1) but also for activated aromatic compounds.



(39) *(40)* *(41)*

(40)	Ar	R	R'
(a)	C_6H_5	CH_3	CH_3
(b)	C_6H_5	C_3H_7-(*i*)	C_3H_7-(*i*)
(c)	C_6H_5	C_4H_9-(*t*)	C_4H_9-(*t*)
(d)	C_6H_5	Cl	Cl
(e)	C_6H_5	CH_3	Cl
(f)	C_6H_5	CH_3	NO_2
(g)	C_6H_4Cl-(*p*)	C_4H_9-(*t*)	C_4H_9-(*t*)

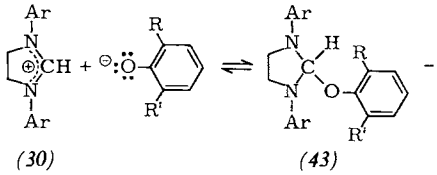
The reaction of unsubstituted phenol and *(4a)* yields a 1:1 adduct, which probably has the structure *(42)*:



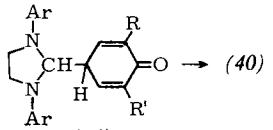
(42)

The *mechanism* differs only in the further reaction from that of the reactions of aliphatic CH-acidic compounds with electron-rich olefins. The first step is probably again the protonation of the electron-rich double bond of the olefin to give *(29)* by the proton of the hydroxyl group. *(29)* decomposes into the imidazolinium cation *(30)* and a nucleophilic carbene *(31)*, which can either dimerize to give the starting olefin or can take part in the reaction as

such. The cation *(30)* reacts first with the phenoxide anion[*], probably at the point of highest electron density[**], *i.e.* the oxygen, with reversible formation of the "OH insertion product" *(43)* (cf. Section 4.2), which reacts further *via (44)* to give the thermodynamically more stable ring-substituted product *(40)*.



(30) *(43)*

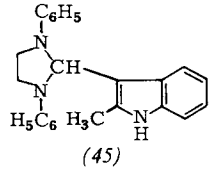


(44)

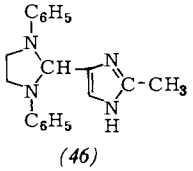
When 2,6-disubstituted phenol *(39c)* deuterated in the hydroxyl group is allowed to react with *(4a)*, a product *(40c)* deuterated in position 2 of the imidazolidine ring should be expected according to this mechanism. However, the deuterium content actually found[31] in position 2 is only about 60%; this is probably due to a fast H-D exchange between the phenol group of the *(40c)* formed and the imidazolinium cation *(30)*.

No reaction with *(4a)* was achieved either with phenetole [no possibility of protonation of the electron-rich double bond of *(4a)*] or with 2,4-di-*tert*-butyl-4-methylphenol (no possibility of electrophilic substitution on the aromatic ring)[31].

Heterocycles containing NH can also form "insertion products" under certain conditions. *(4a)* reacts with 2-methyl-2,3-dihydroindole to form an "NH insertion product" *(59d)* (cf. Section 3.1). The "CH insertion product" *(45)* is obtained, on the other hand, with 2-methylindole[31]. 2,3-Dimethylindole is inert toward *(4a)* under the usual reaction conditions (up to 70 hours in boiling toluene).



(45)



(46)

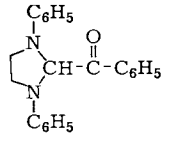
2-Methylimidazole also gives a "CH insertion product" *(46)*, whereas 1-methylimidazole and 1,2-dimethylimidazole do not react with *(4a)*[31]. It follows that in addition to an NH proton [for protonation of the double bond in *(4a)*], another active center must also be present (for the electrophilic substitution). The reaction mechanism is probably analogous to that of phenols.

[*] For the reaction of a dithiocarbene with phenols, cf. [50].

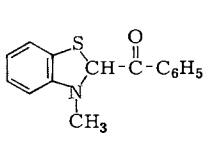
[**] It is possible that *(30)* attacks the *para* position of the phenoxide anion directly in the case of phenols with strong steric hindrance, such as *(39c)*, with formation of *(44)*.

2.3. With Aldehydes

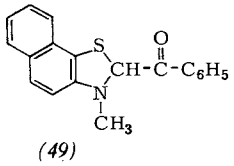
Though aldehydes are not proton-active compounds, their reactions with electron-rich olefins will be discussed here, since the products can also be regarded as "CH insertion products". Benzaldehyde reacts with *(4a)*[6, 9, 53], *(5)*[13, 53], and 3,3'-dimethyl-2,2'-bi(naphtho[2,1-*d*]thiazolinylidene)[53] to give the products *(47)* to *(49)*; furfural reacts with *(4a)* to form the analogous compound *(50)*[6, 29]. Benzoin and furoin are obtained as by-products, *i.e.* the electron-rich olefin or nucleophilic carbene formed *in situ* can replace the cyanide ion[54] in the benzoin condensation.



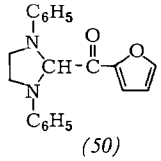
(47)



(48)

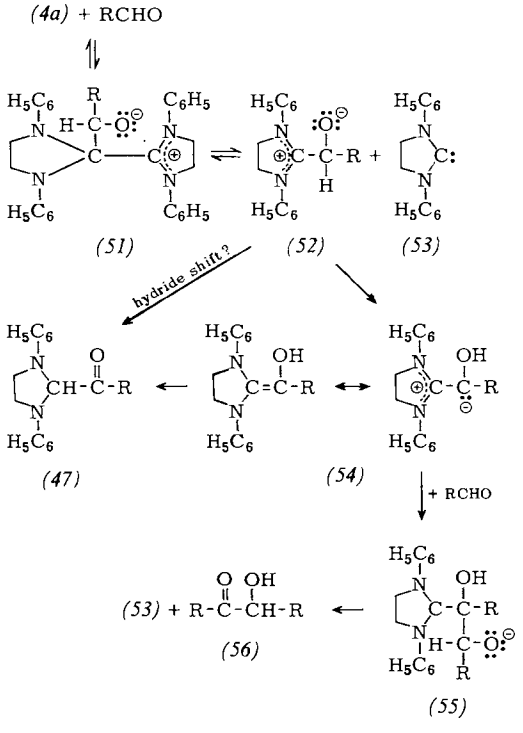


(49)



(50)

Protonation of the double bond of the electron-rich olefin can be ruled out as the initial step of this reaction, since the aldehyde proton possesses no acidity. The electrophilic



(51) *(52)* *(53)* *(47)* *(54)* *(56)* *(55)*

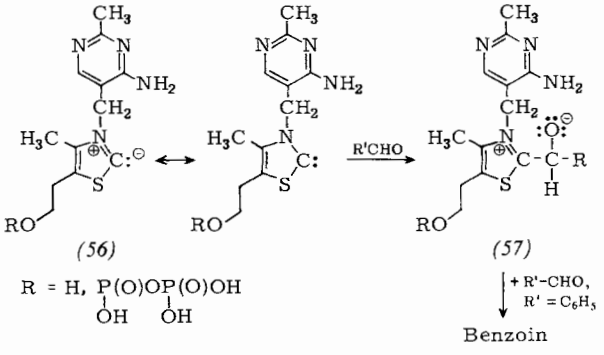
carbonyl carbon atom of the aldehyde probably attacks the electron-rich double bond with formation of *(51)*. A diaminocarbene *(53)* is eliminated to form *(52)*, which either

1. gives the acylimidazolidine *(47)* by a proton shift and ketonization of the enol form *(54)*[*] or

2. reacts by addition of a second aldehyde molecule to form *(55)*, which gives the acyloin *(56)* by proton migration and removal of the carbene *(53)*. The carbene *(53)* can either attack an aldehyde molecule nucleophilically on the carbonyl carbon atom to form *(52)* or can dimerize to form the starting olefin and thus undergo renewed reaction.

This mechanism of acyloin formation is similar to the classical Lapworth mechanism[54].

The carbene-catalyzed acyloin formation seems important in biochemistry. *Breslow*[55] showed in 1958 that a thiazolium zwitterion *(56)* (the limiting resonance form of a nucleophilic carbene) is responsible for the thiamine-catalyzed acyloin formation and for the formation of "active aldehydes" *(57)*. The reactions of the thiamine



zwitterion (thiamine carbene) *(56)* formed *in situ* with aldehydes[56, 57] and α-keto aldehydes[58–62], which lead to C-2-acylated thiamines, hydroxyalkyl(aryl)thiamines, or acyloins has been thoroughly investigated. Benzaldehyde is actually used as a carbene detector[63] in the reactions with 4,5-diphenyldithiolium salts. Neither the 4,5-diphenyldithiolium ion nor the carbene dimer (tetramercaptoethylene) can react with benzaldehyde, which reacts exclusively with the dithiocarbene to form 2-acyl-4,5-diphenyldithiols.

3. Reactions with Formation of a New C—N Bond

3.1. With Primary and Secondary Amines and Hydrazines (Table 2)

Aliphatic, aromatic, and heterocyclic amines react with the electron-rich olefins *(4a)* and *(4c)* with initial formation of extremely readily hydrolyzed "NH insertion products" *(59)*, which can be isolated in the case of the secondary amines, but isomerize to the aminoamidines *(60)* in the cases of primary amines and hydrazines[64].

[*] A hydride shift *(52)*→*(47)*, cf. [13, 50, 63] seems unlikely in comparison with a keto-enol tautomerism. For the formation of an enol acetate, cf. [62].

The reaction rate increases in the order aliphatic < araliphatic < aromatic amines.

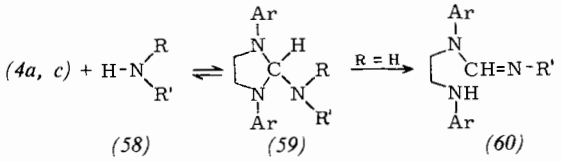
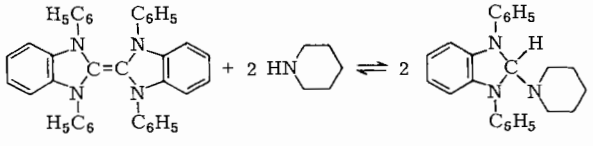


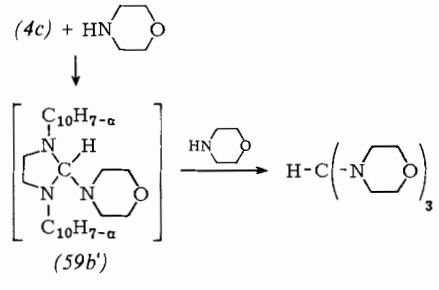
Table 2. Products *(59)* and *(60)* of the reaction of *(4a)* and *(4c)* with amines and hydrazines, respectively [64].

(4)	R *(58)*	R'	*(59)*	*(60)*
(a)	H	CH_2-c-C_6H_{11}	—	*(a)*
(a)	H	c-C_6H_{11}	—	*(b)*
(a)	H	$CH_2C_6H_5$	—	*(c)*
(a)	H	C_6H_5	—	*(d)*
(a)	H	$C_6H_4NO_2$-(*p*)	—	*(e)*
(a)	H	C_6H_4Cl-(*o*)	—	*(f)*
(a)	H	$C_6H_4CH_3$-(*p*)	—	*(g)*
(a)	H	2-Pyridyl	—	*(h)*
(c)	H	$C_6H_4NO_2$-(*p*)	—	*(i)*
(a)	H	$N(CH_3)_2$	—	*(k)*
(a)	H	$NHC_6H_3(NO_2)_2$-(2,4)	—	*(l)*
(c)	H	$NHC_6H_3(NO_2)_2$-(2,4)	—	*(m)*
(a)	—$(CH_2)_5$—		*(a)*	—
(a)	—$(CH_2)_2$—O—$(CH_2)_2$—		*(b)*	—
(a)	—C_6H_4—N=N—(*o*)		*(c)*	—
(a)	—C_6H_4—CH_2—$CH(CH_3)$—(*o*)		*(d)*	—
(a)	CH_3	C_6H_5	*(e)*	—

1,1′3,3′-Tetraphenyl-2,2′-bi(benzimidazolinylidene) *(61)* reacts in a similar manner with piperidine to form *(62)*[65].



After the reaction of 1,1′,3,3′-tetra-(1-naphthyl)-2,2′-bi(imidazolidinylidene) *(4c)* with an excess of morpholine, on the other hand, only trimorpholinomethane was isolated; this was probably formed by transamination from *(59b′)*[31].



3.2. With Carboxamides, Sulfonamides, and Phosphoramides

The reaction of *(4a)* with the carboxamides *(58a)* to *(58h)* stops at the imidazolidine *(59)*, though the structural

Table 3. Products *(59)* and *(60)* [31] of the reaction of *(4a)* with carboxamides *(58a)* to *(58h)*, carbohydrazides *(58i)* and *(58k)*, sulfonamides *(58l)* to *(58n)*, and phosphoramides or phosphonamides *(58o)* to *(58r)*.

(58)	R	R′	*(59)*	*(60)*
(a)	H	CHO	*(f)*	—
(b)	CH_3	CHO	*(g)*	—
(c)	H	$COCH_3$	*(h)*	—
(d)	H	$COC(CH_3)=CH_2$	*(i)*	—
(e)	H	$CO—CH=CH—CH_3$	*(k)*	—
(f)	H	$CO—CH=CH—C_6H_5$	*(l)*	—
(g)	H	$CO—C_6H_5$	*(m)*	—
(h)	H	$CO—OC_2H_5$	*(n)*	—
(i)	H	$NH—CO—CH_3$	—	*(n)*
(k)	H	$NH—CO—C_6H_5$	—	*(o)*
(l)	H	$SO_2—CH_3$	—	*(p)*
(m)	H	$SO_2—C_6H_5$	—	*(q)*
(n)	H	$SO_2—C_6H_4CH_3$-(*p*)	—	*(r)* [a]
(o)	H	$PO(OC_2H_5)_2$	—	*(s)*
(p)	H	$PO(OC_6H_5)_2$	—	*(t)*
(q)	H	$PS(C_2H_5)OC_6H_5$	—	*(u)*
(r)	H	$PS(C_2H_5)OC_6H_3CH_3$, Cl-(3,4)	—	*(v)*

[a] Contrary to our earlier belief [19], the compound exists in the open-chain form *(60)*.

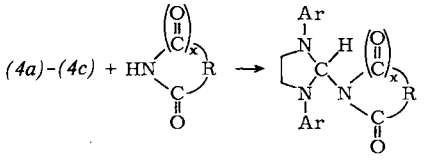
conditions for ring cleavage are satisfied. This behavior may be due to carboxamide resonance.

Carbohydrazides *(58i)* and *(58k)*, sulfonamides *(58l)* to *(58n)*, and phosphoramides or phosphonamides *(58o)* to *(58r)*, on the other hand, react *via (59)* with ring cleavage to give *(60)* (see Table 3).

Whereas the imidazolidine structure *(14)* was isolable in some cases as well as the open structure *(15)* after the reactions of active methyl and methylene compounds with *(4a)* (cf. Table 1), the reaction with compounds containing NH_2 groups leads exclusively to products having the formula *(59)* or *(60)*. The presence of a mixture of isomers has not so far been detected.

3.3. With Lactams and Imides

The tetraaminoethylenes *(4a)* to *(4c)* also react with lactams *(63)* and imides *(64)* with cleavage of the molecule



(4a)-(4c) + HN(C=O)$_x$R(C=O) → N(Ar)C(=NH)N(Ar)C(=O)$_x$R

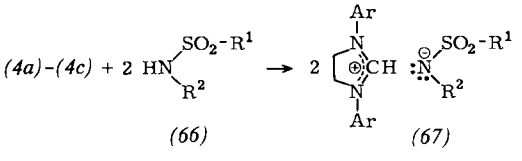
(63) x = 0 *(65)*
(64) x = 1

(4)	*(63)*, *(64)*	*(65)*	R
(a)	*(63a)*	*(a)*	$—(CH_2)_3—$
(a)	*(63b)*	*(b)*	$—(CH_2)_4—$
(a)	*(63c)*	*(c)*	$—(CH_2)_5—$
(a)	*(63d)*	*(d)*	$—(CH_2)_7—$
(a)	*(63e)*	*(e)*	1,8-Naphthalenediyl
(a)	*(63f)*	*(f)*	$—C_6H_4—O$-(*o*)—
(b)	*(63a)*	*(g)*	$—(CH_2)_3—$
(c)	*(63a)*	*(h)*	$—(CH_2)_3—$
(a)	*(64a)*	*(i)*	*o*-Phenylene
(a)	*(64b)*	*(k)*	4-Cyclohexene-1,2-diyl
(a)	*(64c)*	*(l)*	$—CH_2—CH_2—$
(b)	*(64d)*	*(m)*	—CH=CH—

to form "NH insertion products" *(65a)* to *(65m)*. The compounds *(65a)* to *(65m)* are more resistant to hydrolysis than *(59a)* to *(59e)*.

3.4. With Strongly Acidic NH Compounds[66]

If the acidity of the NH compounds is increased by the introduction of two strongly electron-attracting groups, the reaction with *(4)* leads to the imidazolinium salts *(67)* because of the low nucleophilic strength of the amidate anion. Whereas amines activated by two carbonyl groups, such as phthalimide *(64a)*, give "NH insertion products", amines that are activated by one SO_2 group and one CO group, such as *(66a)* to *(66e)* form the salts *(67a)* to *(67f)* with *(4a)* to *(4c)*[*]. Similarly, the extremely acidic amines *(66f)* to *(66h)*, which are activated by two SO_2 groups, and the SO_2-PO activated amines *(66i)* to *(66l)* give the imidazolinium salts *(67g)* to *(67m)* and *(67n)* to *(67p)* respectively. These reactions are acid-base reactions between the strong π bases *(4a)* to *(4c)* and the strong NH acids *(66a)* to *(66l)*.

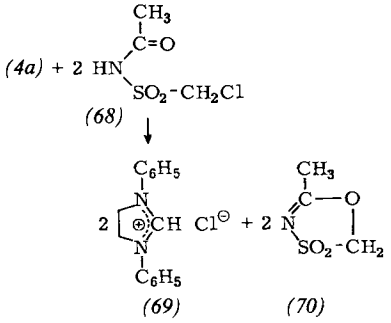


(4a)-(4c) + 2 HN(SO$_2$-R^1)R^2 → 2 [Ar-N-CH-N-Ar]$^{\oplus}$ [N(SO$_2$-R^1)R^2]$^{\ominus}$

(66) *(67)*

(4)	*(66)*	*(67)*	R^1	R^2
(a)	*(a)*	*(a)*	CH_3	$COOC_2H_5$
(a)	*(b)*	*(b)*	C_6H_5	$COOC_2H_5$
(a)	*(c)*	*(c)*	C_6H_5	$COCH_3$
(a)	*(d)*	*(d)*	C_6H_5	COC_6H_5
(a)	*(e)*	*(e)*	—C_6H_4CO-(*o*)—	
(c)	*(e)*	*(f)*	—C_6H_4CO-(*o*)—	
(a)	*(f)*	*(g)*	CH_3	SO_2CH_3
(a)	*(g)*	*(h)*	CH_3	$SO_2C_6H_5$
(a)	*(h)*	*(i)*	$C_6H_4CH_3$-(*p*)	$SO_2C_6H_4CH_3$-(*p*)
(a)	*(i)*	*(k)*	C_6H_4Cl-(*p*)	$SO_2C_6H_4Cl$-(*p*)
(b)	*(h)*	*(l)*	$C_6H_4CH_3$-(*p*)	$SO_2C_6H_4CH_3$-(*p*)
(c)	*(h)*	*(m)*	$C_6H_4CH_3$-(*p*)	$SO_2C_6H_4CH_3$-(*p*)
(a)	*(i)*	*(n)*	C_6H_5	$PO(OC_2H_5)_2$
(a)	*(k)*	*(o)*	$C_6H_4NO_2$-(*m*)	$PO[N(C_2H_5)_2]_2$
(a)	*(l)*	*(p)*	C_6H_5	$PO(NHC_6H_5)_2$

On the other hand, the *N*-acylated chloromethanesulfonamide *(68)* reacts with *(4a)* with elimination of HCl to



(4a) + 2 HN(C(=O)CH$_3$)SO$_2$-CH$_2$Cl → *(68)*

2 [C$_6$H$_5$-N-CH-N-C$_6$H$_5$]$^{\oplus}$ Cl$^{\ominus}$ + 2 N(C(=O)CH$_3$)SO$_2$-CH$_2$

(69) *(70)*

[*] The compounds ethyl 2-diazo-2-[*N*-(1,3-diphenyl-2-imidazolidinyl)-*N*-(*p*-toluenesulfonyl)aminocarbonyl]acetate and 2-diazo-*N*-(1,3-diphenyl-2-imidazolidinyl)-*N*-(*p*-toluenesulfonyl)acetoacetamide, which are described in [19], also occur in the form of the imidazolinium salts, as is shown by the spectroscopic data.

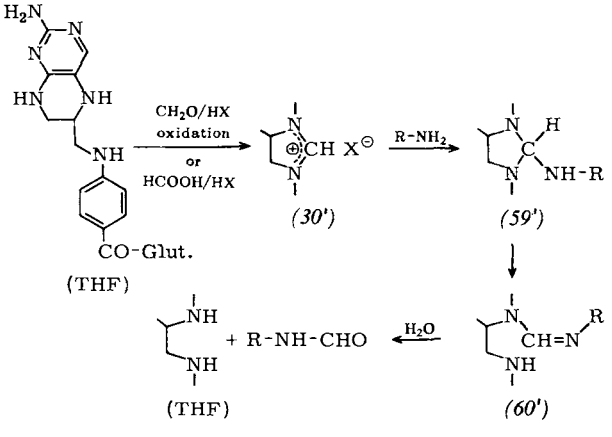
give 5-methyl-1,3,4-oxathiazoline 3,3-dioxide *(70)* together with 1,3-diphenylimidazolinium chloride *(69)* in a yield of more than 90%[31][*].

3.5. Mechanistic Considerations

For the mechanism of the formation of the "NH insertion products" *(59)* and *(60)* cf.[64]. The initial step, *i.e.* the proton transfer from the nitrogen of the amino compound to the nucleophilic double bond of the electron-rich olefin, is followed by cleavage of the molecule into an imidazolinium cation *(30)* and a nucleophilic carbene *(31)*.

In the case of the strongly acidic NH compounds *(66)*, the reaction stops at this stage, and one obtains the imidazolinium amidates *(67)*. In the case of more weakly acidic NH compounds, the mechanism is probably similar to that of the reactions with CH-acidic compounds[**] (cf. Section 2.1).

Tetrahydrofolic acid (THF) is important as a cofactor for the biochemical transfer of formaldehyde and formic acid to amines[80]. Formylation of the THF and cyclization yields an imidazolinium cation *(30')* similar to *(30)*, which then reacts with amines to give formimino-THF with formation of an "NH insertion product" *(59')* and ring cleavage to form *(60')* (in the case of primary amines)[81]. Since the hydrolysis of the aminoamidines *(60)* can be carried out in such a way that the *N*-formyl compound of *(58)* is formed in addition to dianilinoethane[31], the hydrolysis of *(60')* to form THF and the *N*-formyl compound also seems plausible. *(4a)* and the imidazolinium cation *(30)*, which can be easily obtained from it, can thus serve as model substances for the biochemical formaldehyde transfer reaction[81].



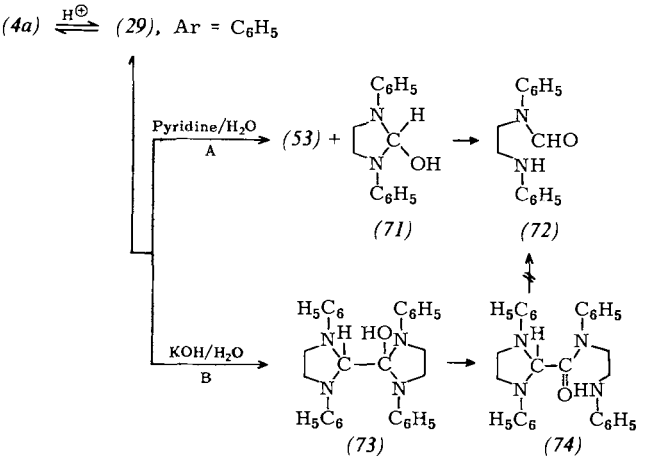
[*] For the preparation of aromatically substituted 1,3,4-oxathiazoline 3,3-dioxides from *N*-acylated chloromethanesulfonamides and bases, cf. [67, 68].

[**] The ability of the azolium and dithiolium salts, when used as such, to react with amines to form "NH insertion products" is shown by the reactions of *N*-methylbenzothiazolium salts with piperidine [13] and diethylamine [14], and of dithiolium salts with piperidine, benzylamine, dibenzylamine, ethylamine, and NH_3 [63, 69] and from the detailed investigations on the reactions of thiamine with bases [70—73], in which an intramolecular "NH insertion product" (free thiamine base) was obtained among other products [74—76]. The reactions of the aminal esters [77] and amide acetals [78, 79] with amines and amides to form amidines probably also proceed *via* a cation similar to the ion *(30)* [38].

4. Reactions with Formation of a New C—O Bond

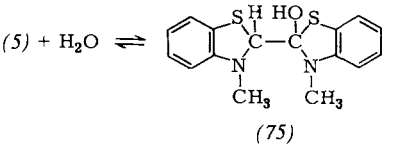
4.1. Hydrolysis of *(4a)* and *(5)*

On hydrolysis of *(4a)*, two different products are formed, depending on the reaction conditions. Hydrolysis in pyridine/water leads with molecular cleavage to *N*-formyl-*N*,*N'*-diphenylethylenediamine *(72)*, whereas hydrolysis with aqueous potassium hydroxide solution leads, with retention of the original C—C bond, to *(74)*[6, 16].



The hydrolysis is probably initiated by the addition of a proton to the nucleophilic double bond of the electron-rich olefin to form *(29)*. At low concentrations of hydroxide ions (path A), *(29)* is split into a carbene *(53)* and an imidazolinium cation *(30)*, Ar=C_6H_5, which adds a hydroxide ion to give *(71)*. Compound *(71)* rearranges with β elimination to form *(72)*. The alkaline hydrolysis of the imidazolinium cation *(30)*, Ar=C_6H_5, is plausible in view of the hydrolysis of azoli(ni)um salts[83].

At high concentrations of hydroxide ions (path B), the cation *(29)* adds a hydroxide ion to form *(73)*, which undergoes ring cleavage to give *(74)*. It has been shown that *(74)* does not change into *(72)* under the reaction conditions[16]. On hydrolysis of *(5)*, the reaction appears to stop at compound *(75)* [addition of water to the double bond][*][13]. Ring cleavage to give a compound corresponding to *(74)* has not been observed.

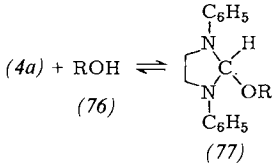


4.2. Reactions with Alcohols

Little is known about the reactions of electron-rich olefins with alcoholic or phenolic OH groups with cleavage of the molecule and formation of a new C—O bond. *(4a)*

[*] Structure *(75)* appears more plausible from a mechanistic viewpoint than a structure suggested in [14, 82].

reacts with the alcohols *(76a)* to *(76d)* in good yields to give the readily hydrolyzed cyclic aminal esters *(77a)* to *(77d)*[84].



(4a) + ROH ⇌ *(76)* → *(77)*

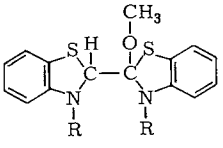
(a), R = CH_3
(b), R = CH_2-C_6H_5
(c), R = $CH(C_6H_5)_2$
(d), R = $CH(CH_2)_5$

The reaction of tetrakis(dimethylamino)ethylene with methanol leads with cleavage of the molecule and replacement of dimethylamino groups by ethoxy groups to dimethoxy(dimethylamino)methane, dimethylamine, and, with retention of the central C—C bond, 1,2-bis(dimethylamino)-1,1,2-trimethoxymethane as the main products[85]. For the reaction of a phenol with formation of an "OH insertion product", cf. Section 2.2.

The mechanism is probably similar to the hydrolysis mechanism by path A, *i.e.* proton transfer from the OH group to the double bond of *(4a)* to give the cation *(29)*, Ar=C_6H_5, which decomposes into the imidazolinium ion *(30)*, Ar=C_6H_5, and a nucleophilic carbene *(53)*. The reaction of *(30)*[*] with alcohol yields *(77)*.

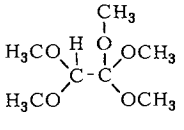
The reaction *(4a)*⇌*(77)* is reversible. *(77a)* loses methanol when heated in xylene, with regeneration of *(4a)*[84].

A reaction by path B is observed for *(5)* and for tetramethoxyethylene. An addition to the double bond leads to the compounds *(78)*[13,90] and *(79)*[91] respectively.



(78)

(a), R = CH_3
(b), R = C_2H_5



(79)

5. Closing Remarks

The reactivity of the electron-rich olefins *(4)* and *(5)* with proton-active compounds can be attributed in the majority of cases to the reactivities of the fragments formed by cleavage of the protonated olefin [*e.g. (29)*], *i.e.* to the azoli(ni)um ion [*e.g. (30)*] and the nucleophilic carbene [*e.g. (31)*]. Since the nucleophilic carbene formed *in situ* can probably dimerize to give the starting olefin or can be protonated by the proton-active compound to form the azoli(ni)um ion, while the azoli(ni)um ion exists in equilibrium with the carbene in the presence of bases [cf. the base-catalyzed H-D exchange of azoli(ni)um salts, which can proceed only *via* a carbene, Section 2.1], it does not seem possible to distinguish the reactions of the azoli(ni)um ion and of the carbene in these cases. The same product is obtained from both[*].

Received: June 7, 1972 [A 913 IE]
German version: Angew. Chem. *84*, 1022 (1972)
Translated by Express Translation Service, London

[*] For the reaction of imidazolium or dithiolium salts with alcohols to form "OH insertion products", cf. [73, 86, 87]. For the reaction of a dithiocarbene formed *in situ* with methanol, cf. [88], and for the reaction of the nucleophilic carbene cycloheptatrienylidene, also formed *in situ*, with ethanol to form an "OH insertion product", cf. [89].

[*] For use of azides in differentiation between the reactions of *(5)* and the carbenes formed *in situ*, cf. [21].

[1] *T. L. Cairns* and *B. C. McKusick*, Angew. Chem. *73*, 520 (1961).
[2] *D. N. Dhar*, Chem. Rev. *67*, 611 (1967).
[3] *N. Wiberg*, Angew. Chem. *80*, 809 (1968); Angew. Chem. internat. Edit. *7*, 766 (1968).
[4] *R. W. Hoffmann*, Angew. Chem. *80*, 823 (1968); Angew. Chem. internat. Edit. *7*, 754 (1968).
[5] *D. M. Lemal* in *S. Patai*: The Chemistry of the Amino Group. Interscience, New York 1968.
[6] *H.-W. Wanzlick*, Angew. Chem. *74*, 129 (1962); Angew. Chem. internat. Edit. *1*, 75 (1962).
[7] Cf. *R. Gompper* and *B. Wetzel*, Tetrahedron Lett. *1971*, 529.
[8] Review of tetrathioethylenes: *D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett*, and *N. D. Canfield*, J. Amer. Chem. Soc. *93*, 2258 (1971).
[9] *H.-W. Wanzlick* and *E. Schikora*, Chem. Ber. *94*, 2389 (1961).
[10] *H.-W. Wanzlick* and *E. Schikora*, Angew. Chem. *72*, 494 (1960).
[11] *D. M. Lemal, R. A. Lovald*, and *K. I. Kawano*, J. Amer. Chem. Soc. *86*, 2518 (1964).
[12] *H. E. Winberg, J. E. Carnahan, D. D. Coffman*, and *M. Brown*, J. Amer. Chem. Soc. *87*, 2055 (1965).
[13] *J. Metzger, H. Larivé, R. Dennilauler, R. Baralle*, and *C. Gaurat*, Bull. Soc. Chim. France *1964*, 2857.
[14] *J. J. Vorsanger*, Bull. Soc. Chim. France *1964*, 119.
[15] *A. Piskala*, Tetrahedron Lett. *1964*, 2587.
[16] *H.-W. Wanzlick, B. Lachmann*, and *E. Schikora*, Chem. Ber. *98*, 3170 (1965).
[17] *H.-W. Wanzlick* and *B. König*, Chem. Ber. *97*, 3513 (1964).
[18] *H. Reimlinger*, Chem. Ber. *97*, 3503 (1964).
[19] *J. Hocker* and *M. Regitz*, Chem. Ber. *103*, 1486 (1970).
[20] *M. Regitz, A. Liedhegener*, and *D. Stadler*, Liebigs Ann. Chem. *713*, 101 (1968).
[21] *H. Quast* and *S. Hünig*, Chem. Ber. *99*, 2017 (1966).
[22] *M. Regitz, J. Hocker, W. Schössler, B. Weber*, and *A. Liedhegener*, Liebigs Ann. Chem. *748*, 1 (1971).
[23] *H. E. Winberg* and *D. D. Coffman*, J. Amer. Chem. Soc. *87*, 2776 (1965).
[23a] *H.-J. Schönherr* and *H.-W. Wanzlick*, Liebigs Ann. Chem. *731*, 176 (1970).
[24] *M. Regitz* and *J. Hocker*, Synthesis *1970*, 301.
[25] Cf. also *J. Hocker* and *R. Merten*, Liebigs Ann. Chem. *751*, 145 (1971).
[26] *R. Richter* and *H. Ulrich*, J. Org. Chem. *36*, 2005 (1971).
[27] *M. Regitz, J. Hocker*, and *B. Weber*, Angew. Chem. *82*, 394 (1970) Angew. Chem. internat. Edit. *9*, 375 (1970).
[28] *J. Hocker*, Dissertation, Universität Saarbrücken 1969.
[29] *H.-W. Wanzlick* and *H.-J. Kleiner*, Chem. Ber. *96*, 3024 (1963).
[30] *H.-W. Wanzlick* and *H. Ahrens*, Chem. Ber. *97*, 2447 (1964).
[31] *J. Hocker*, unpublished.
[32] *H.-W. Wanzlick* and *H. Ahrens*, Chem. Ber. *99*, 1580 (1966).
[33] *E. Buchner*, Ber. Dtsch. Chem. Ges. *28*, 215 (1895).
[34] *A. Ledwith* and *E. C. Friedrich*, J. Chem. Soc. *1964*, 504.
[35] *P. Yates* and *F. Garneau*, Tetrahedron Lett. *1967*, 71.
[35a] *O. Tsuge, K. Yanagi*, and *M. Horie*, Bull. Chem. Soc. Jap. *44*, 2171 (1971).
[36] *J. Gehlhaus*, Diplomarbeit, Universität Heidelberg 1967, cited in [4].

[37] *H. Bredereck, W. Kantlehner*, and *D. Schweizer*, Chem. Ber. *104*, 3475 (1971).

[38] *J. M. Brown* and *B. D. Place*, Chem. Commun. *1971*, 533.

[39] Cf. also *G. Simchen, S. Rebsdat*, and *W. Kantlehner*, Angew. Chem. *79*, 869 (1967); Angew. Chem. internat. Edit. *6*, 875 (1967); *G. Simchen* and *W. Kantlehner*, Tetrahedron *28*, 3535 (1972).

[40] *P. Haake, L. P. Bausher*, and *W. B. Miller*, J. Amer. Chem. Soc. *91*, 1113 (1969).

[41] *H.-J. Schönherr* and *H.-W. Wanzlick*, Chem. Ber. *103*, 1037 (1970).

[42] *R. Breslow*, J. Amer. Chem. Soc. *79*, 1762 (1957).

[43] *R. A. Coburn, J. M. Landesberg, D. S. Kemp*, and *R. A. Olofson*, Tetrahedron *26*, 685 (1970), and previous papers.

[44] *S. Takahashi* and *H. Kano*, Tetrahedron Lett. *1965*, 3789.

[45] *D. S. Kemp* and *J. T. O'Brien*, J. Amer. Chem. Soc. *92*, 2554 (1970).

[46] *A. C. Rochat* and *R. A. Olofson*, Tetrahedron Lett. *1969*, 3377.

[47] *T. Eicher, S. Hünig*, and *P. Nikolaus*, Chem. Ber. *102*, 3176 (1969); cf. also [48].

[48] *H. A. Staab, M.-Th. Wu, A. Mannchreck*, and *G. Schwalbach*, Tetrahedron Lett. *1964*, 845.

[49] *W. Hafferl, R. Lundin*, and *L. L. Ingraham*, Biochemistry *2*, 1298 (1963).

[50] *H. D. Hartzler*, J. Amer. Chem. Soc. *92*, 1413 (1970).

[51] *H. C. Sorensen* and *L. L. Ingraham*, J. Heterocycl. Chem. *1971*, 551.

[52] *K. M. Pazdro* and *W. Polaczkowa*, Roczniki Chem. [Ann. Soc. Chim. Polonorum] *45*, 1487 (1971).

[53] *B. Lachmann, H. Steinmaus*, and *H.-W. Wanzlick*, Tetrahedron *27*, 4085 (1971).

[54] *A. Lapworth*, J. Chem. Soc. *83*, 995 (1903); *85*, 1206 (1904).

[55] *R. Breslow*, J. Amer. Chem. Soc. *80*, 3719 (1958).

[56] *A. Schellenberger*, Angew. Chem. *79*, 1050 (1967); Angew. Chem. internat. Edit. *6*, 1024 (1967); *A. Takamizawa, K. Hirai, Y. Hamashima*, and *S. Matsumoto*, Tetrahedron Lett. *1967*, 5071.

[57] *C. S. Miller, J. M. Spraque*, and *I. P. Krampitz*, Ann. N. Y. Acad. Sci. *98*, 401 (1962).

[58] *A. Takamizawa, S. Matsumoto*, and *S. Sakai*, Chem. Pharm. Bull. [Tokyo] *17*, 343 (1969).

[59] *G. Kohlhaw, B. Deus*, and *H. Holzer*, J. Biol. Chem. *240*, 2135 (1965).

[60] *L. O. Krampiz, G. Greull, C. S. Miller, J. B. Bicking, H. R. Skeggs*, and *J. M. Sprague*, J. Amer. Chem. Soc. *80*, 5893 (1958).

[61] *A. Takamizawa, S. Matsumoto*, and *S. Sakai*, Chem. Pharm. Bull. [Tokyo] *17*, 128 (1969).

[62] *A. Takamizawa, S. Matsumoto*, and *S. Sakai*, Tetrahedron Lett. *1968*, 2189; *J. C. Sheehan* and *D. H. Hunneman*, J. Amer. Chem. Soc. *88*, 3667 (1966); *T. C. Bruice* and *N. G. Kundu*, J. Amer. Chem. Soc. *88*, 4097 (1966); *J. D. Vaugham, Z. Mughrabi*, and *E. Chung Wu*, J. Org. Chem. *35*, 1141 (1970).

[63] *K. M. Pazdro* and *W. Polaczkowa*, Roczniki Chem. [Ann. Soc. Chim. Polonorum] *45*, 811 (1971).

[64] *J. Hocker* and *R. Merten*, Chem. Ber. *105*, 1651 (1972).

[65] *J. Bourson*, Bull. Soc. Chim. France *1971*, 3541.

[66] *J. Hocker* and *R. Merten*, Synthesis (1972), in press.

[67] *K. Dickoré, R. Wegler*, and *K. Sasse*, Angew. Chem. *74*, 874 (1962); Angew. Chem. internat. Edit. *1*, 594 (1962).

[68] *K. Dickoré*, Liebigs Ann. Chem. *671*, 135 (1964).

[69] *K. M. Pazdro* and *W. Polaczkowa*, Roczniki Chem. [Ann. Soc. Chim. Polonorum] *44*, 1823 (1970).

[70] *A. Takamizawa, K. Hirai*, and *Y. Hamashima*, Tetrahedron Lett. *1967*, 5077.

[71] *A. Takamizawa* and *Y. Hamashima*, DOS 1695695, Shionogi, Osaka (Japan).

[72] *A. Takamizawa, K. Hirai*, and *T. Ishiba*, Chem. Pharm. Bull. [Tokyo] *19*, 2222 (1971).

[73] *A. Takamizawa* and *K. Hirai*, Chem. Pharm. Bull. [Tokyo] *17*, 1931 (1969).

[74] *A. Takamizawa, K. Hirai*, and *Y. Hamashima*, Vitamin [Kyoto] *34*, 280 (1966).

[75] *A. Takamizawa, K. Hirai, T. Ishiba*, and *I. Makino*, Chem. Pharm. Bull. [Tokyo] *19*, 759 (1971).

[76] *A. Takamizawa*, DOS 1695721, Shionogi, Osaka (Japan).

[77] *H. Bredereck, G. Simchen*, and *B. Funke*, Chem. Ber. *104*, 2709 (1971).

[78] *H. Weidinger* and *H. Eilingsfeld*, Belg. Pat. 629972 (1963), Badische Anilin- u. Soda-Fabrik; Chem. Abstr. *61*, 1803c (1964).

[79] *H. E. Winberg*, US-Pat. 3121084 (1964), E. J. du Pont de Nemours & Co.; Chem. Abstr. *60*, 13197d (1964).

[80] *L. Jaenicke*, Angew. Chem. *73*, 449 (1961).

[81] *L. Jaenicke* and *E. Brode*, Liebigs Ann. Chem. *624*, 120 (1959).

[82] *H. Wahl* and *J.-J. Vorsanger*, Bull. Soc. Chim. France *1965*, 3359.

[83] *W. H. Mills, L. M. Clark*, and *J. A. Aeschlimann*, J. Chem. Soc. *123*, 2353 (1923).

[84] *B. Lachmann* and *H.-W. Wanzlick*, Liebigs Ann. Chem. *729*, 27 (1969).

[85] *W. P. Norris*, Tetrahedron *28*, 1965 (1972).

[86] *G. Scherowsky*, Liebigs Ann. Chem. *739*, 45 (1970).

[87] *K. M. Pazdro* and *W. Polaczkowa*, Roczniki Chem. [Ann. Soc. Chim. Polonorum] *45*, 1249 (1971).

[88] *H. D. Hartzler*, J. Amer. Chem. Soc. *92*, 1412 (1970).

[89] *T. Mukai, T. Nakazawa*, and *K. Isobe*, Tetrahedron Lett. *1968*, 565.

[90] *H.-W. Wanzlick, H.-J. Kleiner, I. Lasch, H. U. Füldner*, and *H. Steinmaus*, Liebigs Ann. Chem. *708*, 155 (1967).

[91] *R. W. Hoffmann, J. Schneider*, and *H. Häuser*, Chem. Ber. *99*, 1892 (1966); *J. Schneider*, Dissertation, Universität Heidelberg 1966.

Aromatic Keto Compounds as Initiators in Photopolymerizations

By H.-G. Heine, H.-J. Rosenkranz, and H. Rudolph[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

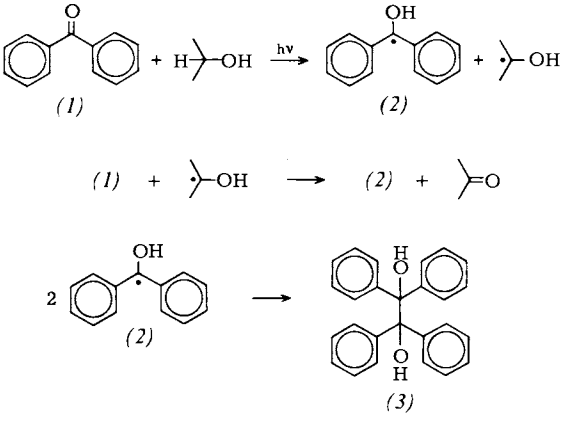
The present article deals with the primary photochemical reactions of carbonyl compounds commonly used as photoinitiators. It is shown that radical formation results mainly from three processes, *i.e.* hydrogen abstraction, β-cleavage, and α-cleavage. The difference in the suitability of the radicals for chain initiation is discussed.

Introduction

Photopolymerizations are initiated by radical formation through the action of light on light-sensitive compounds (photoinitiators) added to the vinyl monomers. Compounds of many classes can be used for this initiation[1]; the most important of these are carbonyl compounds with UV absorptions in the range between 300 and 400 nm. The known compounds of this type that are suitable for practical use and the reactions of these compounds that lead to the initiation of a polymerization chain form the subject of the present article.

1. Chain Initiation by Hydrogen Abstraction

The photoreduction of benzophenone *(1)* to benzopinacol *(3)* is probably one of the best-known light-induced reactions. There have been numerous attempts to make use

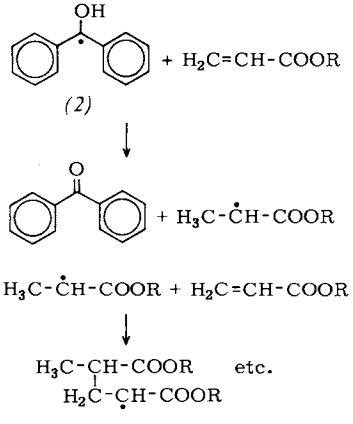


of the ability of benzophenone to form free radicals by hydrogen abstraction in the excited triplet state for the initiation of vinyl polymerizations[2]. However, these attempts have led to conflicting results. Thus in the common acrylic or methacrylic esters, such as methyl, ethyl, or *n*-butyl acrylate or methacrylate, benzophenone has only a very weak initiator action, if any. On the other hand, if benzophenone is exposed to light in a mixture of these esters with a solvent containing ether groups (diethyl ether, tetrahydrofuran, polyethylene glycol, or methyl glycol acetate), polymerization begins after a very short time[3]. Benzophenone has an equally good initiator action even without solvents in esters of acrylic acid with an alcohol containing ether groups, such as diethylene glycol diacrylate. Very slow polymerization is observed, on the other hand, when benzophenone and alkyl acrylates are exposed to light in isopropanol.

This observation is surprising at first, since kinetic measurements indicate that hydrogen abstraction occurs at almost equal rates on exposure of benzophenone to light in ethers and in isopropanol[4], and the quantum yield of the photoreduction in isopropanol is almost 1. According to investigations by *Elad*[5], however, the free radicals formed from ethers have a strong tendency to add to double bonds. Though a corresponding addition of semipinacol radicals has occasionally also been observed[6], ether radicals add preferentially when present together with semipinacol radicals[7].

The difference in the initiator action of benzophenone in the presence of isopropanol and ethers corresponds to the variation in the ease of addition of the free radicals formed by hydrogen abstraction from the solvent. The role of the semibenzopinacol radicals *(2)* invariably formed in photoinitiation with benzophenone, which, according to *Braun*[8], also initiate polymerizations by hydrogen transfer, appears to be of minor importance according to these findings.

As mentioned previously, the initiation of polymerization by hydrogen abstraction is effected by triplet-excited



[*] Dr. H.-G. Heine, Dr. H.-J. Rosenkranz, and Dr. H. Rudolph
Wissenschaftliches Hauptlaboratorium der Bayer AG
415 Krefeld-Uerdingen (Germany)

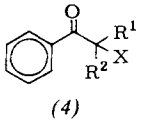
benzophenone ($E_T = 68.5$ kcal/mol[9]). It is therefore not surprising that benzophenone is practically inactive in polymerizable mixtures containing styrene ($E_T = 61$ kcal/mol[10]), *e.g.* in solutions of unsaturated polyesters in styrene[11], even if the unsaturated polyester contains groups suitable for hydrogen abstraction, *e.g.* by incorporation of oxaalkyldiols. In this case, exposure to light results in quenching of the triplet-excited benzophenone by styrene without any chemical reaction.

In some cases, however, an energy transfer of this type is the basis of the initiation of a polymerization chain, as in the benzophenone-sensitized system maleic anhydride/cyclohexene[12]. This initiation mechanism is of no practical importance, since it leads only to oligomeric products.

Many other, mainly aromatic carbonyl compounds and α-diketones behave photochemically in the same way as benzophenone[13], and are fundamentally capable of initiating polymerizations by hydrogen abstraction[14]. However, these compounds are less important, either because of a less favorable UV absorption or because of a lower quantum yield in the primary step. Only a few quinones, *e.g.* anthraquinone derivatives, exhibit good initiator activity[15]. These compounds have a long-wave absorption, which allows excitation even with daylight. They are used as initiators in copying systems involving crosslinking by photopolymerization (dry-resist foils for the production of printed circuits).

2. Chain Initiation by β-Cleavage

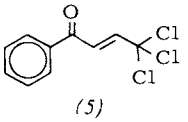
Another type of initiation is exhibited by aromatic α-haloketones *(4)* which are frequently mentioned in the literature[16] as photoinitiators. In addition to phenacyl chloride and bromide, which are possibly the best-known representatives, this group of compounds includes desyl chloride and practically all phenyl ketones with one or more halogen atoms in the α-position.



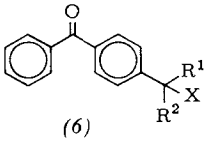
(4)

X = Cl, Br
$R^1 = R^2$ = Cl, Br, H, Alkyl, Phenyl
$R^1 \neq R^2$ = Cl, Br, H, Alkyl, Phenyl

It is not surprising that ω-trichlorocrotonophenone *(5)*[17] and halogenated *p*-alkylbenzophenones *(6)*[18] are also good photoinitiators. These vinylogous and phenylogous α-haloketones react in the same way as the compounds of type *(4)* on exposure to light, with homolysis of a



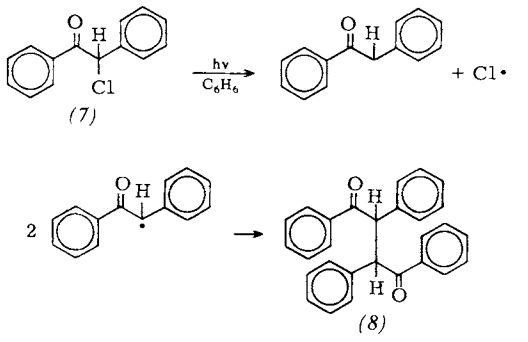
(5)



(6)

X = Cl, Br
$R^1 = R^2$ = Cl, Br, H, Alkyl
$R^1 \neq R^2$ = Cl, Br, H, Alkyl

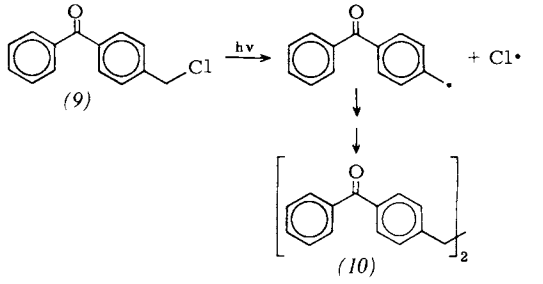
C—halogen bond. This cleavage has been described in the literature for the formation of bidesyl *(8)* by photolysis of desyl chloride *(7)*[19].



(7)

(8)

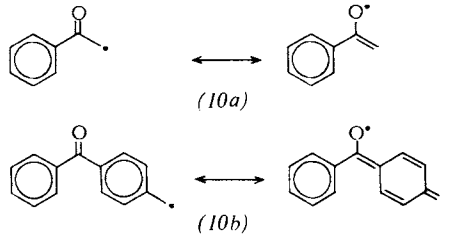
We have investigated photoinitiation by *p*-halomethylbenzophenones. After exposure of *p*-chloromethylbenzophenone *(9)* to light in benzene, we were able to isolate the dimer *(10)* as a secondary product of the phenylogous β-cleavage[20].



(9)

(10)

The photolysis of this group of initiators evidently yields two radicals of differing reactivity, *i.e.* halogen and phenacyl radicals or their vinylogs and phenylogs. The pronounced tendency of halogen radicals to add to double bonds and thus to initiate polymerization processes is well known[21], and there can be little doubt that chlorine or bromine radicals liberated when these initiators are exposed to light are of primary importance in chain initiation. The resonance stabilization of the phenacyl radical *(10a)* and to an even greater extent of the *p*-benzoylbenzyl radical *(10b)* probably explains a reduced tendency for these radicals to add to unsaturated systems.



(10a)

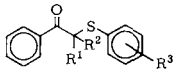
(10b)

The chloromethylated benzophenones, as very effective initiators, are used in the photopolymerization of acrylic acid derivatives. Moreover, bromomethylated benzophenones are suitable for the light-induced curing of unsaturated polyester resin-styrene mixtures. The cleavage

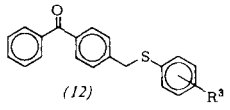
into radicals is evidently faster in this case than the quenching of the excited benzophenone chromophore by styrene[18].

As well as the haloketones, the ketosulfides *(11)* and *(12)*, which are obtainable by reaction of these compounds with thiophenols, can also be used as photoinitiators[22] (Table 1). They react in the same way as the

Table 1. Reactivity of the keto sulfides *(11)* and *(12)* in the light-induced curing of unsaturated polyesters [*].



(11)



(12)

	R^1	R^2	R^3	Bleeding time of paraffin (min)	Hardness (min)
(11)	H	H	H	1.3	16
	CH_3	H	H	1.0	11
	CH_3	CH_3	H	1.2	16
	C_6H_5	H	H	0.9	12
	C_6H_5	CH_3	H	2.3	14
	CH_3	CH_3	*p*-Cl	0.9	8—9
	CH_3	CH_3	Cl_5	1.4	16
(12)			H	1.2	12
			Cl_5	0.9	13

[*] The polymerization experiments were carried out with a solution of an unsaturated polyester (Roskydal W 13, Farbenfabriken Bayer, solids content 54 wt. % in styrene) containing 0.1 wt. % of paraffin (m.p. 52—53°C) in the form of a 10% (w/w) solution in toluene. 2 wt. % of photoinitiator was added to this mixture. Coated films 500 µm thick were exposed to a fluorescent tube (Osram L 40 W/70-1) at a distance of 5 cm, and the time taken for the paraffin to bleed out was determined. The exposure time required for complete hardening was taken as the time when the coating could no longer be marked with a rounded pencil lead of hardness 6 H.

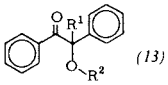
haloketones on exposure to light, with β-cleavage, which is not suppressed by triplet quenchers such as 1,3-cyclohexadiene or piperylene. The thiyl radicals formed are probably mainly responsible for the initiation of polymerization; addition reactions of thiyl radicals to double bonds are generally known, and are used in preparative chemistry[23]. The equally well-known reversibility of these reactions, which partly forms the basis of the action of thiols as regulators in thermal polymerization processes, is probably the reason for the unsatisfactory quality of some polymers prepared with photoinitiators listed in Table 1.

3. Initiation of Polymerization by α-Cleavage

Benzoin and its derivatives are extremely important as photoinitiators. They are currently used in unsaturated polyester resin varnishes, in compositions for the production of acrylate-based printing plates, and in printing inks that are dried by UV light. Benzoin was first claimed for light-induced polymerization in 1945[24], but it was more than ten years before a polymerization process initiated by benzoin ethers was used in practice[25]. This was the process introduced by DuPont under the name Dycryl for the production of plastic printing plates for relief printing and dry offset.

A further ten years passed before the light-induced copolymerization of unsaturated polyesters with styrene in the presence of benzoin ethers as initiators was developed into an industrially used vanishing and coating process[26]. As the importance of this process grew, a more thorough knowledge of the classes of substances that could be used became desirable. We have therefore synthesized a large number of benzoin derivatives *(13)*, a selection of which is shown in Table 2[27].

Table 2. Reactivity of some benzoin derivatives *(13)* in the light-induced curing of unsaturated polyester resins.



(13)

R^1	R^2	Paraffin bleeding time [a] (min)	Hardness [a] (min)
H	H	2.5	13.5
CH_3	H	1.5	13
CH_2—CH=CH_2	H	1.2	14
C_6H_5	H	1.7	12
CH_2OH	H	0.8	6
H	CH_3	0.6	5
H	C_2H_5	0.6	5.5
H	*i*-C_3H_7	0.5	4.5
H	C_6H_5	1.5	10.5
H	$Si(CH_3)_3$	1.2	6.5
CH_3	CH_3	0.7	6
C_6H_5	CH_3	1.1	9
CH_2OH	*i*-C_3H_7	0.7	6
$CH_2CH_2COOC_2H_5$	C_2H_5	0.5	5
CH_2—CH=CH_2	CH_3	0.5	4.5
CH_2—O—Tos	H	2.3	14
CH_2OCOCH_3	H	2.1	13
H	$COCH_3$	>15	
CH_2—$OCOCH_3$	*i*-C_3H_7	0.9	13

[a] See footnote [*] to Table 1.

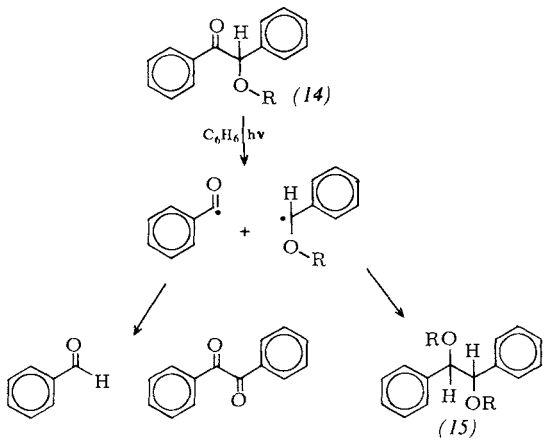
It can be seen that benzoin alkyl ethers and α-alkylated benzoins are particularly reactive. Benzoin itself has only a relatively low reactivity in the system investigated. Among the initiators listed, however, only those that exhibit high reactivity without impairing the storage life of the resin are suitable for practical use. This condition is satisfactorily fulfilled only by benzoin ethers of secondary alcohols and by the α-substituted benzoin and their ethers. Some of these compounds were used for investigations on the photochemical behavior of this class of substances as well as on the initiation process.

The photochemical decomposition of benzoin has been known for a long time[28]. The cleavage into benzoyl and hydroxybenzyl radicals[30] as postulated by *De Mayo*[29] seems plausible also in the light of studies on deoxybenzoins[31].

It seemed obvious that α-cleavage must also be the primary photochemical process in photopolymerizations initiated by benzoin alkyl ethers. When benzoin ethers *(14)* are exposed to light, benzaldehyde and benzil can in fact be isolated as reaction products of the benzoyl radical, and the dimerization product *(15)* as a reaction product of the alkoxybenzyl radical[32].

In the presence of oxygen, the initially formed radicals are completely captured with formation of benzoic acid

and esters of benzoic acid, respectively. As is shown by quenching experiments with naphthalene or piperylene, α-cleavage of the benzoin ethers cannot be quenched in



benzene. Even with piperylene as the solvent, no inhibition is observed. α-Cleavage is evidently faster than the transfer of energy to the triplet quenchers piperylene ($E_T = 59$ kcal/mol)[33] and naphthalene ($E_T = 61$ kcal/mol)[9], the rate of which is practically diffusion-controlled (5×10^9 liter/mol·s in benzene). α-Cleavage thus competes with intersystem crossing, whose rate for acetophenone has been estimated to be $10^{10} s^{-1}$[34], and therefore probably takes place from an excited singlet state. The solvent dependence of the long-wave UV maximum ($\lambda_{max} = 330$ nm in ethanol; 345 nm in cyclohexane) indicates that this is an (n→π*) state.

This could be one of the reasons for the difference in the reactivities of the benzoin derivatives listed in Table 2, since, as was mentioned earlier, styrene like piperylene has a strong quenching action on (n→π*) triplet excited phenyl ketones[9]. The photoreactions of some of the benzoin derivatives that are not very effective as photoinitiators in this system take place preferentially from an excited triplet state. For example, the photolysis of benzoin acetate in benzene is suppressed by piperylene (1 M)[35]. Quenching experiments also indicate that benzoin, which is relatively inactive in unsaturated polyester/styrene mixtures, undergoes the α-cleavage mainly from a triplet state. α-Alkylated benzoins and in particular their ethers, which have a very good initiator action (Table 2), again react preferentially from the excited singlet state[32], which suggests that the rate of formation of free radicals is increased for these compounds by the higher degree of substitution on the α-C atom. They also have a more favorable UV spectrum than benzoin for excitation with conventional UV lamps (Fig. 1).

The difference in the behavior of the benzoin derivatives listed in Table 2, and particularly the pronounced differences between benzoin alkyl ethers and benzoin esters, could be explained by the stabilizing effect of the α-hetero atom on the radicals being formed. However, kinetic studies on the photochemical α-cleavage of some phenyl ketones show that the transition state of the free-radical formation lies on the reaction coordinate at a very early stage[36]; at this stage, the free-radical character is not yet very highly developed, and radical-stabilizing substituents could thus have little effect on the rate of α-cleavage. An explanation that seems much more plausible is one involving polar effects, such as have recently been discussed by *Rüchardt* for thermal free-radical reactions[37].

Whereas it was possible to establish the facts presented above by kinetic and analytical studies, it is relatively difficult to determine the subsequent steps of the photoinitiation of free-radical polymerizations by benzoin derivatives.

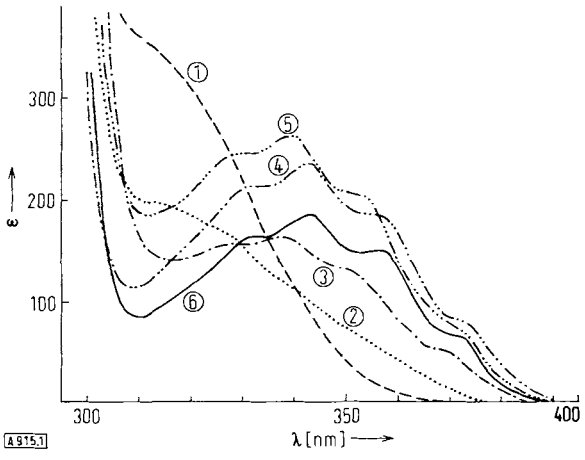


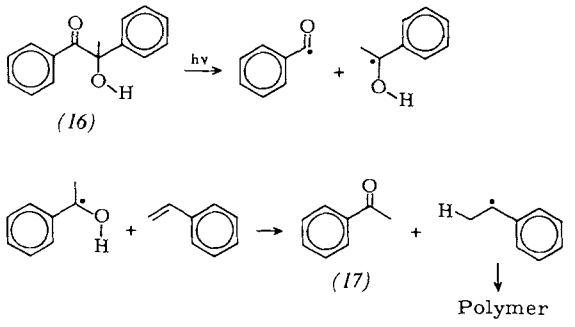
Fig. 1. UV spectra of some benzoin derivatives in benzene. 1, Benzoin 2, α-methylbenzoin; 3, α-hydroxymethylbenzoin; 4, benzoin isopropyl ether; 5, benzoin phenyl ether; 6, α-methylbenzoin methyl ether.

The addition of acyl radicals generated thermally or by irradiation to unsaturated compounds has been described in numerous reports[38]; that of benzoyl radicals to maleic esters was also observed by *Patrick*[39]. The corresponding reaction of acyl radicals with styrene is described as exothermic[40]. Chain initiation by the benzoyl radical formed on photolysis of the benzoin derivatives is therefore quite conceivable.

On the other hand, the behavior of the second fragment, *i.e.* the substituted benzyl radical, is less uniform in the presence of unsaturated compounds. Our experiments have shown that benzyl ether radicals from the photolysis of benzoin alkyl ethers dimerize even in the presence of piperylene and styrene, while the formation of benzaldehyde and benzil from the benzoyl radicals is suppressed in the presence of small quantities of these unsaturated compounds by addition to the double bonds[32]. These observations indicate that α-alkoxybenzyl radicals have less tendency to add to unsaturated compounds.

Another possible mode of reaction of the substituted benzyl radicals is the fragmentation postulated by *Braun* for semibenzopinacol radicals *(2)*[8]. The secondary radical similarly formed from semibenzopinacol ether radicals is thought to be responsible for the actual chain initiation in various thermally initiated free-radical polymerizations[41]. A mode of reaction that agrees with this mechanism has been observed in photopolymerizations initiated by benzoin derivatives only for benzoin and its α-substituted derivatives. Thus α-methylbenzoin *(16)* gives the

expected carbonyl compound acetophenone *(17)* on exposure to light in styrene.



The most effective benzoin-based photoinitiators, *i.e.* the benzoin alkyl ethers and the α-alkylbenzoin ethers, evidently do not undergo fragmentations of this type in the presence of unsaturated compounds. Thus the expected carbonyl compounds were not detected when benzoin isopropyl ether or α-methylbenzoin methyl ether was exposed to light[42].

However, since only very low concentrations are used in photoinitiation with these compounds (1 to 2% based on the unsaturated polyester) and the mobility of the free radicals formed is very quickly restricted by the rapid gelling of the system, it may be assumed that the dimerization observed on exposure to light in solution does not take place during the photoinitiation of unsaturated polyesters. It is more likely that the benzyl ether radicals ultimately also add to double bonds in the same way as thermally produced alkoxybenzyl radicals add to maleic anhydride[43], and thus initiate polymerization chains, or that they react with growing free-radical chains to cause chain termination. This is probably the explanation of *Mochel*'s report[44] of the incorporation of radioactivity into the polymethyl methacrylate obtained by photoinitiation with [methyl-^{14}C]-benzoin methyl ether.

In our view, the difference in the reactivities of the benzoyl and substituted benzyl radicals is essential to the suitability of many benzoin derivatives for photoinitiation. Only in this way, apparently, is it certain (and this also applies to the other types of initiators mentioned here) that a chain growth initiated by an initiator radical is not prematurely terminated by combination with another chain initiated at the same time in its immediate vicinity or with a reactive second radical.

Received: July 3, 1972 [A 915 IE]
German version: Angew. Chem. *84*, 1032 (1972)
Translated by Express Translation Service, London

[1] For a review, see: *J. Kosar:* Light-Sensitive Systems. Wiley, New York 1965.

[2] *G. Delzenne*, Ind. Chim. Belge *24*, 739 (1959); *G. Oster* and *N.-L. Yang*, Chem. Rev. *68*, 125 (1968); *R. M. Leekley* and *R. L. Sorensen*, DAS 954 127 (Dec. 13, 1956), Time Inc.

[3] *H.-J. Rosenkranz*, unpublished results.

[4] *A. Beckett* and *G. Porter*, Trans. Faraday Soc. *59*, 2038 (1963); *S. G. Cohen* and *S. Aktipis*, J. Amer. Chem. Soc. *88*, 3587 (1966).

[5] *D. Elad*, Fortschr. Chem. Forsch. 7, 528 (1966).

[6] *G. O. Schenck, G. Matthias, M. Pape, M. Cziesla*, and *G. v. Bünau*, Liebigs Ann. Chem. *719*, 80 (1968).

[7] See [5], pp. 544ff.

[8] *D. Braun* and *K. H. Becker*, Makromolekulare Chem. *147*, 91 (1971).

[9] *W. G. Herkstroeter, A. A. Lamola*, and *G. S. Hammond*, J. Amer. Chem. Soc. *86*, 4537 (1964).

[10] *D. F. Evans*, J. Chem. Soc. *1957*, 1351.

[11] A review of the chemistry of unsaturated polyesters is to be found in the monograph "Polyesters and their Applications" of Bjorksten Research Laboratories (Reichhold, New York 1956).

[12] *W. Hartmann*, Dissertation, Universität Göttingen 1965.

[13] *D. L. Bumbury* and *C. T. Wang*, Can. J. Chem. *46*, 1473 (1968); *F. D. Lewis*, Tetrahedron Lett. *1970*, 1373.

[14] *B. W. Howk* and *R. A. Jacobson*, US-Pat. 2413973 (Jan. 7, 1947), DuPont; see also [1].

[15] *N. T. Notley*, US-Pat. 2951758 (Sept. 6, 1960), DuPont; *A. L. Barney, V. A. Engelhardt*, and *L. Plambeck, Jr.*, US-Pat. 3046127 (July 24, 1962), DuPont.

[16] *C. M. McClosky* and *J. Bond*, Ind. Eng. Chem. *47*, 2125 (1955); *C. C. Sachs* and *J. Bond*, US-Pat. 2548685 (Dec. 21, 46) and 2641576 (Nov. 6, 1948), A. H. Kerr and Comp., Inc.

[17] DOS 1922627 (Farbenfabriken Bayer AG).

[18] DOS 1949010 (Farbenfabriken Bayer AG).

[19] *J. C. Sheehan* and *R. M. Wilson*, J. Amer. Chem. Soc. *86*, 5277 (1964).

[20] *H.-M. Fischler* and *H.-G. Heine*, unpublished results.

[21] *C. Walling:* Free Radicals in Solution. Wiley, New York 1957, p. 239.

[22] *C. C. Petropoulos*, J. Polymer. Sci. *A2*, 69 (1964); DOS 1769168 (Farbenfabriken Bayer AG).

[23] *K. Griesbaum*, Angew. Chem. *82*, 276 (1970); Angew. Chem. internat. Edit. *9*, 273 (1970).

[24] *C. L. Agre*, US-Pat. 2367661 (Dec. 31, 1941), DuPont; *R. E. Christ*, US-Pat. 2367670 (Jan. 23, 1945), DuPont.

[25] *L. Plambeck*, US-Pat. 2760863 (Dec. 19, 1952), DuPont; *F. Roblin*, Grafic Arts Progress *1960*, 53.

[26] *K. Fuhr, H. Rudolph, H. Schnell*, and *M. Patheiger*, DAS 1694149 (May 6, 1967), Farbenfabriken Bayer AG.

[27] DOS 1769576, DOS 1769853, DOS 1769854, DOS 1807301, DOS 1807297, DOS 1902051, DOS 1919678, DOS 2022507 (Farbenfabriken Bayer AG); *H.-G. Heine*, Liebigs Ann. Chem. *735*, 56 (1970); *H.-G. Heine* and *H. Rudolph, ibid. 754*, 28 (1971).

[28] *G. Ciamician* and *P. Silber*, Ber. Dtsch. Chem. Ges. *34*, 1530 (1901).

[29] *G. Kornis* and *P. DeMayo*, Can. J. Chem. *42*, 2822 (1964).

[30] *E. J. Baum, L. D. Hess, J. R. Wyat*, and *J. N. Pitts, Jr.*, J. Amer. Chem. Soc. *91*, 2461 (1969); *A. M. Trozzolo, ibid. 92*, 1772 (1970).

[31] *J. Kenyon, A. R. A. A. Rassoul*, and *G. Soliman*, J. Chem. Soc. *1956*, 1774.

[32] *H.-G. Heine*, Tetrahedron Lett., in press.

[33] *R. E. Kellogg* and *W. T. Simpson*, J. Amer. Chem. Soc. *87*, 4230 (1965).

[34] *D. R. Kearns* and *W. A. Case*, J. Amer. Chem. Soc. *88*, 5087 (1966).

[35] *J. C. Sheehan, R. M. Wilson*, and *A. W. Oxford*, J. Amer. Chem. Soc. *93*, 7222 (1971).

[36] *H.-G. Heine*, Tetrahedron Lett. *1972*, 3411.

[37] *C. Rüchardt*, Angew. Chem. *82*, 845 (1970); Angew. Chem. internat. Edit. *9*, 830 (1970).

[38] Summary: [21], pp. 273ff.

[39] *T. M. Patrick, Jr.*, J. Org. Chem. *17*, 1009 (1952).

[40] See [21], p. 242.

[41] *G. E. Hartzell* and *E. S. Huyser*, J. Org. Chem. *29*, 3341 (1964).

[42] *H.-G. Heine*, unpublished results.

[43] *R. J. Longley, Jr.* and *T. M. Patrick, Jr.*, US-Pat. 2841592 (June 23, 1953), Monsanto Chem. Corp.

[44] *W. E. Mochel, J. L. Crandall*, and *J. H. Peterson*, J. Amer. Chem. Soc. *77*, 494 (1955).

Structure Determinations of Nitrogen Compounds with the Aid of NQR, NMR, and ESCA Spectroscopy

By Hans G. Fitzky, Detlef Wendisch, and Reimer Holm[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

Since it is often necessary or desirable to determine the structures of compounds containing nitrogen directly *via* the nitrogen atoms, the nuclear quadrupole resonance (NQR) and the nuclear magnetic resonance (NMR) as well as the photoelectron and the Auger-electron spectroscopy (ESCA) of nitrogen are becoming increasingly important. A comparative review of these three methods on the basis of measurement effect, information obtainable, applications, and limitations forms the subject of this article.

Introduction

Three new fields of the spectroscopy of nitrogen compounds, which have not yet been extensively used, are the ^{14}N nuclear quadrupole resonance[1], the ^{14}N and ^{15}N nuclear magnetic resonance[2], and the photoelectron spectroscopy of nitrogen[3]. Though these methods have been in practical use for a number of years, their wide application has been prevented mainly by experimental difficulties. In recent years there have been reports of some important technical improvements, which should lead to an increase in the capabilities of these methods and hence also to their wider use. On the other hand, an assessment of the methods with regard to their capabilities is possible on the basis of existing knowledge.

The usual methods of nuclear magnetic resonance and IR and mass spectroscopy often do not yield conclusive answers in the determination of the structures of nitrogen compounds. Thus in mass spectroscopy, compounds that are difficult to volatilize sometimes suffer pyrolysis. Moreover, difficulties in interpretation often arise in the formation of zwitterions from salt-like nitrogen compounds or *N*-oxides. In IR analyses, it is difficult to distinguish between C=N and C=C bonds or between nitro and nitroso groups; it is also difficult to detect azo groupings and tertiary amines. The structures of molecules containing several nitrogen atoms, such as substituted polynuclear heterocycles, often cannot be determined by conventional NMR spectroscopy; the ^{1}H resonance of compounds containing nitrogen is always negatively influenced by the nuclear quadrupole moment of the ^{14}N nucleus. It is therefore often necessary or desirable to determine the structures of compounds containing nitrogen directly *via* the nitrogen atoms.

1. Nuclear Quadrupole Resonance

Since its introduction by *Dehmelt* and *Krüger*[4,5] in 1950, nuclear quadrupole resonance spectroscopy has been increasingly used for the investigation of chemical bonds in crystalline solids. Primarily through the work of *Townes* and *Dailey*[6], it was possible to use the spectroscopic data to establish the electron structure of the chemical bond. The method is applicable to compounds of 130 isotopes whose nuclear spin is greater than 1/2. Nuclear quadrupole resonance thus complements nuclear magnetic resonance, since it can be used for the detection of the very nuclei whose measurement with the aid of nuclear magnetic resonance is impossible because of excessive line broadening due to quadrupole coupling.

Apart from the investigations on halogen compounds, which have been the main subject of studies carried out so far, spectra of ^{14}N were also recorded. Investigations on a large number of nitrogen compounds have shown that not only are answers provided for problems of bonding theory, but the method can also be applied to structural analysis as carried out recently in the nuclear quadrupole resonance of chlorine[7,8].

1.1. Principles of ^{14}N Nuclear Quadrupole Resonance

1.1.1. The Nuclear Quadrupole

Nuclei having a nuclear spin greater than 1/2 have a nuclear charge distribution in the form of an ellipsoid of rotation, and consequently possess a nuclear quadrupole moment, whose magnitude and sign depend on the nature and magnitude of the ellipticity (Fig. 1). The nucleus ^{14}N

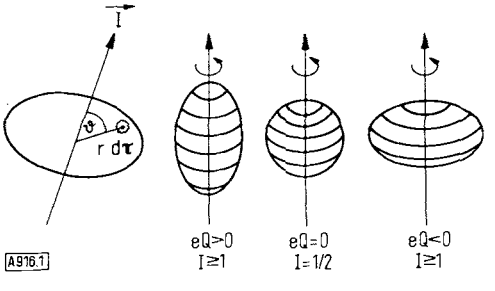


Fig. 1. Electric nuclear quadrupole moment. Definition of the scalar electric quadrupole moment:
$eQ = \int \varrho r^2 (3\cos^2\vartheta - 1) d\tau$.
e = nuclear charge, I = nuclear spin quantum number.

[*] Dr. H. G. Fitzky, Dr. D. Wendisch, and Dr. R. Holm
Ingenieur-Bereich Angewandte Physik, Bayer AG
509 Leverkusen-Bayerwerk (Germany)

(content in the natural nitrogen isotope mixture: 99.635%) has the nuclear spin I = 1 and the relatively small quadrupole moment $eQ = +0.016 \times 10^{-24}\,cm^2$. The nuclear quadrupole can assume positions that differ in energy in relation to the direction of the nuclear spin moment I in the inhomogeneous internal electric field of the molecule. The energies are determined by the magnitude of the quadrupole moment eQ and the field inhomogeneity at the position of the nucleus q, the possible orientations of the nucleus, *i.e.* the number of terms, being determined by the spin quantum number I. The field gradient provides the chemical information. Its magnitude is determined exclusively by the bonding electrons in incomplete shells, mainly p electrons. Complete shells and s electrons make no contribution, because of their spherically symmetrical density distribution. The influence of the d electrons is weaker than that of the p electrons by a factor of about 10.

1.1.2. The Nuclear Quadrupole in an Axially Symmetrical Field Gradient

If the field gradient at the position of the nucleus is characterized by the second derivatives of the electrostatic potential, one obtains the Laplace equation

$$\frac{d^2V}{dx^2} + \frac{d^2V}{dy^2} + \frac{d^2V}{dz^2} = \sigma$$

with the gradients

$$q_x = \frac{d^2V}{dx^2}, \quad q_y = \frac{d^2V}{dy^2}, \quad q_z = \frac{d^2V}{dz^2}$$

If the field gradient is axially symmetrical, *e.g.* about the z axis joining the nuclei, then $q_x = q_y$ and $q_z = -2q_x = -2q_y$.

The classical equation for the energy of the quadrupole nucleus in an axially symmetrical field (Fig. 2)

$$E = (1/8)e^2 q_z Q(3\cos^2\varphi - 1)$$

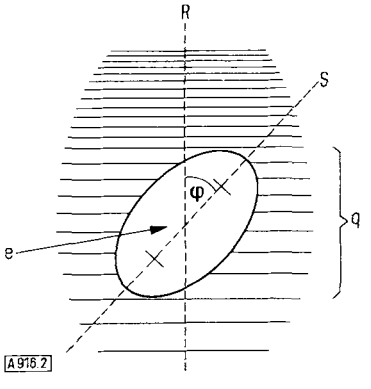


Fig. 2. Nuclear quadrupole in an inhomogeneous electric field. Q = quadrupole moment, e = charge of the proton, q = average value of the field gradient at the position of the nucleus, R = direction of the field gradient (also quantization axis), S = spin axis (+Q).

leads, with quantization of the angle φ, to the quantum-mechanical energy

$$E_m = (1/4)e^2 q_z Q \frac{3m^2 - I(I+1)}{I(2I-1)}$$

where $m = I, I-1, \ldots -I$.

For ^{14}N, with I = 1, axial symmetry gives a transition (Fig. 3) having the frequency $\nu = (3/4)e^2 q_z Q$ corresponding to $\Delta m = \pm 1$.

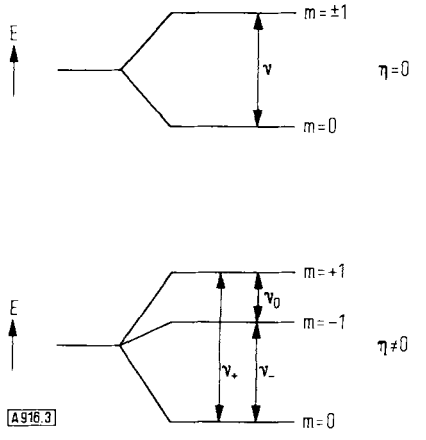


Fig. 3. Energy level diagram of the ^{14}N quadrupole nucleus in axially symmetrical (top) and non-axially symmetrical field gradients (bottom).

1.1.3. The Nuclear Quadrupole in an Asymmetric Field Gradient

In the presence of a non-axially symmetrical field, *i.e.* for $q_x \neq q_y$, the m degeneracy of the term is eliminated, so that further transitions occur. If the degree of asymmetry is characterized by the parameter

$$\eta = \frac{q_x - q_y}{q_z} \quad \text{with} \quad 1 > \eta > 0,$$

the three possible transitions of the ^{14}N nucleus are found to be

$$\nu_+ = (3/4)e^2 q_z Q(1 + \eta/3)$$
$$\nu_- = (3/4)e^2 q_z Q(1 - \eta/3)$$
$$\nu_0 = \nu_+ - \nu_-$$

1.1.4. Field Gradient and Chemical Shift

The resonance frequencies are proportional to the field gradients at the position of the nucleus q, which is predominantly determined by the p electrons of the valence shell. An approximate calculation of q is possible by the method of *Townes* and *Dailey*[1,6]. The influence of the p electrons is represented by the equation

$$q = N_x q_x + N_y q_y + N_z q_z$$

in which the numbers N of p_x, p_y, and p_z electrons are taken into account. For a full P shell, with

$N_x = N_y = N_z = 2$
$q_x = 0$; it follows that
$q_z = -2q_x = -2q_y$

Substitution in the above equation gives the basic equation of *Townes* and *Dailey*:

$$q = q_z[N_z - (1/2)(N_x + N_y)]$$

In the case of one unpaired p electron, the field gradient has a maximum (*e.g.* $N_x = N_y = 2$, $N_z = 1$, chlorine atom). This gives a maximum resonance frequency of *e.g.* $(1/2)e^2q_{at}Q = 54.87$ MHz for chlorine. The other extreme is reached in the chloride ion, with the completely filled P shell and extremely low resonance frequencies. The ionic character of a bond very strongly influences the position of the resonance frequency. In singly coordinated compounds, the three main factors affecting the chemical shift can be taken into account relatively easily as follows.

The ionic character i of a bond, which is characterized *e.g.* by the difference in electronegativity between the bonded atoms[9], secondly the degree of s hybridization s, which leads to a decrease in the field gradient because of the spherical symmetry of the s electrons, and thirdly the multiple bond character π, which influences the magnitude and the symmetry of the field gradient, can be represented as follows:

$$e^2q_zQ/(e^2q_{at}Q) = (1 - i)(1 - s) - \pi$$

The multiple bond component (conjugation effect) due to p_π bonding is found to be

$$\pi = \frac{2}{3} \cdot \frac{e^2q_zQ}{e^2q_{at}Q}\eta$$

1.2. Possibility of Use for Structural Analysis

The very frequent predominance of the ionic contribution in chlorine compounds facilitates the construction of shift tables (named by analogy with usage in NMR) as an aid in structural analysis[10-13]. Similar classifications are based on the electronic properties of atoms and groupings, which are described by the Hammett σ constant and the Taft σ parameter (inductive effects)[1].

Two difficulties arise in the use of these methods for the construction of a shift table for nitrogen compounds. Firstly, for the nitrogen atom, because of its ^4S ground state, $e^2q_{at}Q = 0$, so that a value of about 8.4 MHz must be assumed for an unpaired p electron[1, 14], and secondly, the multiple coordination of the bonded atoms leads to difficulties in establishing the principal axes of the field gradients, which make a general representation difficult. However, the method of *Townes* and *Dailey* can again be used here[14], and it is found that within certain classes of substances the concept of the relation between the chemical shift and the electronic properties of the atoms and groupings can be applied here in the same way as for the chlorine compounds (Table 1).

Table 1. NQR shifts and electronegativity.

^{14}N-Resonance		^{35}Cl-Resonance	
Compound	Resonance frequency (MHz)	Compound	Resonance frequency (MHz)
NC—CN	4.269	NC—CCl_3	41.46
Cl_3C—CN	4.052	Cl_3C—CCl_3	40.67
Cl—CN	3.219 [a]	Cl—CCl_3	40.60
H—CN	4.018	H—CCl_3	38.28
C_6H_5—CN	3.885	C_6H_5—CCl_3	38.70
CH_2=CH—CN	3.800	CH_2=CH—CCl_3	38.30
C_2H_5—CN	3.775	C_2H_5—CCl_3	–
CH_3—CN	3.737	CH_3—CCl_3	37.94

[a] Because of a high conjugation component, which is expressed in the structure Cl^+=C=N^- and leads to an excessively high π-electron density on the N, Cl—CN lies at a very low frequency.

A more comprehensive shift table is shown in Figure 4, which is based on an empirical evaluation of the available resonance frequencies of ^{14}N compounds. The shift range is much smaller than for the chlorine resonance, but because of the smaller line width of 0.3 to 1 kHz, the ratio

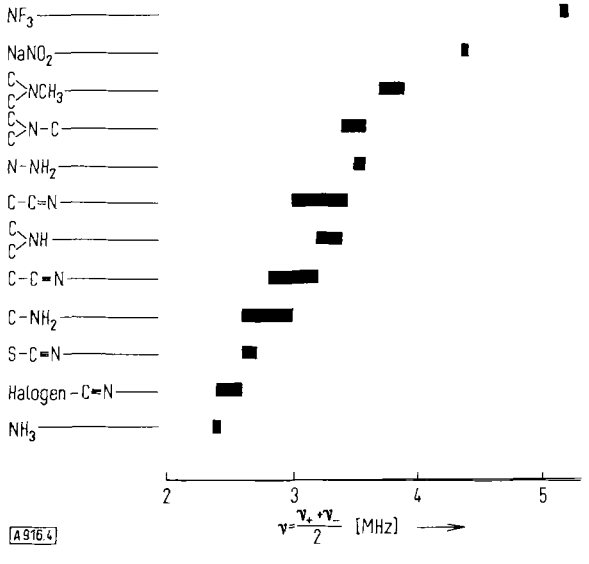


Fig. 4. Correlation of position of the ^{14}N-NQR resonance and type of structure.

of the shift range to the line width is roughly the same for ^{14}N as for chlorine. The electronegativity of the bonding partner, as in the case of chlorine, influences the position of the ^{14}N resonance most strongly, *e.g.* in the series NF_3, $N(CH_3)_3$, NH_3. The monotonic increase in shift in the series C≡N, C=N, and C—N is also typical. A significant analytical advantage over IR spectroscopy is the possibility of recognizing C···N in the presence of C=C. The differences between primary amines of the type C—NH_2 and N—NH_2 are also remarkable.

Table 2. New *N*-chlorine resonances.

Compound	^{35}Cl-Resonance frequency (MHz)
N,N'-Dichloroazodicarboxamidine	45.550
Trichloroisocyanuric acid	46.430
N,2,3,4,4,5,5,6,6-Nonachloro-2-cyclohexeneimine	48.275
N-Chlorotrichloroacetoimide chloride	49.083
	48.707
N-Chloroisocyanide dichloride	49.205 (2 lines)

The question whether a Cl—N or a C—Cl bond is present can be easily settled with the aid of the chlorine nuclear quadrupole resonance, since the chlorine resonance for N—Cl bonds is situated above 43.8 MHz, whereas the maximum frequency for C—Cl bonds is 41.5 MHz. To supplement the data known earlier[1], Table 2 gives further *N*-chlorine resonances[15].

Additional information on the symmetry of the molecule is provided by the spectra in the form of two transitions, whose frequency difference is proportional to the asymmetry of the field gradient. Symmetrically tricoordinate nitrogen as in hexamethylenetetramine gives only one transition, as do monocoordinate —C≡N compounds with vanishingly small π-bond components[16]. In general, the position and number of lines and the distance between them will be used in the assignment of structures to new substances. Doubling of the number of lines may be due to crystal field effects depending on the arrangement of two molecules per unit cell. For a reliable analysis, it is always essential to find at least the $\nu_{\pm}$ transitions; where the unit cell contains several molecules, it is advisable, for reliable pairing of the $\nu_{\pm}$ transitions, to determine also the difference frequencies ν_0, though these lie at very low frequencies and have very weak line intensities.

1.3. Experimental for the Nitrogen Resonance

1.3.1. Nuclear Quadrupole Resonance Spectrometer

Transitions between the energy levels of the nuclear quadrupole (Fig. 3) are induced by the magnetic coupling of the nuclear spin with the magnetic high frequency field[17]. A spectrometer therefore consists essentially of a slow-drive variable high-frequency generator, which produces a high-frequency magnetic field of variable frequency and intensity, into which the substance to be investigated is introduced. Quadrupole nuclei with relatively long spin-lattice relaxation times, such as ^{14}N, require low high-frequency power, which cannot be satisfactorily produced with the superregenerative oscillator used for the chlorine resonance. The system used almost exclusively so far for the detection of the nitrogen resonance is the marginal oscillator[18-21], an oscillator detector system in which the oscillator swings constantly, but the amplitude depends sensitively on the damping of the frequency-determining oscillator circuit because of nuclear quadrupole resonance absorption. The marginal oscillator is usually frequency-modulated with a bisymmetric rectangular voltage for better marking of the resonance absorption, the frequency deviation chosen being roughly equal to half of the line width. The first derivative of the line shape is obtained with phase-sensitive rectification of the nuclear resonance signal, or the second derivative on adjustment of the lock-in rectifier to twice the modulation frequency (Fig. 5).

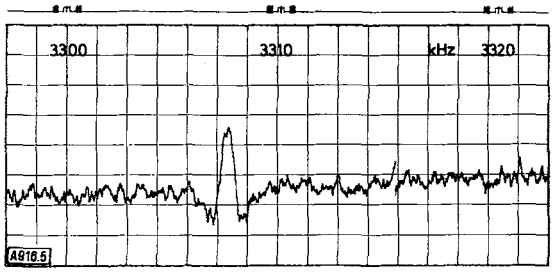


Fig. 5. Part of a ^{14}N nuclear quadrupole resonance spectrum (10 g of hexamethylenetetramine at 300 K); range covered with one instrument setting: 60 kHz at 3300 kHz. Recording time: 50 minutes.

The time taken to record a long spectrum is much greater for the nitrogen resonance than for the chlorine resonance, since, because of the lower line intensities, higher time constants of the detector are required and the marginal oscillator, unlike the superregenerative oscillator, requires manual resetting of the marginality and intensity at frequency intervals of 100 to 300 kHz to maintain maximum detection sensitivity. The usual recording rates are between 10 and 30 Hz/s. The frequency range between 0.5 and 5 MHz can be covered with about 4 interchangeable oscillator inductances. Electronic counters are used for accurate frequency measurement. Accurate frequency marks may be superimposed on the spectra for calibration (edge marks in Fig. 5).

1.3.2. Execution of the Measurements

The quantities of material used for the measurement are 5 to 50 g; the purity should be 98 to 100%. Sufficiently intense spectra are obtainable only with well crystallized compounds. Liquids must accordingly be cooled, usually to 77 °K (liquid nitrogen). Since the electric field of the crystal influences the position of the lines, frequencies are usually given for 77 °K to make the data comparable. Frequency tables for analytical purposes have been given in various publications[22-25].

In addition to impurities incorporated into the crystal, thermally induced mechanical stresses also lead to pro-

nounced broadening of the lines, which may hinder detection. The measurement is often hindered by piezoelectric resonances, particularly at 77 °K, which lead to the appearance of numerous "false" resonances[26].

The spectrum used for the structural analysis must contain one line ($\eta = 0$) or three lines ($\eta \neq 0$) per nitrogen nucleus, with appropriate multiplication where there are several molecules per unit cell. No superposition of lines is to be expected, owing to the low line width and the large shift range.

2. Nuclear Magnetic Resonance

Nuclear magnetic resonance has been used in the past mainly as proton resonance spectroscopy for the determination of the structures of compounds containing nitrogen. In some cases, however, this indirect information was insufficient, or even unobtainable, so that it was often desirable or necessary to use the nitrogen itself.

2.1. Principles and Experimental for the Nitrogen Resonance

The two naturally occurring isotopes of nitrogen, ^{14}N (natural abundance 99.635%) and ^{15}N (natural abundance 0.365%), have a spin that differs from zero, and can therefore be detected in principle in NMR experiments. The nucleus ^{14}N has the spin $I = 1$, and hence has a quadrupole moment (see Section 1). Its low magnetic moment ($\mu = 0.40357$ nuclear magnetons) causes an extremely low sensitivity, which is only 1.01×10^{-3} of that of the ^{1}H nucleus for a constant magnetic field. ^{15}N, with $I = (-)1/2$, also has only an extremely low relative sensitivity (1.04×10^{-3}).

In the case of ^{14}N, the line broadening caused by the quadrupole moment and the very low relative sensitivity lead to experimental difficulties; the difficulties encountered with ^{15}N are due to its low natural abundance and an extremely low sensitivity. Some of the difficulties can be overcome by the use of materials enriched in ^{15}N for the measurements[27]; this is an expensive process, and cannot be carried out in every case.

Increases in the signal/noise ratio in the ^{14}N spectra have been achieved by the use of the INDOR (internuclear double resonance) technique[28]. *Baldeschwieler* and *Randall*[29] described a double resonance technique for the measurement of the ^{14}N shifts that is particularly suitable for compounds in which nitrogen is bonded directly to hydrogen. The ^{1}H spectrum of the compound is observed and the ^{14}N nucleus is simultaneously irradiated with its resonance frequency by means of a variable-frequency oscillator; spin decoupling has been achieved when the fine structure of the NH proton signal disappears. The ^{14}N shifts are finally determined by measurement of the frequency differences that are necessary for decoupling in the various compounds. This process becomes more effective when a high-field spectrometer is used, *e.g.* a commercially obtainable 220 MHz spectrometer designed in such a way that the acceptance of the ^{14}N frequency of 15.89 MHz is possible[30-31]. However, the accuracy of the Baldeschwieler-Randall method for the determination of ^{14}N shifts is limited at very short ^{14}N relaxation times and where proton exchange processes occur.

The recording of nitrogen resonance spectra has recently been facilitated by:

improvement of the sensitivity of the spectrometers,
improved methods of spectrum accumulation,
refined double resonance techniques,
execution of the measurements as pulse experiments with subsequent Fourier transformation.

2.2. Chemical Shifts

Changes in the paramagnetic term of the Ramsay equation for the shielding constant[32] are regarded as the main reason for the large differences in the chemical shifts of compounds containing nitrogen. The simple shielding theory of *Karplus* and *Pople*[33], which takes into account only the paramagnetic contribution σ_p to the shielding constant, satisfactorily explains the chemical shifts of some linear triatomic molecules and ions[34]. Changes in the ionic character of the nitrogen atom influence the orbital angular momentum, on which the magnitude of the paramagnetic term depends[35]. For an inert gas configuration the orbital angular momentum is zero, and the paramagnetic term has a very small value. This case is found for the nitrogen atom in the ammonium ion. With increasing electronegativity of an atom or group bonded directly to the nitrogen, the ionic character of the nitrogen decreases and the paramagnetic contribution to the shielding increases, so that shifts of the N signals to lower fields are finally observed. The electronegativity is a very important factor in saturated nitrogen compounds, whereas the paramagnetic term becomes dominant in aromatic and conjugated compounds. For some systems it was found that charge-transfer interactions and hyperconjugation also have an influence. The large variations of the line widths of ^{14}N signals depend both on the hybridization and steric factors and on the symmetry and charge distribution. Figure 6 shows a survey of typical ^{14}N shifts for some classes of compounds.

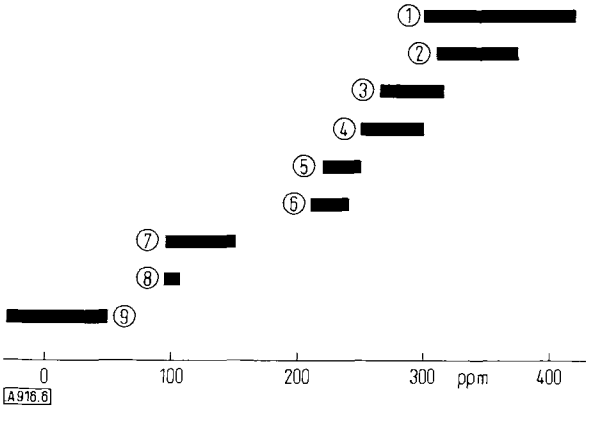


Fig. 6. Positions of the ^{14}N-NMR resonances (based on NO_3^-) of: (1) ammonium compounds, (2) amines, (3) vinylogous amides, (4) amides, (5) pyrroles, (6) thioamides, (7) cyanides, (8) thiocyanates, (9) nitro compounds.

The chemical shifts of the ^{14}N and ^{15}N signals are based on different reference substances, a situation analogous to that in the early stages of proton resonance. Thus ^{14}N shifts have been referred to the NO_2^- ion[36], the NO_3^- ion[37] (as an external standard), and the NH_4^+ ion[38]. Nitromethane has been used as an internal standard[39,40]. For ^{15}N shifts, *Roberts et al.* used liquid $^{15}NH_3$ as an external standard[27,41]. The resonance position of the $^{15}NH_4^+$ ion has been used by other workers as the reference value[42-44]. Efforts are being made at present to construct a unified table for ^{14}N and ^{15}N signal shifts[30,31]. *Becker* has proposed the use of tetramethylammonium iodide as an internal standard, and in this case positive ppm values should be used in the direction of increasing frequency[31].

2.3. Coupling Constants

The observation of coupling constants of ^{14}N with other nuclei is impossible in most cases because of the quadrupole moment. The observation of couplings becomes possible only with a highly symmetrical field gradient at the nitrogen nucleus, since the symmetry leads to a sufficiently large increase in the spin-lattice relaxation time T_1. These difficulties do not arise for ^{15}N. The coupling constants can be determined unequivocally by measurements on materials enriched in ^{15}N. Table 3 shows a survey of some ^{15}N—H coupling constants.

Table 3. Examples of ^{15}N—H couplings from measurements on substances enriched in ^{15}N.

Compound	Coupling Constants (Hz)	Ref.
Diphenylurea	$J_{^{15}N-H} = 89.7 \pm 0.1$	[45]
Diphenylthiourea	$J_{^{15}N-H} = 89.8 \pm 0.2$	[45]
Benzylidenemethylamine	$J_{^{15}N-C-H} = 0.6$	[27]
N-Methylphthalimide	$J_{^{15}N-C-H} = 1.4$	[27]
N,N-Dimethyl-*N'*-phenylformamidine	$J_{^{15}N=C-H} = 2.4 \pm 0.1$	[45]
Benzylideneaniline	$J_{^{15}N=C-H} = 3.8 \pm 0.1$	[45]
Formamide	$J_{^{15}N-C-H} = 19.0$	[46]
N,N-Dimethylformamide	$J_{^{15}N-C-H} = 15.6$	[47]
Pyridine	$J_{^{15}N-C-H\alpha} = -10.76$	[48]
	$J_{^{15}N-C-H\beta} = -1.53$	
	$J_{^{15}N-C-H\gamma} = \pm 0.21$	

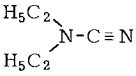
Roberts et al. have interpreted the ^{15}N—H couplings in the sense of the Fermi contact term of the coupling mechanism[27]. Except in a few cases (high anisotropy of the electron distribution on the nitrogen atom), a quantitative correlation is possible between the s character of ^{15}N—H bonds and the ^{15}N—H coupling constants. Values between 88 and 94 Hz correspond to a partial s bond character of 31 to 34%[27].

2.4. Examples of Applications

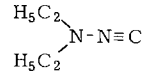
Some examples of the application of the nitrogen resonance are given below.

Cyanamides and Carbodiimides

By recording the ^{14}N spectrum of diethylcyanamide[49], it was possible to show that the molecule has a nitrile structure *(1)* and not an isocyanide structure *(2)*. The ^{14}N spectrum of this compound has two signals at +149



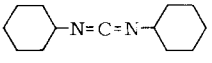
(1)



(2)

and +285 ppm (referred to the absorption line of NO_3^- in an NH_4NO_3 solution). The higher-field signal was assigned to the N atom of the amino type on the basis of its shift[36]. Since methyl isocyanide has a ^{14}N shift of +240 ppm, the diethylcyanamide signal at +149 ppm cannot be attributed to an isocyanide nitrogen.

The ^{14}N spectrum of *N,N'*-dicyclohexylcarbodiimide contains only one signal at +240 ppm (referred to NO_3^-), which can be reconciled with a symmetrical structure *(3)*[49].



(3)

The ^{14}N nuclear resonance allows a distinction between the isomeric fulminate, cyanate, and isocyanate compounds. This is of interest in view of the frequently observed isomerization fulminate→cyanate or isocyanate[50] and nitrile oxide→isocyanate[51]. Thiocyanato and isothiocyanato complexes can also be distinguished[52].

The ^{14}N resonance has been successfully used for the study of transition metal complexes with ligands containing nitrogen[52-55]. Table 4 contains a survey of the ^{14}N shifts of some complexes of this type[55]. Where there is a direct metal-nitrogen bond, the ^{14}N signal of the complex

Table 4. ^{14}N shifts of some transition metal complexes with ligands containing nitrogen [55].

Complex	$\delta_{^{14}N}$ [a] (ppm)	Geometry
$Ru(NH_3)_6Cl_2$	+316	octahedral
$Rh(NH_3)_6Cl_3$	+295	octahedral
$Co(NH_3)_6Cl_3$	+286	octahedral
H_2RuCl_5NO	−107	octahedral
$Co(CO)_3NO$	−149	tetrahedral
$Fe(CO)_2NO_2$	−167	tetrahedral
$Na_2Pd(NO_2)_4$	−134	planar
$Na_3Co(NO_2)_6$	−135	octahedral
$Na_2Pt(NO_2)_4$	−136	planar
$K_2Ni(CN)_4$	− 46	planar
$K_2Pd(CN)_4$	− 33	planar
$K_2Pt(CN)_4$	− 20	planar
$K_2Zn(CN)_4$	− 35	tetrahedral
$K_2Cd(CN)_4$	− 45	tetrahedral
$Na_4Os(CN)_6$	− 31	octahedral
$Na_3Co(CN)_6$	− 34	octahedral
$NaAu(CN)_2$	− 16	linear
$Hg(CN)_2$	− 40	linear

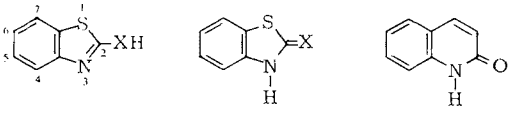
[a] Referred to the ^{14}N signal of acetonitrile; reference values: $\delta_{^{14}N}$ for $NaNO_2 = -385$ ppm, $\delta_{^{14}N}$ for $KCN = -5$ ppm.

occurs at a higher field than that of the free ligand, since the lone pair of electrons on the nitrogen in the complex contributes only slightly to the negative or paramagnetic term of the Ramsay equation. Shifts to lower fields are observed if there is no direct metal-nitrogen bond. Pseudohalogen-metal compounds with ligands containing nitrogen have also been investigated with the aid of the ^{14}N resonance[56].

The kinetics of the NH_3 exchange between nickel-ammine complexes and ammonia in aqueous and in nonaqueous solutions has also been successfully studied with the aid of the ^{14}N resonance[57].

Heterocycles Containing Nitrogen

The ^{14}N nuclear resonance was very useful for differentiating between tautomeric structures in heterocycles containing nitrogen. Mention should be made here of investigations on 2-substituted benzothiazoles[58], which can exist in the tautomeric forms *(4)* and *(5)*. The derivatives substituted in position 4 and 6 give chemical shifts as expected for aromatic compounds such as pyridine or isoquinoline. However, the 2-amino and 2-methylamino compounds absorb in the region of 310 to 320 ppm, so that these exist in the amino form *(4)* rather than in the imino form *(5)*. 2-Hydroxybenzothiazole and 2-mercaptobenzothiazole give ^{14}N shifts that indicate the presence of a nitrogen of the thiazoline type *(5)*. Similar behavior is observed for 2- and 8-hydroxyquinolines, in which only the isomers substituted in position 2 can exist in the oxo form *(6)*[59]. 8-Hydroxyquinolines again exhibit an absorption in a region to be expected for a ring nitrogen, as in quinoline, whereas the resonances at higher fields must be attributed to the isomers substituted in position 2. The observation of the ^{14}N—H coupling is further evidence that these isomers exist exclusively in the oxo form.

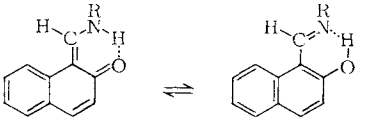


(4) *(5)* *(6)*

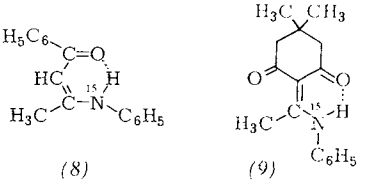
X = O, S, NH, NCH_3

An example of a combination of the nitrogen resonance with other NMR spectroscopic studies is the ^{13}C, ^{14}N, and ^{1}H measurements on *m-/p*-substituted *N*-methylpyridinium iodides[60]. A distinct dependence of the chemical shifts on the nature of the substituent was found for all three nuclei. The resonances occur at higher fields with increasing π-electron density. In the case of the ^{14}N shielding it was possible to attribute this to the change in the paramagnetic shielding term, whereas the neighbor anisotropy was held to be responsible in the cases of ^{13}C and ^{1}H. This explanation is based on the observation that the calculated C and H charge densities showed no significant changes within the series in question. Excellent correlations between the shifts and the Hammett substituent constants were obtained by the use of σ^+ values for the substituents that act as donors. A similar substituent dependence was found for the direct ^{13}C—H methyl coupling constants, whose magnitude increases with decreasing charge density on the nitrogen[60].

The observation of ^{15}N coupling constants can be a particularly sensitive method for the study of isomerism and valence-tautomerism phenomena. In the case of ^{15}N—H coupling, this is most easily accomplished by measurement of the proton resonance of material enriched in ^{15}N. If for instance a fast intramolecular proton exchange occurs between two positions in a system, *e.g.* between oxygen and nitrogen, the ^{15}N—H coupling is a good measure of the residence time of the proton on the nitrogen. This method has been used for the investigation of the keto-enol equilibrium (as a function of temperature and solvent) in various Schiff bases derived from anilides, aldehydes, and ketones[61-64]. For example, the low value of 33 Hz for $J_{^{15}N-H}$ in 1-([^{15}N]-phenyliminomethyl)-2-naphthol has been explained by the assumption that this compound exists predominantly in the enolimine form *(7b)*, since much higher values were found for typical keto amine structures *(8)* [$J_{^{15}N-H}$ = 89.2 Hz] and *(9)* [$J_{^{15}N-H}$ = 84.7 Hz].



(7a) *(7b)*



(8) *(9)*

Of the many ^{15}N—H studies that have been carried out, only a few will be mentioned here:

cis-trans isomerism in formanilide[47]; investigations on cytosine derivatives[65]; structural investigations on the phenyldiazonium ion[66]; *syn-anti* isomerism in oximes[67]; studies on configuration in *N*-nitrosamines[68]; *N*-nitrosohydrazides[69], *N*-nitrosohydroxylamines[70], and alkyl nitrites[71].

The nitrogen resonance should also be important in the future for analysis. For example, a method was recently described in which the amino function (primary, secondary, and tertiary) of organic compounds is characterized on the basis of the ^{14}N shifts of the protonated amines[72]. The method has been used in the meantime in the investigation of the thermal degradation of polyamides[73].

3. Photoelectron and Auger-Electron Spectroscopy (ESCA)

Electron spectroscopy may be defined as the measurement of the kinetic energy distribution of electrons emitted by a sample on irradiation with UV light, X-rays, or electrons. Only the special case of excitation with X-rays

will be considered here. This method was introduced by *K. Siegbahn*, who called it ESCA (electron spectroscopy for chemical analysis)[74-76]. It is applicable to all elements, and in principle allows the study of bonding effects on all participating atoms.

Excitation with UV light is not atom-specific. Auger lines have so far been used only in surface analysis for the detection of the element nitrogen, and no further chemical information was deduced from them. In the ESCA spectrum, the N 1s photoelectron line is much more intense than the Auger lines. Since the results are easier to interpret and the escape depth of the electrons is larger for the N 1s line because of the higher kinetic energy, the Auger lines are disregarded in the following discussion.

3.1. Principles and Experimental

An electron spectrometer consists essentially of the following parts: specimen chamber, X-ray tube, energy analyzer, and detector system. When X-rays fall on the substance, photoelectrons are emitted, and their kinetic energy is measured with the aid of the energy analyzer.

The use of electron spectrometers expanded rapidly when easy-to-operate instruments with electrostatic energy analyzers became commercially available. A decisive step toward an increase in resolution was achieved by retarding the electrons and carrying out the energy analysis at low kinetic energies[77]. The sensitivity was considerably increased by imaging the sample on the entry slit of the analyzer. A channeltron (open secondary-electron multiplier) is normally used as the electron detector.

In view of the necessary mean free path of the electrons, a vacuum of at least 10^{-5} torr must be maintained. The method is therefore applicable primarily to solids having a sufficiently low vapor pressure (with cooling if necessary). With a suitable specimen chamber, however, gases can also be investigated by differential pumping[75].

Photoelectron spectroscopy is based on the Einstein equation

$$E_{kin} = h\nu - E_I$$

where E_{kin} is the kinetic energy of the photoelectron, $h\nu$ is the energy of the incident X-ray quantum, and E_I is the ionization energy (in our case that of the N 1s level). Since the ionization energy of the N 1s level is about 400 eV, the expected positions of the photoelectron lines on excitation with Al-K_α (1487 eV) and with Mg-K_α X-rays (1254 eV) are roughly 1085 and 850 eV respectively.

It is important for the investigation of solids that the energy losses of the emitted electrons during their passage through the material are not continuous but quantized (excitation of plasmons)[78,79]. Electrons that have suffered no energy loss contribute to a sharp line, which is separated by at least one minimum from a tail on the low kinetic energy side due to inelastically scattered electrons.

As the mean free path for electron-electron scattering is about 30 Å for kinetic energies of 1000 eV only those electrons originating in the uppermost monolayers can contribute to the lines. It must therefore always be remembered that ESCA is a method of surface analysis, and that the information comes from a surface layer with a thickness of only about 30 Å[80]. This has the advantage on the one hand that very small quantities of material are necessary; 5 to 10 monolayers uniformly distributed on the specimen holder (about 0.5 cm^2) are sufficient for an analysis (this corresponds to about 10^{-8} g). The uniform distribution over a fairly large area is necessary for intensity reasons because of the small layer thickness that contributes to the signal. On the other hand, the possibility of special surface effects (*e.g.* oxidation) must be taken into account. The purity of the substance is of no importance. Mixtures can also be investigated.

ESCA is a statistical method of measurement. Within the stability range of the instrument, therefore, the detection limit is a question of time. If the N content is greater than 1%, the time required to record the N 1s spectrum is 1/2 to 1 h.

3.2. "Chemical Shift"

ESCA can contribute to the determination of the structures of organic and inorganic molecules since the accuracy of measurement is sufficient for the detection of shifts of the N 1s level under the influence of the neighboring atoms. The shifts arise as follows: Partial withdrawal of electrons causes the remaining electrons to become more tightly bound to the nucleus; this results in a higher ionization energy and hence in a lower kinetic energy of the photoelectrons. A partial negative charge on the atom has the opposite effect. One thus obtains information about the electron density in the vicinity of the nucleus, from which one can deduce *e.g.* the oxidation state, valency, *etc.*

It must be stressed, however, that one should not expect too much. It can be seen from Figures 9 and 10 that the ratio of the maximum shift to the observed line width is only of the order of 10; in other words, the sharpness of separation is not very high. The following difficulties must be taken into account in particular for solids. The shift expected for a free ion is partly compensated by the Madelung potential. The line width is always greater than for gases. It consists (apart from apparatus effects, which are normally negligible) of the width of the incident X-ray line and the width of the N 1s level investigated. Too little is known about the latter at present (broadening due to band structure, lifetime of the excited state) to enable us to decide whether the sharpness of separation is generally improved by an order of magnitude by the use of an X-ray monochromator[81] (decrease in the width of the X-ray line from about 1 eV to about 0.1 eV). On changing from Al-K_α (half width 1 eV) to Mg-K_α (half width 0.8 eV), we have not always obtained a correspondingly higher resolution[*]. On the basis of the line width, the chemical shift can be measured with an accuracy of

[*] Recently we had the opportunity to carry out measurements on a spectrometer with X-ray monochromator. In some cases we could obtain line widths of 0.8 eV for the N 1s lines.

± 0.2 eV, However, if the position of a line of substance A is to be compared with that of a line of substance B, the question of suitable calibration of the spectra arises, particularly if different spectrometers were used; on the one hand electrostatic charging in insulating specimens due to the emission of electrons leads to a shift of the spectra, and on the other the work function of the spectrometer material, which can be uncertain by up to 1 eV due to surface coatings, enters into all measurements on solids. Ionization by the X-rays (in spectrometers without a monochromator, mainly of the high-energy tail of the bremsstrahlung) opposes charging and at least a rather uniform charge distribution is reached on the surface of the specimen. The contamination with carbon (*e.g.* adsorbed pump oil) that is always present on the surface of the substance or a standard mixed with the substance and investigated at the same time may be used as a reference. *Bremser*[82] suggested the use of LiF as a standard of this type; in most of the work published so far the results were referred to the C 1s level of hydrocarbons[74] ($E_I = 284.0$ eV) or, particularly in studies on nitrogen compounds, to the N 1s level of KNO_3[83] ($E_I = 407.0$ eV).

Nearly all these difficulties disappear in measurements on gases. Only in such measurements, therefore, does one find satisfactory agreement between measured and calculated ionization energies and a linear correlation between the shift and the calculated charge of the atom[84] (Fig. 7).

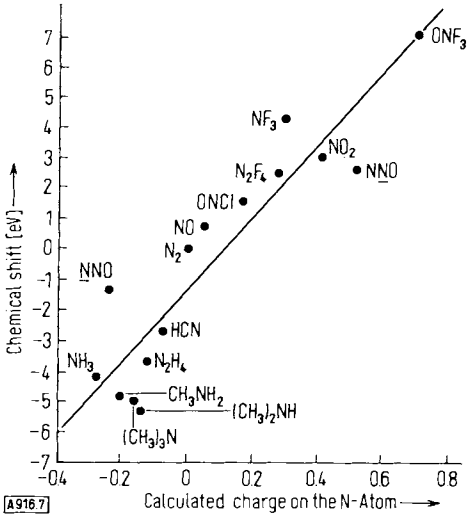


Fig. 7. Correlation of shift values with calculated charge on the N atom (gaseous compounds, reference: N_2) [84].

One may expect the use of an X-ray monochromator here to lead to a distinct improvement of the resolution as soon as the intensity problem has been solved (*e.g.* by suitable detectors and by the use of high-output X-ray tubes)[81].

3.3. Examples

Figure 8 shows the N 1s ionization energies of some classes of nitrogen compounds, arranged in order of decreasing electron density on the N atom (standard: KNO_3 = 407.0 eV). It can be seen that *e.g.* nitro groups or *N*-oxides differ markedly from trivalent nitrogen in N—H or N—C bonds. Figure 9 shows, as an example, the spectrum of 7-nitrobenzothiazole *N*-oxide. The line at the lowest kinetic energy (highest ionization energy) is due to the nitrogen in the nitro group (lowest electron density). Clearly separated from this are the line of the *N*-oxide and a third line, whose intensity increased with the duration of the exposure to X-rays, while that of the *N*-oxide line decreased. This is explained by the removal of oxygen as a result of the exposure to X-rays. Radiation damage of this type is occasionally observed for sensitive bonds[85].

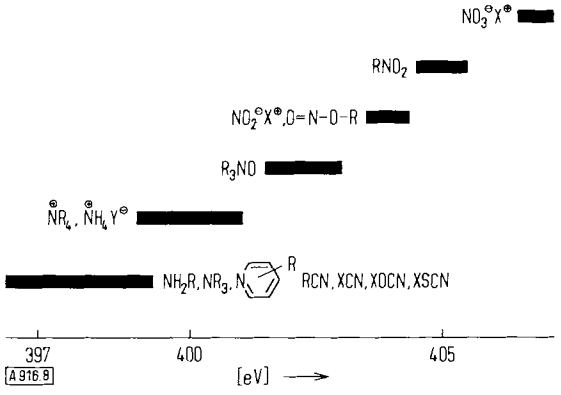


Fig. 8. N 1s ionization energies of various types of structure.

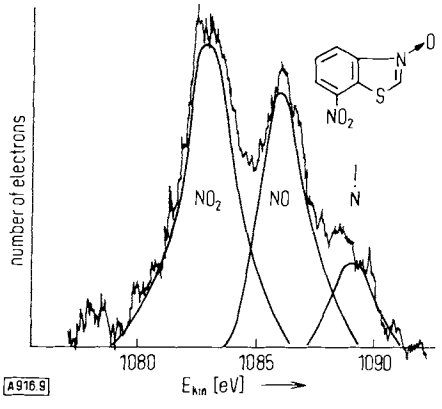


Fig. 9. N 1s photoelectron spectrum of 7-nitrobenzothiazole *N*-oxide. The band indicated by the exclamation point arises during irradiation (Al-K_α) as a result of removal of oxygen.

Another typical example is the N 1s spectrum of *N*-(2-pyridyl)-*p*-nitrobenzenesulfonamide[3,76], which has three lines. The line at the lowest kinetic energy is again due to the nitrogen in the nitro group, and that at the highest kinetic energy to the pyridine nitrogen. On the other hand, the ionization energy of the amino nitrogen in 4-amino-4'-nitroazobenzene[3] differs only slightly from that of the azo nitrogen, so that a somewhat broadened unsymmetrical line appears in the region of the trivalent nitrogen signal. 4-Aminobenzenesulfonamide[3] gives only one sharp N 1s line, from which it follows that the ionization energies and hence the electron densities are the same for the amino and sulfonamide nitrogen atoms. Conversely, the two lines separated by 4 eV in the spectrum of $Na_2N_2O_3$[86] point to the presence of two dissimilar nitrogen atoms in the $N_2O_3^{2-}$ ion.

A rough assignment of the ionization energies is also possible for complexes, *e. g.* for *trans*-$[CO(NH_2—CH_2—CH_2—NH_2)_2(NO_2)_2]NO_3$[86]. However, the deduction of bonding details from the spectra requires careful calibration and the measurement of a sufficiently large number of reference substances. Thus *Hendrickson*, *Hollander*, and *Jolly*[86] showed that the ionization energies for NH_3 ligands in Co(III) Rh(III), Ir(III), and Cr(III) complexes correspond to those of the ammonium ion in NH_4NO_3. On the other hand, the ionization energies for $NaNO_2$ and coordinated NO_2 are approximately equal. The same authors found that the CN line for metal nitrosyl cyanides remains constant, whereas the NO line is displaced; this points to the possibility of charge transfer by back-bonding from the metal.

There is practically no overlap between the quaternary *N*-compound region and other signal regions (Fig. 8). *Jack* and *Hercules*[83] have shown by very careful measurements that the N 1s ionization energy for tetraalkylammonium compounds is comparable with that of corresponding pyridines, but greater than for analogous polynuclear aromatic compounds. To determine the effects of substituents on the ring, the effects of the anions and of the Madelung potential were also taken into account within the groups of pyridinium and tetraalkylammonium salts.

Since the chemical shift depends on the electron density on the N atom, ESCA is very suitable for the detection of polar structures such as occur *e.g.* in azides and amine imides (cf. Fig. 10). The difference in the ionization energies in the amine imide is a direct measure of the localization of the charges on the individual N atoms. The N 1s ionization energy of the corresponding hydrazide lies exactly between the two values for the amine imide. The same is true in general for the detection of charge separations in mesoionic compounds[87]. If, for example, in the corresponding salt one charge is taken over by another ion, the difference in the ionization energies reduces to the difference between the partly positive and the neutral N atom[88].

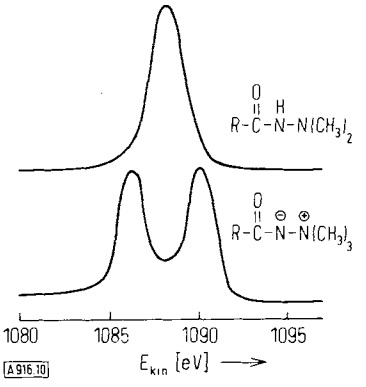


Fig. 10. N 1s photoelectron spectra of a hydrazide and of an amine imide.

The intensity of the N 1s line is a measure of the number of N atoms in the surface layer measured. With the aid of calibration measurements, the N content of a sample can be determined with an accuracy of a few percent with no extra outlay. Since the interaction with the X-ray quantum is essentially an atomic property, matrix effects are generally small. At most they manifest themselves in an effect on the escape depth of the electrons. This means that when several lines appear because of different bonding states, the intensity of each line corresponds to the number of N atoms in the state in question.

It should be mentioned in passing that the shifts are carefully investigated not only for structural determinations. In surface analysis with ESCA (*e.g.* in the study of catalysts), they form the basis for the identification of compounds[85, 89].

Table 5. Comparative survey of the methods described.

Method	Data, parameters measured	Data for structure determination	Shift range/ line-width	Amount of substance required	Purity of sample	Aggregate state	Recording time
^{14}N-NQR	line frequencies, chemical shifts	size and symmetry of the field gradients, ionic bond character, s-hybridization, multi-bonding components	*ca.* 5000	5—10 g	99—100%; good crystallizability	crystalline, powdered (if necessary, cooling to 77 K)	1—10 h per line
^{14}N-NMR	chemical shifts, line widths, coupling constants with other nuclei	bond character, electronegativity, hyperconjugation, steric factors	8 to 400	0.1—1 g	analysis of mixtures also possible	liquid or in solution	minutes to hours
^{15}N-NMR	chemical shifts, coupling constants with other nuclei	bond character, electronegativity, hyperconjugation, steric factors	*ca.* 5000	0.1—1 g	analysis of mixtures also possible	liquid or in solution	longer than with ^{14}N
ESCA	ionization energy of the N 1s level	electronic density in the neighborhood of the nucleus, partial charge (oxidation state, valency)	*ca.* 10	1 molecular layer per 0.5 cm^2 $\hat{=}10^{-8}$ g	analysis of mixtures also possible	solid (gaseous)	0.5—1 h

4. Comparison of the Methods

Table 5 shows a comparison of the three methods described. Only the data that are relevant to the spectroscopic determination of structures are included. The table is intended to facilitate the selection of an appropriate method or combination of methods in the light of the particular problem in hand and the nature of the material under investigation. If the substance to be examined is sufficiently pure and crystallizable, for example, nuclear quadrupole resonance is probably the method of choice as regards expense. Nuclear magnetic resonance is growing in importance for smaller samples, though these must be liquid or in solution. Whether the ^{14}N or the ^{15}N resonance should be examined is a question of the expense that can be tolerated, the ^{15}N resonance being preferable in cases of doubt because of the favorable shift range/line width ratio of the ^{15}N resonance. Since this ratio is very unfavorable in the ESCA method, this method is suitable only for the fast determination of rough structural information. It should be pointed out, however, that the requirements with regard to quantity and purity of the material are the lowest.

In principle, the three methods provide all the necessary structural information about the nitrogen. However, the outlay can be considerably reduced if information is already indirectly available through the other atoms bonded to the nitrogen. Indirect information of this type is obtainable by the usual spectroscopic methods or *e.g.* from the ^{35}Cl nuclear quadrupole resonance for N—Cl bonds (see Table 2) or the O 1s ESCA spectrum for N—O bonds.

Received: March 22, 1972 [A 916 IE]
German version: Angew. Chem. *84*, 1037 (1972)
Translated by Express Translation Service, London

[1] *E. A. C. Lucken*: Nuclear Quadrupole Coupling Constants. Academic Press, London, New York 1969.

[2] For a review see: *E. F. Mooney* and *P. H. Wilson*, Annu. Rev. NMR Spectrosc. *2*, 125 (1969).

[3] For a review see: *K. Siegbahn et al.*, Ark. Kemi *28*, 257 (1967).

[4] *H. G. Dehmelt* and *H. Krüger*, Naturwissenschaften *37*, 111, 398 (1950); Z. Physik *129*, 401 (1951).

[5] *H. G. Dehmelt*, Z. Physik *130*, 356 (1951).

[6] *C. H. Townes* and *B. P. Dailey*, J. Chem. Phys. *17*, 782 (1949); Phys. Rev. *78*, 346 (1950); J. Chem. Phys. *20*, 35 (1952); *23*, 118 (1955).

[7] *E. G. Brame, Jr.*, Anal. Chem. *43*, 35 (1971).

[8] *H. G. Fitzky*, GIT-Fachz. Lab. *15*, 922, 1100 (1971).

[9] *W. Gordy et al.*: Microwave Spectroscopy. Wiley, New York 1953.

[10] *P. J. Bray* and *R. G. Barnes*, J. Chem. Phys. *27*, 551 (1957); *E. I. Fedin* and *G. K. Semin*, Zh. Strukt. Khim. *1*, 464 (1960); *H. O. Hooper* and *P. J. Bray*, J. Chem. Phys. *33*, 334 (1960).

[11] *E. G. Brame, Jr.*, Anal. Chem. *39*, 918 (1967).

[12] *D. B. Roll* and *F. J. Biros*, Anal. Chem. *41*, 407 (1969).

[13] *H. G. Fitzky*: Colloquium Spectroscopicum Internationale XVI, Heidelberg 1971. Adam Hilger Ltd., London 1971, Vol. 1, p. 64.

[14] *E. Schemp* and *P. J. Bray*, J. Chem. Phys. *49*, 3450 (1968).

[15] *H. G. Fitzky* and *H. Hoyer*, unpublished work.

[16] *W. van Bronswyk*, Struct. Bonding *7*, p. 87. Springer Verlag, Berlin 1970.

[17] *H. Kopfermann*: Kernmomente. Akademische Verlagsgesellschaft, Frankfurt 1956.

[18] *D. Gill et al.*, Rev. Sci. Instrum. *38*, 1588 (1967).

[19] *F. N. H. Robinson*, J. Sci. Instrum. *36*, 481 (1959).

[20] *T. Lakshmi Viswanathan et al.*, Rev. Sci. Instrum. *41*, 477 (1970).

[21] *E. Schemp* and *P. J. Bray*, J. Chem. Phys. *46*, 1186 (1967).

[22] *N. P. Birjukov, M. G. Woronkov*, and *I. A. Safin*: Frequenztabellen der Kernquadrupolresonanz (Russ.). Verlag Chimija, Leningrad 1968.

[23] *V. I. Goldanskii*: The Mössbauer Effect and its Applications in Chemistry. Consultants Bureau, New York 1964.

[24] *S. L. Segel et al.*: Catalog of Nuclear Quadrupole Interactions and Resonance Frequencies in Solids. Iowa State University, 1962, Part I.

[25] DMS-Literaturdienst NMR-EPR-NQR (up to 1968). Verlag Chemie, Weinheim.

[26] *A. Colligiani et al.*, J. Chem. Phys. *52*, 5022 (1970); *A. Matzkanin et al.*, *ibid. 44*, 4171 (1966).

[27] *J. D. Roberts et al.*, J. Amer. Chem. Soc. *86*, 5564 (1964); Proc. Nat. Acad. Sci. USA *51*, 735 (1964).

[28] *E. B. Baker*, J. Chem. Phys. *37*, 911 (1962).

[29] *J. D. Baldeschwieler* and *E. W. Randall*, Proc. Chem. Soc. *1961*, 303.

[30] *E. D. Becker, R. B. Bradley*, and *T. Axenrod*, J. Magn. Resonance *4*, 136 (1971).

[31] *E. D. Becker*, J. Magn. Resonance *4*, 142 (1971).

[32] *N. F. Ramsey*, Phys. Rev. *91*, 303 (1953).

[33] *M. Karplus* and *J. A. Pople*, J. Chem. Phys. *38*, 374 (1963).

[34] *J. E. Kent* and *E. L. Wagner*, J. Chem. Phys. *44*, 3530 (1966).

[35] *A. Saika* and *C. P. Slichter*, J. Chem. Phys. *22*, 26 (1954).

[36] *B. E. Holder* and *M. P. Klein*, J. Chem. Phys. *23*, 1956 (1955).

[37] *D. Herbison-Evans* and *R. E. Richards*, Mol. Phys. *8*, 19 (1964).

[38] *P. Hampson* and *A. Mathias*, Mol. Phys. *11*, 541 (1966).

[39] *M. Witanowski et al.*, J. Amer. Chem. Soc. *86*, 2569 (1964).

[40] *M. Witanowski* and *H. Januszewski*, J. Chem. Soc. *1967*, 1062.

[41] *J. B. Lambert* and *J. D. Roberts*, J. Amer. Chem. Soc. *87*, 4087 (1965).

[42] *G. Olah* and *T. E. Kiovsky*, J. Amer. Chem. Soc. *90*, 4666 (1968).

[43] *G. Olah* and *A. M. White*, J. Amer. Chem. Soc. *90*, 6087 (1968).

[44] *R. J. Chuck, D. G. Gillies*, and *E. W. Randall*, Mol. Phys. *16*, 121 (1969).

[45] *A. K. Bose* and *J. Kugajevsky*, Tetrahedron *23*, 1489 (1967).

[46] *B. Sunners, L. H. Piette*, and *W. G. Schneider*, Can. J. Chem. *38*, 681 (1960).

[47] *A. J. R. Bourn* and *E. W. Randall*, J. Mol. Spectrosc. *13*, 29 (1964).

[48] *R. L. Lichter* and *J. D. Roberts*, J. Amer. Chem. Soc. *93*, 5218 (1971).

[49] *J. D. Ray, L. H. Piette*, and *H. D. Hollis*, J. Chem. Phys. *29*, 1022 (1958).

[50] *W. Beck* and *E. Schuierer*, J. Organometal. Chem. *3*, 55 (1965).

[51] *C. Grundmann* and *J. M. Dean*, J. Org. Chem. *30*, 2809 (1965).

[52] *O. W. Howarth, R. E. Richards*, and *L. M. Venanzi*, J. Chem. Soc. *1964*, 3335.

[53] *M. Shporer, G. Ron, A. Loewenstein*, and *G. Navon*, Inorg. Chem. *4*, 358, 361 (1965).

[54] *B. M. Schmidt, L. C. Brown*, and *D. Williams*, J. Mol. Spectrosc. *2*, 539 (1958).

[55] *R. Bramley, B. N. Figgis*, and *R. S. Nyholm*, J. Chem. Soc. *A 1967*, 861.

[56] *W. Becker* and *W. Beck*, Z. Naturforsch. *25b*, 101 (1970).

[57] *J. P. Hunt, H. W. Dodgen*, and *F. Klanberg*, Inorg. Chem. *2*, 478 (1963).

[58] *A. Mathias*, Mol. Phys. *12*, 381 (1967).

[59] *P. Hampson* and *A. Mathias*, Chem. Commun. *1967*, 371.

[60] *F. W. Wehrli, W. Giger*, and *W. Simon*, Helv. Chim. Acta *54*, 229 (1971).

[61] *G. O. Dudek* and *E. P. Dudek*, J. Amer. Chem. Soc. *86*, 4283 (1964).

[62] *G. O. Dudek* and *E. P. Dudek*, Chem. Commun. *1965*, 464.

[63] *G. O. Dudek* and *E. P. Dudek*, J. Amer. Chem. Soc. *88*, 2407 (1966).

[64] *G. O. Dudek* and *E. P. Dudek*, Tetrahedron *23*, 3245 (1967).

[65] *E. D. Becker, H. T. Miles*, and *R. B. Bradley*, J. Amer. Chem. Soc. *87*, 5575 (1965).

[66] *A. K. Bose* and *J. Kugajevsky*, J. Amer. Chem. Soc. *88*, 2325 (1966).

[67] *J. P. Kintzinger* and *J. M. Lehr*, Chem. Commun. *1967*, 660.

[68] *T. Axenrod et al.*, Chem. Commun. *1968*, 702.

[69] *T. Axenrod et al.*, Tetrahedron Lett. *1968*, 5293.

[70] *T. Axenrod et al.*, Tetrahedron Lett. *1969*, 401.

[71] *T. Axenrod et al.*, Tetrahedron Lett. *1969*, 1397.

[72] *H. Saito, Y. Yoshizawa, Y. Tanaka*, and *K. Nukada*, Tetrahedron Lett. *1971*, 3677.

[73] *Y. Yoshizawa, H. Saito,* and *K. Nukada,* J. Polymer Sci., in press.

[74] *K. Siegbahn et al.:* ESCA: Atomic, Molecular and Solid State Structure Studied by Means of Electron Spectroscopy. Almquist and Wiksell, Uppsala 1967.

[75] *K. Siegbahn et al.:* ESCA applied to free Molecules. North Holland, Amsterdam, London 1969.

[76] *C. Nordling,* Angew. Chem. *84*, 144 (1972); Angew. Chem. internat. Edit. *11*, 83 (1972).

[77] *J. C. Helmer* and *N. H. Weichert,* Appl. Phys. Lett. *13*, 266 (1968).

[78] *C. Nordling, E. Sokolowski,* and *K. Siegbahn,* Phys. Rev. *105*, 1676 (1957).

[79] *Y. Baer, P. F. Heden, J. Hedman, M. Klasson, C. Nordling,* and *K. Siegbahn,* Physica Scripta *1*, 55 (1970).

[80] *Y. Baer, P. F. Heden, J. Hedman, M. Klasson,* and *C. Nordling,* Solid State Commun. *8*, 1479 (1970).

[81] *A. Melera* and *R. Moody,* Lecture, Pittsburgh Conference for Analytical Chemistry and Applied Spectroscopy (1970).

[82] *W. Bremser,* private communication.

[83] *J. J. Jack* and *D. M. Hercules,* Anal. Chem. *43*, 729 (1971).

[84] *P. Finn, R. K. Pearson, J. M. Hollander,* and *W. L. Jolly,* Inorg. Chem. *10*, 378 (1971).

[85] *R. Holm,* GIT-Fachz. Lab. *16*, 12, 112 (1972).

[86] *D. N. Hendrickson, J. M. Hollander,* and *W. L. Jolly,* Inorg. Chem. *8*, 2642 (1969).

[87] *M. Patsch* and *P. Thieme,* Angew. Chem. *83*, 588 (1971); Angew. Chem. internat. Edit. *10*, 569 (1971).

[88] *H. Hagemann* and *K. Ley,* Angew. Chem. *84*, 1063 (1972); Angew. Chem. internat. Edit. *11*, 1012 (1972); *J. Hocker* and *R. Holm,* unpublished data.

[89] *R. Holm,* Angew. Chem. *83*, 632 (1971); Angew. Chem. internat. Edit. *10*, 591 (1971).

Growth Processes due to Reactions in Swellable Cellular Matrixes

By Kuno Wagner and M. Dahm[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

In matrix reactions in swellable cellular matrixes, the solids formed are oriented in space and arranged in the form of cells in strong three-dimensional growth processes. Open-cell, flexible, elastic polyurethanes have a particularly good matrix action. The principle is of general validity, and can be realized with a wide variety of matrixes and reaction types. The dimensional changes, which are always symmetrical, are largely determined by the chemical constitution of the matrix, segment structure, degree of crosslinking, and solvation and hydration behavior. One-component reactions having high rates give sigmoid growth curves and exhibit parallels with growth curves of plant cell walls containing cellulose.

1. Introduction

The development of cellular plastics led at an early date to the application of chemical and physical after-treatments to cellular substrates. Since nearly all high polymers can be converted into cellular materials by appropriate techniques, the number of patents and new patent applications on the modification of existing foams with impregnants, fillers[1], polymers, *etc.* is very large. An example is the preservation of the cavity volume with stiffening of the cell webs by after-treatment and additional crosslinking of the foams with polyisocyanate solutions[2].

One-component and multicomponent reactions on cellular substrates, whose course is reminiscent of plant growth in the phase of non-cell division in elongational growth, form the subject of the present article. We found that cellular substrates (foams)[4] prepared in particular by the diisocyanate polyaddition method[3] are excellent matrixes, with which it is surprisingly easy to produce cellular arrangements of material with formation of new structured spaces. The growth phenomena and dimensional changes observed in the course of these investigations were found in the ion-catalyzed polymerization of formaldehyde[5], and led to an examination of the principles of these phenomena. This work resulted in the recognition of a generally valid principle of the cellular arrangement of matter, which can be applied to any organic cellular substrate and can be realized with any type of reaction from organic or inorganic chemistry. Cell growth and cell expansions are the most important features of the reactions discussed here. The principles of the process have been described, from the standpoint of applications, in the patent literature[5, 6].

Figure 1 shows a Stereoscan photograph of an open-cell, elastic polyurethane matrix, and is intended to provide an introductory indication of the site of the processes discussed here, which consist in the synthesis of organic or inorganic materials in the cell webs, in which the cell webs are greatly extended and these extensions are irreversibly fixed by the solids formed (often with multiple folding of the cell webs). Only then does the surface of the cell webs increasingly become the reaction site. From this moment on, the open-cell character of the substrate can, if desired, be reduced until the cells are completely closed.

[*] Dr. K. Wagner
Wissenschaftliches Hauptlaboratorium der
Farbenfabriken Bayer AG
Dr. M. Dahm
Anwendungstechnische Abteilung der
Farbenfabriken Bayer AG
509 Leverkusen-Bayerwerk (Germany)

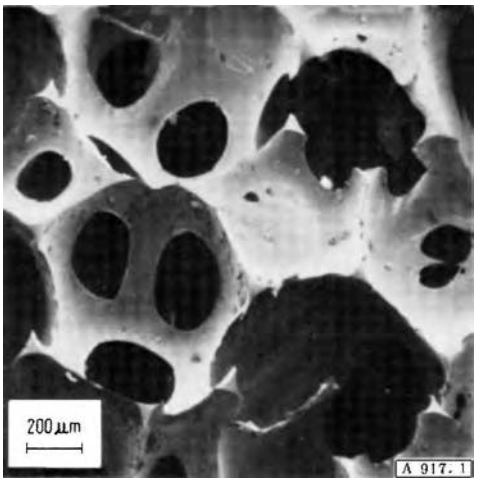


Fig. 1. Cross section through cell webs and cellular spaces of a polyurethane matrix. Stereoscan photograph.

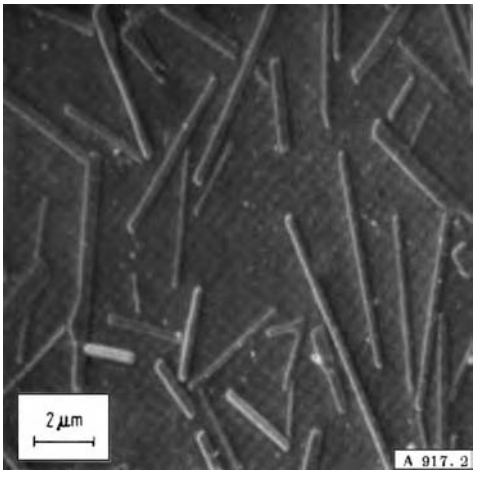


Fig. 2. Formation of polyoxymethylene crystallites on the surface of a cell web during slow growth of the matrix. 3.5 wt.% of polyoxymethylene. Stereoscan photograph.

2. Polymerization of Formaldehyde in Cellular Polyurethanes

We shall first describe the experiment that drew attention to the possibility of preparing homogeneous cellular arrangements of matter in an open-cell, elastic polyurethane matrix.

When gaseous formaldehyde is allowed to act on completely or partly open-cell polyurethane substrates in the presence of catalytic quantities of the tin(II) salt of 2-ethylcaproic acid, polyoxymethylene *(1)* is formed. The polymerizing formaldehyde adapts itself to the existing cell

$$n\ CH_2O\ (\text{gaseous}) \xrightarrow{Sn^{II}} \sim O\text{-}CH_2\text{-}O\text{-}(CH_2O)_{n-2}\text{-}CH_2\text{-}O\sim \quad (1)$$

structure and causes strong three-dimensional extension of the cells. The irreversibly fixed volume extension in extreme cases amounts to about 324% of the starting volume; during this process the material remains completely open-celled. The polyoxymethylenes formed are stabilized at one end to an extent of about 60% by chain termination reactions with NH groups of the matrix, while at the other end they still have hemiacetal groupings, *i.e.* thermally less stable groups. The nitrogen content is the same at all points of the new foam, which has a polyoxymethylene content of about 93 wt.%. Only when the quantity of spatially ordered polyoxymethylene exceeds 93 wt.% does filling of the cell begin, and the growth process comes to a stop.

With the aid of Stereoscan photographs, it is possible to discern the phenomena shown in Figures 2 and 3 in the microscopic and submicroscopic range during the arrangement of the polyoxymethylene in the form of cells. The processes on the cell webs are particularly easy to follow in the period of fast, macroscopically easily measurable growth of the matrix (see Section 7) (Figs. 4 and 5). During the period in which the growth of the matrix is gradually

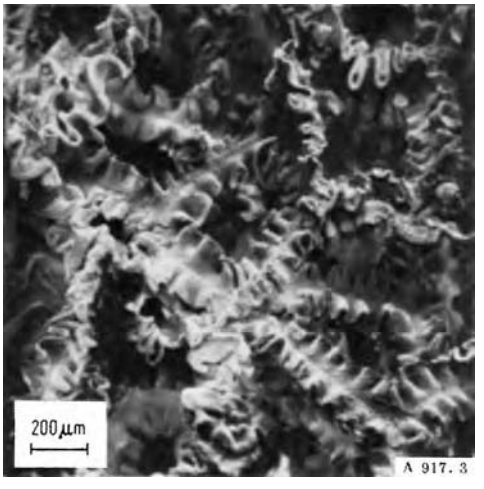


Fig. 3. Multiple folding of cell webs during strong growth. Quantity of polyoxymethylene fixed: 65 wt.%. Stereoscan photograph.

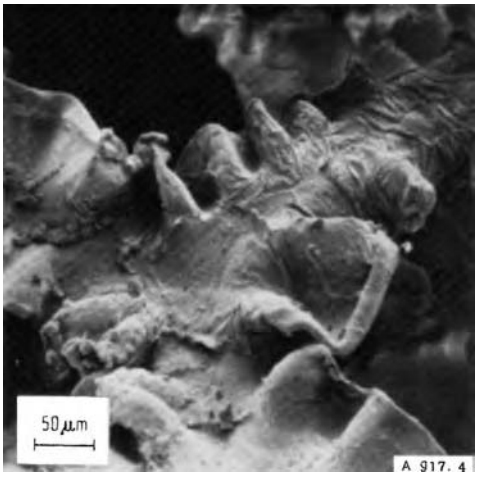


Fig. 4. Folding at crossing points of cell webs during fast growth. Quantity of polyoxymethylene fixed: 65 wt.%. Stereoscan photograph.

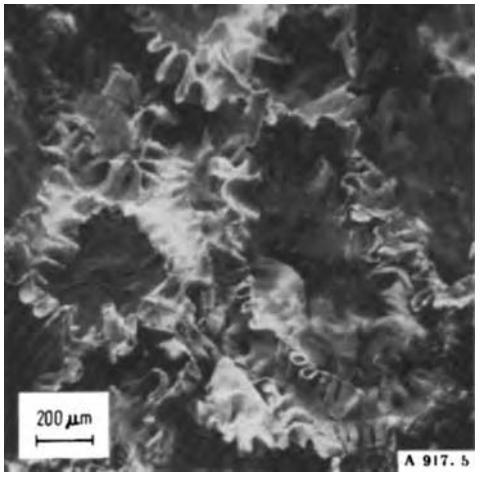


Fig. 5. Symmetrical fold structures on strong growth of the cell webs of the matrix. Quantity of polyoxymethylene fixed: 65 wt.%. Stereoscan photograph.

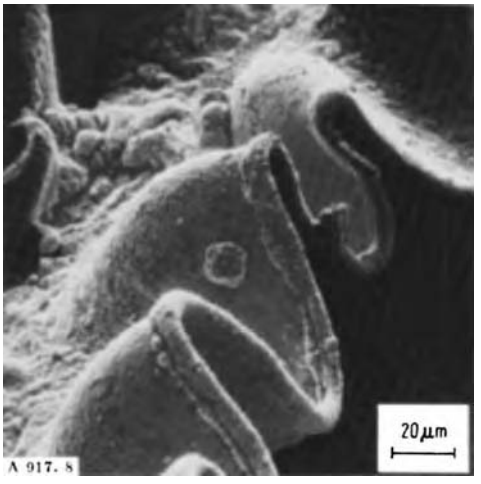


Fig. 8. Part of a sinusoidally folded cell web. Swelling of the marginal zones. Quantity of polyoxymethylene fixed: 88 wt.%. Stereoscan photograph shortly before the start of cell filling.

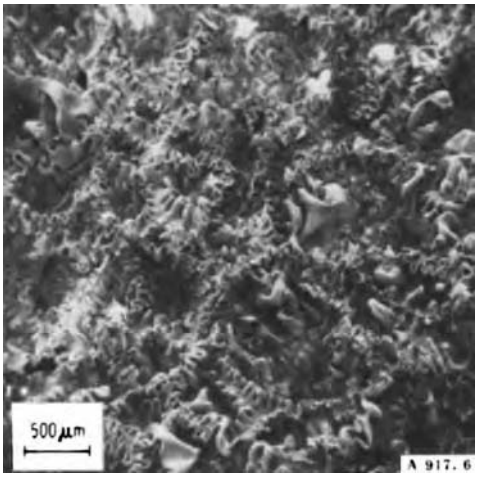


Fig. 6. Folding of cell webs before the start of the period of slow growth. Quantity of polyoxymethylene fixed: 88 wt.%. Stereoscan photograph shortly before the start of cell filling.

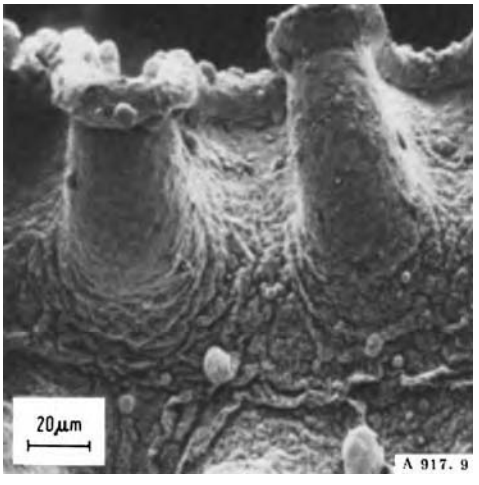


Fig. 9. Vertical view of part of the folded cell web. Quantity of polyoxymethylene fixed: 88 wt.%. Stereoscan photograph shortly before the start of cell filling.



Fig. 7. Folding in part of a cell web and subdivision of primary cellular spaces. Stereoscan photograph shortly before the start of cell filling. Quantity of polyoxymethylene fixed: 88 wt.%.

declining, it is possible to discern the cell structures before filling of the cells begins (Fig. 6). An interesting observation at this stage is the subdivision of primary cellular spaces by folding processes (Fig. 7). Figures 8 and 9 illustrate the extension and folding processes for a small section of a cell web. Both figures clearly show the swelling of the marginal zones of the cell webs, which begins toward the end of the growth period. These cell webs now consist chemically of about 88 wt.% of polyoxymethylene and 12 wt.% of polyurethane, about 60 wt.% of the polyoxymethylene being chemically bonded *via* the NH groups of the matrix. It is instructive to compare the cell webs of the matrix before the start of the reaction (Fig. 1) with the rapidly growing and folding cell webs (Fig. 3) at the same magnification. The multiple folding of the cell webs in the period of rapid growth increases the inner surface of the matrix. Macroscopically, the matrix changes symmetrically in all dimensions, *i.e.* any surfaces and edges always undergo parallel displacements.

Optimum cell extension is achieved when at least one of the reactants is used in the form of a gas or mist. This procedure also allows good control of the evolution and dissipation of the heat of reaction. In principle, however, the swelling and its irreversible fixation can also be achieved

a) with a liquid or gaseous compound that condenses in the foam, with stiffening by reaction with itself,

b) with a liquid, gaseous, or molten compound, with stiffening by reaction with a second compound,

c) with several liquid or gaseous compounds or compounds that crystallize out, with stiffening by reaction of these compounds with one another,

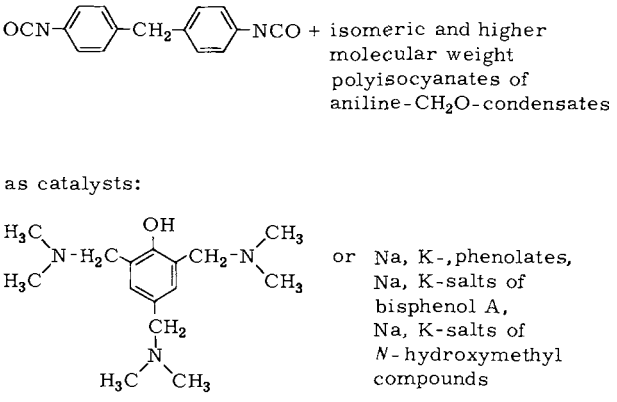
d) with reaction intermediates (oligomers) that have a swelling action and become stiff,

e) with inert organic solvents, with stiffening of the swollen structure by reactive compounds with or without a swelling action.

3. Diisocyanate Polyaddition and Diisocyanate Polymerization in Cellular Polyurethanes

It will now be shown with the aid of selected examples that swelling and irreversible fixation of the resulting structure and volume expansion can be achieved by a wide range of reaction types. In view of the economic importance of polyisocyanate chemistry, the emphasis in this section is placed on isocyanate reactions and connections with the chemistry of monomers that can be polymerized by free-radical or ionic mechanisms.

Reaction type:

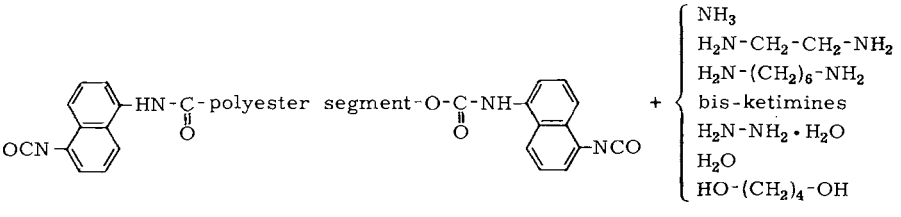


Open-cell, rigid polyisocyanurate foams are formed. Fixed volume increase: 80 to 100%, density 35 to 60 kg/m^3. Foams in which the matrix used accounts for a surprisingly small fraction of the whole can be prepared.

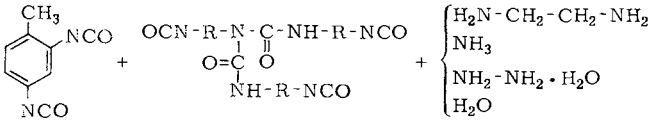
Modifications are possible in this type of reaction with various polyisocyanates, diols, diamines, and masked polyamines, such as polyketimines and poly-Schiff bases. The swelling of the matrix is initiated by the reactant together with perchloroethylene, acetone, or ethyl acetate. The reaction can be initiated by catalysts fixed in the matrix.

Combination foams having particularly high strengths and elasticities are obtained by application of the elastomer synthesis principle (preparation of Vulkollan)[7] to the following matrix reactions:

Reaction type:



Reaction type:



Highly crosslinked, rigid polybiuret polyureas are formed. Fixed volume increase: 100 to 120%, density 30 to 50 kg/m^3.

Another example is the rapid polymerization of isocyanurates in polyurethane matrixes swollen with isocyanates and ethyl acetate.

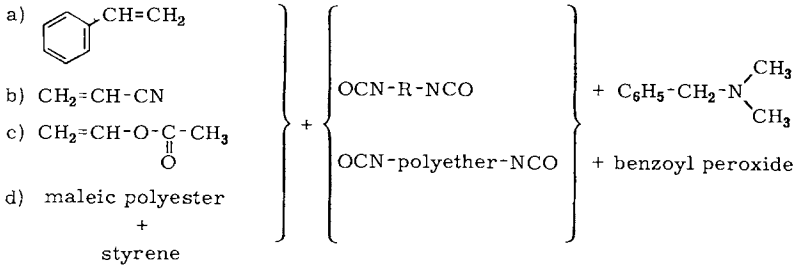
Polyurethane elastomers (soft and hard Vulkollan) are formed in the matrix[8]. Fixed volume increase: 0 to 25%. The preferred reactants here are 1,5-naphthylene diisocyanate, 4,4'-diisocyanatodiphenylmethane, or hexamethylene diisocyanate and chain extenders such as H_2O, ethylenediamine, or NH_3 introduced in the gaseous state.

4. Coupled NCO Polyadditions, NCO Polymerizations, and Vinyl Polymerizations in Cellular Polyurethanes[8]

Tertiary bases such as dimethylbenzylamine are able to accelerate peroxide-initiated vinyl polymerizations or to

cause them to proceed at lower temperatures. The large quantities of heat that are liberated in isocyanate polyadditions and polymerizations can be used to initiate free-radical vinyl polymerizations.

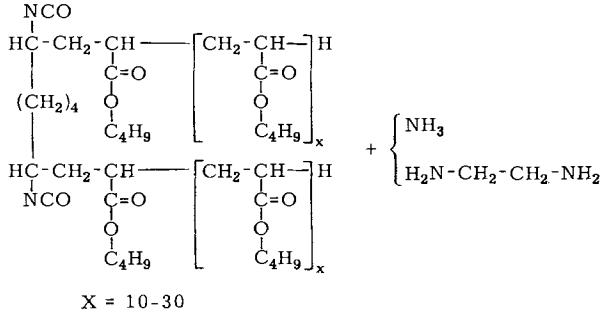
Reaction type:



Elasticized polystyrene foams are formed. Fixed volume increase: 200%. A large number of polyisocyanates and vinyl compounds having a swelling action are also available for this type of reaction. Styrene and maleic acid polyesters are particularly interesting.

Matrix reactions of gaseous ammonia with polyisocyanate telomers[8] based on aliphatic, cycloaliphatic, and araliphatic polyisocyanates[9] containing *e.g.* high contents of grafted butyl acrylate or styrene lead to combination foams with surprising combustion behavior.

Reaction type:

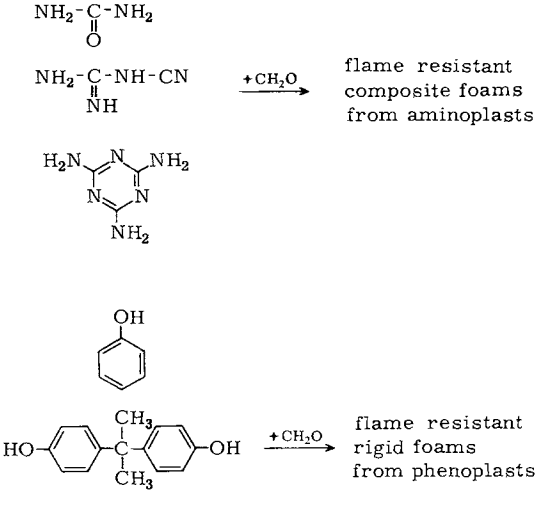


Open-cell, self-extinguishing, light-fast rigid foams are formed. Fixed volume increase: 100%, density: 35 kg/m^3. Contents of only about 28% of butyl acrylate telomers are sufficient, after conversion into polyureas, to make the foam self-extinguishing. The products are light-fast, since the original matrix is completely covered. Similarly, self-extinguishing composite foams can also be prepared from polyisocyanates grafted with large quantities of polystyrene or with polyvinyl acetate. The small extent of surface burning of these foams and the small amount of smoke gas evolved are striking, as is the fact that the effects that can be obtained are distinctly superior to those obtained with vinyl chloride telomers. The thermoplasticity and a certain ratio of the content of vinyl polymer to that of bound urea are more important to these properties than the chlorine content due to the polyvinyl chloride incorporated.

The type of reaction described has some advantages over the free-radical matrix polymerization of unsaturated compounds. Polymerizations of styrene, vinyl acetate, and vinyl chloride proceed slowly and are sensitive to oxygen. The styrene-maleic anhydride polymerization is an interesting matrix reaction because of its rapidity, as is the polymerization of unsaturated polyesters of maleic acid with styrene. Composite foams with high vinyl acetate, vinyl chloride, or acrylate contents can also be obtained in a fast reaction *via* NCO telomers and their reaction with amines.

5. Variation of the Matrix

Substrates with optimum swellability are obtained[10] by the incorporation of segments having maximum solubility in the reactants used or in solutions of the reactants. For example, cellular polyurethanes having a high polyethylene oxide content are strongly to extremely strongly swellable in aqueous solutions. The use of these substances for matrix reactions allows condensation reactions of carbonyl compounds with substances that can form aminoplasts or phenoplasts[11].



The irreversibly fixed volume increase is 150%. The strong swelling of polyurethane foams in aqueous phenol or in phenol-bisphenol A mixtures is surprising. Volume increases of 200% can be achieved by formaldehyde condensation, and up to 300% with incorporated polyacetal seg-

ments. The products are used as soil improvers for the storage of water and plant nutrient salts as well as bactericidal, herbicidal, and fungicidal agents.

5.1. Matrix Reactions with Aggressive Gases

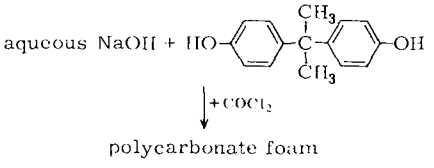
With a suitable procedure, aggressive gaseous components such as phosgene can also be used without discoloration and damage to the matrix and to the resulting composite foam[11].

swelling-components for the matrix:

$$(C_2H_5)_3N + H_2N\text{-}(CH_2)_6\text{-}NH_2 \xrightarrow{+\,COCl_2}$$

open-cell polyurea foam

swelling-components for the matrix:



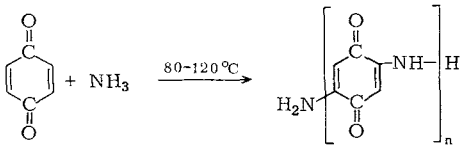
polycarbonate foam

Remarkably soft cellular materials with good feel are obtained with about 40 wt.% of polycarbonates. This is due to the formation of short-chain polycarbonate segments, which react *via* chlorocarbonyl groups with NH groups of the matrix and act as built-in plasticizers.

Dicyanates[11] and diepoxides[11], compounds that can undergo fast Diels-Alder reactions[11], and solutions or latices of high molecular weight substances that can undergo precipitation reactions with crosslinking can also be used for matrix reactions.

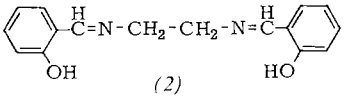
5.2. Heat-Resistant Foams

The extremely high reactivity of benzoquinone or tetrachlorobenzoquinone with ammonia, aromatic polyamines, or polyketimines[11] allows the preparation of graphite-like composite foams, with a volume increase of about 95%.



The matrix component, which corresponds to about 30 wt.%, can be burned off in air. The resulting product is an open-cell foam that is resistant to high temperatures and has a graphite-like luster. Such products, which are obtainable by matrix reactions from quinone, phenoplast, aminoplast, polyacrylonitrile, and polystyrene chemistry, can be used *e.g.* as supports for catalysts.

Matrix reactions leading to a cellular arrangement of ion exchangers, redox systems (quinone-hydroquinone segments) or complexing agents, *e.g.* of the type *(2)*, are also of interest. Reactions of this type may be coupled with the

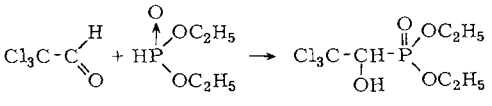


(2)

fixation of cell-filling solids, *e.g.* using cationic or anionic polyurethane dispersions as impregnants and adhesion promoters[12].

5.3. Cellular Arrangement of Low Molecular Weight Organic Substances in Polyurethane Matrixes

Reactions leading to crystalline, low molecular weight substances can also proceed with strong growth phenomena and dimensional changes if one reactant has a swelling action on the matrix. Thus numerous bactericidal, herbicidal, and insecticidal substances can be arranged in the form of cells. In the case of the matrix reaction volume increases of about 130% can be irreversibly fixed[13].



6. Inorganic Matrix Reactions

The dust-free cellular arrangement of aluminum oxide, titanium oxide, polymeric silica, or asbestos-like, fibrous high polymers is possible by the use of matrixes that are strongly swollen in water, *i.e.* of polyurethanes having high contents of polyethylene oxide or polyacetal. An interesting matrix reaction in this connection is the charging of the substrate with water-soluble sodium silicates followed by gassing with carbon dioxide or phosgene and ammonia, since this method allows a very uniform production of free silica, which condenses in the matrix to form rings, chain molecules, and sheet structures. For the completely dust-free arrangement of the macromolecular silica, the simultaneous use of water-dispersible latices, particularly of anionic polyurethane dispersions[12], as adhesion promoters can be recommended.

7. Sigmoid Growth Curves in Matrix Reactions

A number of matrix reactions that proceed rapidly, *e.g.* reactions of formaldehyde, lead to dimensional changes that are always symmetrical but vary with time. A plot of the linear growth of a cellular polyurethane matrix at a

constant CH_2O gas pressure of 760 mm as a function of time gives a sigmoid growth curve (Fig. 10)[5].

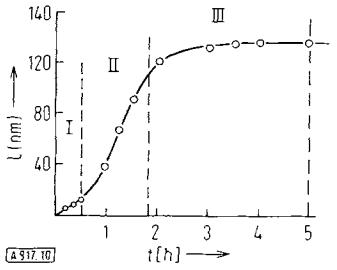


Fig. 10. Linear (L) growth of a cellular polyurethane matrix as a function of time in the formation of polyoxymethylene. Dimensions at $t = 0$: 20 cm × 7 cm × 0.5 cm.

This shape of curve arises as follows[13]. The slow start of growth (I) is due to diffusion of the formaldehyde into the cell webs of the matrix and the slow start of the polymerization of formaldehyde after an "equilibrium concentration" of formaldehyde has been reached in the matrix. This concentration is around 0.9 wt.% of formaldehyde. The fast polymerization of formaldehyde begins slightly above this concentration, the swelling being irreversibly fixed. Rapid growth is recorded in this phase (II). When the growing matrix reaches a polyoxymethylene content of about 60 wt.%, the swelling slows down considerably. The growth slowly declines (III).

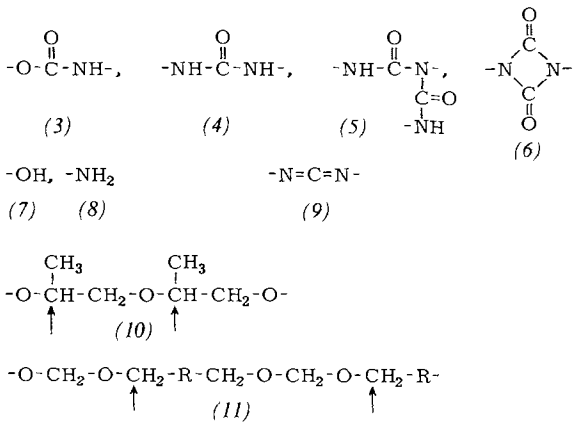
8. Matrix Reactions as Analytical Aids

To give some idea of the possibilities for the separation of substances, let us first divide the matrix reactions described into two groups. Group 1 comprises reactions in which the solids formed do not react with active centers of the matrix. Group 2 comprises reactions in which the matrix, *via* its active centers, enters into reactions with crosslinked or uncrosslinked solids formed (condensations, polyadditions, polymerizations, grafting).

Group 1 includes the crystallization of sugars, amino acids, etc., *i.e.* of nutrients for biological reactions, in the matrix. These nutrients, possibly together with gelatins, can be fixed over a large area without dusting, and can be easily exposed to oxygen or kept under anaerobic conditions.

On subsequent dissolution of such mixtures of solids out of the matrix, the smaller molecules accumulate in the matrix. By the choice of extracting agents that have a strong or moderate swelling action, one can achieve separation effects[13] that probably lead in many cases to results similar to those obtained in gel chromatography.

Solids formed by reactions of Group 2, which are not themselves crosslinked, and which are covalently bonded to the matrix, must have reacted with one or more of the groups *(3)* to *(11)* of the substrate *e.g.* in polycondensations, polyadditions, polymerizations, or grafting reactions. The arrows in *(10)* and *(11)* indicate points where groups can be grafted by free-radical transfer.



By dissolving out the unbound part of the material, it is possible to obtain information *e.g.* about the extent to which the active sites of the matrix have reacted, graft yields, molecular weights of the substances fixed to the matrix, *etc.* The question of the possibility of grafting the matrix with a vinyl monomer can also be clarified.

9. Closing Remarks

The described principle for the cellular arrangement of matter is generally valid and by no means necessitates the use of crosslinked matrixes. For uncrosslinked matrixes one uses reactants and solvents that are "poor solvents", and the collapse and dissolution of the cellular matrix can thus be avoided. In many cases, particularly in polyurethane, polypeptide, polyamide, and cellulose chemistry, groups and segments that tend to form hydrogen bonds can assume the role of crosslinking sites (physical crosslinking). Matrixes of this type behave as highly crosslinked systems in swelling processes with moderately solvating reactants.

The use of microporous films or membranes as cellular matrixes also leads to dimensional changes that can be irreversibly fixed. Specific modification of the properties of membranes is possible in this way, interest here being centered on microporous films and membranes of anionic and cationic polyurethane ionomers. Swellable nonwoven fabrics made from natural and synthetic materials can also be used as matrixes.

We are grateful to Professor Holtschmidt and Professor Ley for their support of this work, to Drs. Piechota, Patzelt, von Gyzicki, and Rothermel for discussions on questions of applications, to Herr Horacek for processing studies, to Dr. Hentze for the measurements of heats of swelling and of reaction, and to Dr. Holm for the Stereoscan photographs.

Received: April 24, 1972 [A 917 IE]
German version: Angew. Chem. *84*, 1001 (1972)
Translated by Express Translation Service, London

[1] *F. W. A. Kurz*, Brit. Pat. 1054421 (1964).
[2] *N. H. Stark*, DBP 1224033 (1962).
[3] *O. Bayer et al.*, DRP 728981 (1937); Angew. Chem. *60*, 257 (1948).
[4] Further developments of foams on the basis of the fundamental patents of *A. Höchtlen* and *W. Droste* [DBP 913474 (1941)] and of *K. Zaunbrecher* and *H. Barth* [DBP 936113 (1942)].

[5] *K. Wagner*, DOS 1911644 (1969).
[6] *K. Wagner et al.*, DOS 1911643 (1969); 1911645 (1969); 1953347 (1969); 2037613 (1970).
[7] *O. Bayer* and *E. Müller*, Angew. Chem. *72*, 934 (1960); *E. Müller*, Kaut. Gummi, Kunstst. *18*, 67 (1965).
[8] *K. Wagner* and *M. Dahm*, DOS 1911645 (1969).
[9] *K. Wagner* and *W. von Bonin*, DOS 1720747 (1967).
[10] *K. Wagner* and *M. Dahm*, unpublished.
[11] *K. Wagner*, DOS 1953347 (1969).
[12] *M. Dahm et al.*, DOS 2031160 (1970).
[13] *K. Wagner*, unpublished.

The Chemistry of Phenylcyclobutenediones

By Walter Ried and Arthur H. Schmidt[*]

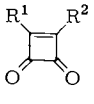
Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

Phenylcyclobutenediones are easily obtainable and very stable. Depending on the nature of the substituent R in position 3, they may be formally regarded as vinylogous carboxylic acid derivatives (R = halogen, OCH_3, OH, SH) or as α,β-unsaturated diketo compounds (R = H, alkyl, aryl). Their behavior in reactions justifies this approach. Ring contraction, ring expansion, and ring cleavage reactions are described.

1. Introduction

Investigations on cyclobutenedione *(1)*, which has been known in the unsubstituted form for only a short time[1], have been concerned with three characteristic derivatives:

1. phenylcyclobutenedione *(2)*,
2. benzocyclobutenedione *(3)*,
3. squaric acid *(4)*.



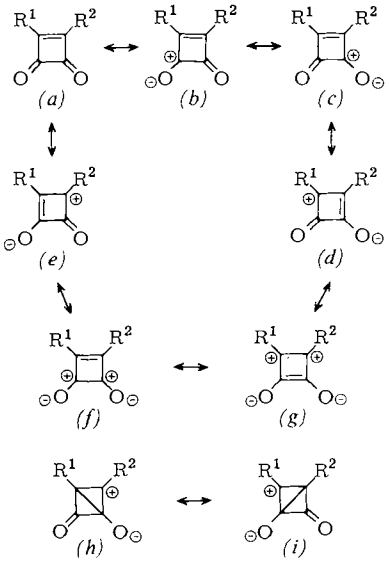
(1), $R^1 = R^2 = H$
(2), $R^1 = C_6H_5$, $R^2 = H$
(3), $R^1 + R^2 = -CH=CH-CH=CH-$
(4), $R^1 = R^2 = OH$
(5), $R^1 = R^2 = C_6H_5$
(6), $R^1 = O^{\ominus}$, $R^2 = H$

Since reviews on syntheses and reactions of squaric acid[2, 3] and of benzocyclobutenedione[4, 5] have recently been published, our attention will be focused here on the phenylcyclobutenediones[6].

2. Stability of Cyclobutenediones

Simple LCAO-MO calculations indicate that cyclobutenedione *(1)* should have a delocalization energy of 1.24 β[7].

Depending on the substituents in positions 3 and 4, this value increases to 3.68 β for phenylcyclobutenedione *(2)* and to 6.03 β for 3,4-diphenylcyclobutenedione *(5)*. The ground state of the cyclobutenediones can accordingly be described by the resonance structures *(a)* to *(g)*.



If the formulas *(h)* and *(i)* are also taken into account, further stabilization should result from electronic cross-ring interaction between the orbitals of the carbon atoms in the 1,3 and 2,4 positions. The delocalization energy of cyclobutenedione *(1)* then increases from 1.24 β to 1.99 β[8].

[*] Prof. Dr. W. Ried and Dr. A. H. Schmidt [**]
Institut für Organische Chemie der Universität
6 Frankfurt/M., Robert-Mayer-Strasse 7—9 (Germany)
[**] Present address: Department of Chemistry, Columbia University New York, N. Y. 10027 (USA)

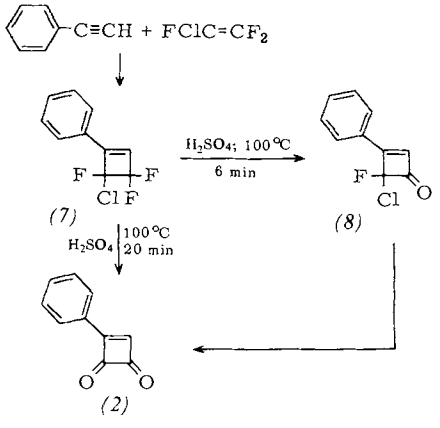
and that of dioxocyclobutenolate *(6)*[9] from 6.11 β to 6.94 β[7].

Since all data on the ring strain of the cyclobutenediones is associated with great uncertainty, the values for their resonance energy can be given only very approximately. Thus a value of between 31 and 60 kcal/mole has been suggested for phenylcyclobutenedione *(2)*[7].

3. Synthesis of Simple Phenylcyclobutenediones

3.1. Phenylcyclobutenedione

The first cyclobutenedione, *i.e.* phenylcyclobutenedione *(2)*, was prepared by *J. D. Roberts et al.*[7, 10] by cycloaddition of chlorotrifluoroethylene to phenylacetylene and hydrolysis of the resulting 4-chloro-3,3,4-trifluoro-1-phenylcyclobutene *(7)* with sulfuric acid (reaction temperature: 100 °C; contact time: 20 minutes). Phenylcyclobutenedione *(2)* is obtained by this method in the form of yellow crystals in a yield of 86%.

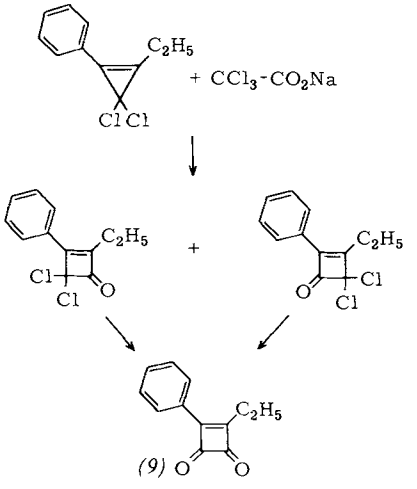


When *(7)* is hydrolyzed for a short time (6 minutes) with sulfuric acid, 4-chloro-4-fluoro-3-phenylcyclobutenone *(8)* can be intercepted. The action of sulfuric acid on *(8)* then leads to *(2)*[7].

Other methods for the preparation of *(2)* are based on the same synthetic scheme. Thus cycloaddition of a perhalogenated ethylene[11] to phenylacetylene leads to tetrahalogenated phenylcyclobutenes, which are subjected to acid hydrolysis either immediately[7] or after conversion into dihalogenated phenylcyclobutenones[7, 12] or into substituted phenylcyclobutenes[13].

Cyclobutenediones substituted on the phenyl ring [3,3'-(1,4-phenylene)dicyclobutene-1,2-dione[14], 4-nitrophenylcyclobutenedione, 4-methoxyphenylcyclobutenedione[15]] and cyclohexenylcyclobutenedione[16] have also been prepared on the basis of the synthesis of *(2)*. The reaction of cyclohexenylcyclobutenedione with an equimolar quantity of bromine results in the aromatization of the cyclohexenyl residue, so that small quantities of *(2)* are formed in addition to unidentified products[16].

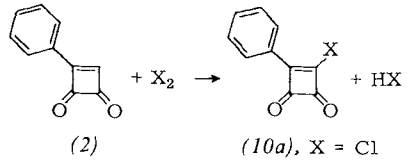
Other phenylcyclobutenediones were obtained in the same way as *(2)* by acid hydrolysis of dihalogenated phenylcyclobutenones and tetrahalogenated phenylcyclobutenes. Phenylcyclobutenediones can also be obtained by substitution reactions of *(2)* and its derivatives. As is shown by the synthesis of 3-ethyl-4-phenylcyclobutenedione *(9)*, dihalogenated phenylcyclobutenones can be obtained in moderate yields by the action of excess sodium trichloroacetate on dihalocyclopropenes or acetylenes[17, 18].



Tetrahalogenated arylcyclobutenes can be prepared by the reaction of perfluorocyclobutene or 1,2-dichlorotetrafluorocyclobutene with aryllithium[19, 20] or aryl Grignard compounds[20, 21]. Tetrafluoro-1,2-diphenylcyclobutene obtained in this way was used for the synthesis of 3,4-diphenylcyclobutenedione *(5)*[22].

3.2. Derivatives of Phenylcyclobutenedione

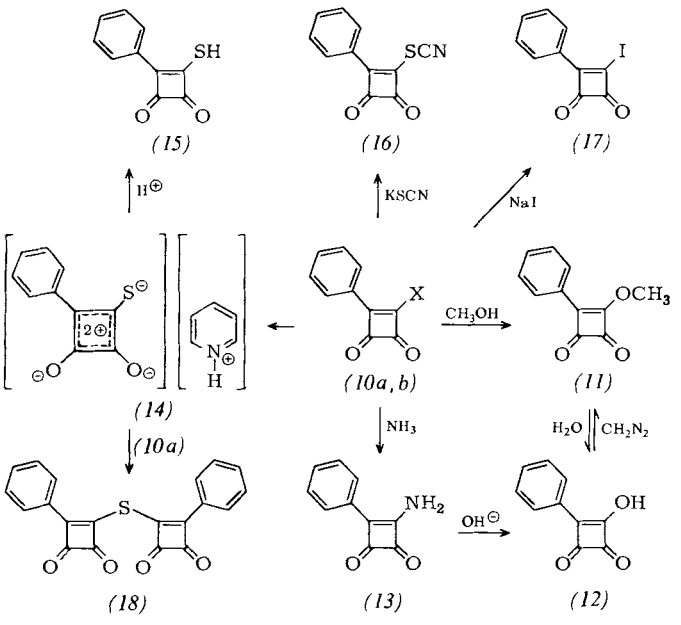
A striking property of phenylcyclobutenedione *(2)* is the ease with which it can be halogenated in glacial acetic acid. The chloro and bromo derivatives *(10a)* and *(10b)* are formed with elimination of hydrogen halide.



(2) *(10a)*, X = Cl
(10b), X = Br

No corresponding reaction has been observed in CCl_4. This suggests that the solvent takes part in the reaction. Since all attempts to intercept intermediates have been unsuccessful, it is not possible to decide whether the halogen is introduced by an addition-elimination step or by direct electrophilic attack[7].

(10a) and *(10b)* are characterized by high reactivity. Their reactions with methanol, water, and ammonia yield the derivatives *(11)*, *(12)*, and *(13)* respectively.



The action of an acetone solution of NaI on bromophenylcyclobutenedione *(10b)* leads to the iodine compound *(17)*[7]. We obtained the thiocyanato derivative *(16)* in a similar manner[23]. The synthesis of the thiol *(15)* was achieved only recently[24]. The path followed leads *via* the pyridinium salt *(14)*, from which *(15)* can be liberated with acids. The reaction of *(14)* with *(10a)* yields the sulfide *(18)*.

4. Physical Properties

4.1. Solubility

The phenylcyclobutenediones *(2)*, *(10a)*, *(10b)*, *(11)*, *(17)*, *(16)*, *(15)*, *(12)*, and *(13)* show a pronounced lightening in color in this order. Whereas *(2)*, *(10a)*, and *(10b)* are deep yellow, *(12)* and *(13)* form white crystals. The compounds *(2)*, *(10a)*, *(10b)*, and *(17)* dissolve readily in the common organic solvents, and *(12)* is also readily soluble in water. The thiol *(15)* and the thiocyanate *(16)* are moderately soluble, whereas *(13)* is practically insoluble in organic solvents. However, *(13)* can be satisfactorily dissolved with concentrated sulfuric acid or boiling glacial acetic acid.

4.2. Acidity

As a vinylogous carboxylic acid, *(12)* is unusually acidic. Its pK_a value is 0.37[7], which is higher than the values for picric acid (0.71[25]) and for squaric acid *(4)*[26,27]. Table 1 shows the pK_a values of some hydroxycyclobutenediones.

Table 1. pK_a values of some hydroxycyclobutenediones.

	pK_a	Ref.
(12)	0.37 ± 0.04	[7]
(2), $R^1 = p\text{-}CH_3OC_6H_4$, $R^2 = OH$	2.05	[20]
(2), $R^1 = CH_3$, $R^2 = OH$	0.69 ± 0.03	[28]
(4)	1; 2.2	[26]
	1.5; 2.93	[20]

4.3. Spectra

A reliable analytical detection of the phenylcyclobutenediones is possible with the aid of their IR spectra. The two carbonyl groups give strong absorptions in the region between 1800 and 1740 cm^{-1}, which are characteristic of the stretching vibrations of carbonyl functions in four-membered ring systems. The conjugated C=C double bond absorbs at about 1600 cm^{-1}, while the C=C vibrations of the phenyl ring appear in the region between 1550 and 1450 cm^{-1}. The CH deformation vibrations of the monosubstituted phenyl residue, as expected, are found at 740 and 690 cm^{-1}.

The ^{1}H-NMR spectrum of *(2)* contains the following signals[29]: $\delta = 7.3$ to 7.6 ppm (3 H; M), $\delta = 7.8$ to 7.9 ppm (2 H; M), $\delta = 9.45$ ppm (1 H; S). The position of the signal for the olefinic four-membered ring proton corresponds to that of an aldehyde proton[30]. The ^{1}H-NMR spectra of other phenylcyclobutenediones have been described by *J. E. Thorpe*[31].

The UV spectra of the phenylcyclobutenediones in ethanol show a broad absorption band with a maximum in the region of 280 to 330 nm. In apolar solvents (isooctane), the absorption band splits into a principal band and a small secondary band or shoulder. The phenylcyclobutenediones have no absorption in the visible region; the yellow color of *(2)*, *(10a)*, *(10b)*, and *(11)* is explained by the strong spread of the principal UV band into the visible region[7].

5. Reactions of the Phenylcyclobutenediones

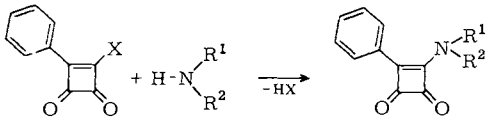
Whereas *(10)*, *(11)*, and *(13)*, as vinylogous carboxylic acid derivatives, react mainly with substitution, *(2)* and *(12)* exhibit great versatility in their reactions. In addition to the reaction of *(2)* with halogens, which was mentioned above, additions of nucleophiles and condensations have also been observed. The products may be stable and isolable, or they may react further with expansion, cleavage, or contraction of the four-membered ring.

5.1. Substitution Reactions

5.1.1. With Amines and Hydrazines

The reaction of *(10a)* and *(10b)* with aliphatic[32] and aromatic amines[33] leads smoothly to the vinylogous amides *(19)* (Method a).

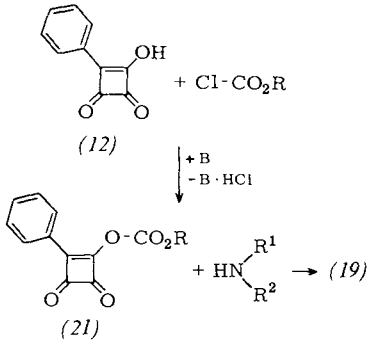
(11) reacts similarly with amines[31,34]. Its reaction with hydrazines also allows the synthesis of vinylogous hydrazides *(20)*[35] (Method b). The "mixed anhydrides" *(21)*,



(10a), X = Cl
(10b), X = Br
(11), X = OCH_3

(19)
(20), $R^1 = NR^3R^4$

which are obtainable from *(12)* and alkyl esters of chlorocarbonic acid, can also be used for the preparation of *(19)*[36] (Method c). Their use not only allows the reaction to be carried out under extremely mild condition but also



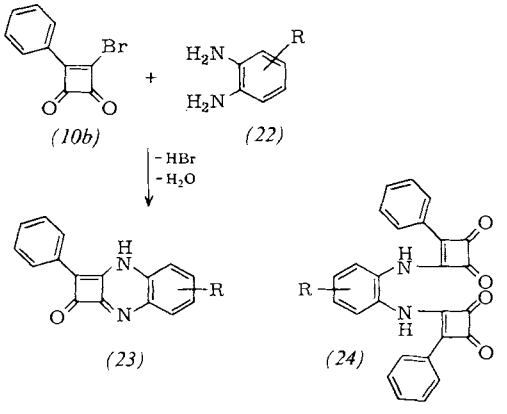
(12)

(21)

offers great flexibility with regard to the nucleophile[36]. Some amides *(19)* and hydrazides *(20)* prepared by various methods are listed in Table 2.

Table 2. Examples of amides *(19)* and hydrazides *(20)*.

R^1	R^2	M. p. (°C)	Yield (%)	Method	Ref.
H	H	282–283 (dec.)	82	a	[7]
CH_3	H	267–269	100	a	[32]
C_2H_5	H	214–216	100	a	[32]
CH_2—C_6H_5	H	235–236	86	a	[32]
cyclo—C_6H_{11}	H	190–192	51	c	[36]
C_6H_5	H	252	56	a, c	[33, 36]
4-Cl—C_6H_4	H	224	92	a	[33]
4-CH_3O—C_6H_4	H	190	41	a	[33]
CH_3	CH_3	133–134	75	b	[31]
C_2H_5	C_2H_5	84–85	51	b	[31]
CH_2—C_6H_5	CH_2—C_6H_5	88–89	30	b	[31]
C_6H_5	CH_3	200	34	a, b	[33, 31]
C_6H_5	C_2H_5	176	32	a	[33]
C_6H_5	C_4H_9	95	20	a	[33]
$N(CH_3)_2$	H	151–154	83	b	[35]
Piperidyl	H	217–218	79	b	[35]
NH—SO_2—C_6H_4—CH_3-(1,4)	H	231–232	43	b	[35]



(10b) *(22)*

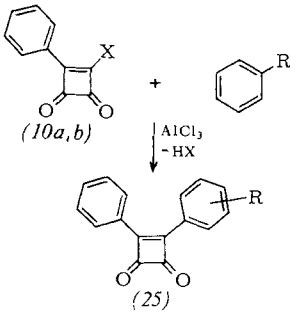
(23) *(24)*

The reaction of the halophenylcyclobutenediones *(10)* with amines was also extended to *o*-phenylenediamines *(22)*. The products were cyclobuta[*b*]quinoxalines *(23)*[37]. It was possible to show that the most strongly basic amino group of the component *(22)* always attacks position 3 of the bromo compound *(10b)*, and the position of the substituent R in the quinoxalines *(23)* is fixed in this way. Only with symmetrical *o*-phenylenediamines were compounds of the type *(24)* formed as by-products.

For the reaction of the phenylcyclobutenediones *(10)* to *(12)* with aziridine, see Ref. [32, 38].

5.1.2. With Aromatic Compounds

An elegant method for the preparation of arylphenylcyclobutenediones *(25)* is based on the reaction of *(10)* with aromatic compounds in the presence of molar quantities of aluminum chloride[2, 39].



(10a,b) *(25)*

The reaction conditions are the same as for a Friedel-Crafts acylation with acyl halides. As can be seen from Table 3, wide variation of the aromatic component is possible. The reaction can also be carried out with heterocycles that possess aromatic character, such as thiophene.

Table 3. Arylphenylcyclobutenediones *(25)*.

R	M. p. (°C)	Yield (%)
H	98	65
4-CH_3	138.5	48
2,4-$(CH_3)_2$	127	54
4-F	168	67.5
4-Cl	157	67
4-Br	152	32
4-OCH_3	144	77
4-$N(CH_3)_2$	177	5

5.1.3. With Electron-Rich Olefins

The logical extension of the reactions described in Sections 5.1.1 and 5.1.2 to electron-rich olefins (enamines, ketene aminals, ketene acetals) leads in the presence of an equimolar quantity of triethylamine to the phenylcyclobutenediones *(26)*[40] (Table 4).

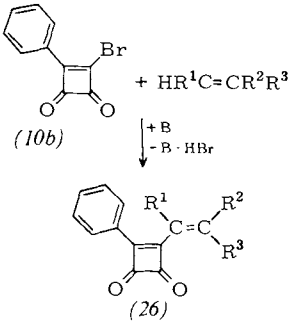
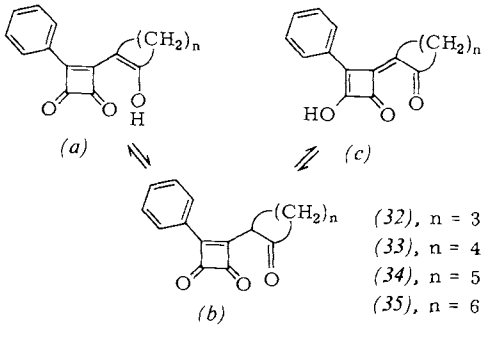


Table 4. Phenylcyclobutenediones of the type *(26)*.

	R¹	R²	R³	M. p. (°C)	Yield (%)
(27)	C_6H_5	Piperidyl	H	212–213	47
(28)		$-(CH_2)_3-$	Morpholino	160–162 (dec.)	65
(29)		$-(CH_2)_4-$	Morpholino	136–138	56
(30)		$-(CH_2)_5-$	Morpholino	146–148	65
(31)		$-(CH_2)_6-$	Morpholino	167–168	46

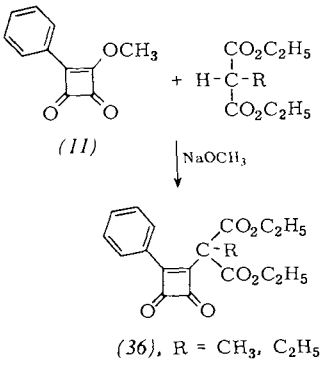
The configuration of the phenylcyclobutenediones of the type *(27)* has been established by NMR spectroscopy. The cyclobutenyl and the piperidyl residues were found to be *trans* to each other[40].

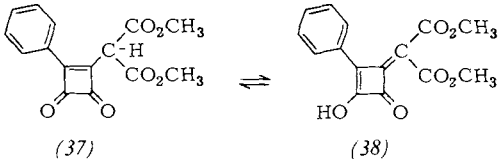
The compounds *(28)* to *(31)* can be readily hydrolyzed with hydrochloric acid to *(32)* to *(35)*. The equilibrium between the forms *(a)* to *(c)* favors the form *(a)* in *(32)* ($n=3$), while the keto form *(b)* is favored in *(33)* to *(35)* ($n=4$—6). The occurrence of the cyclobutenol *(c)* has not been observed in any case.

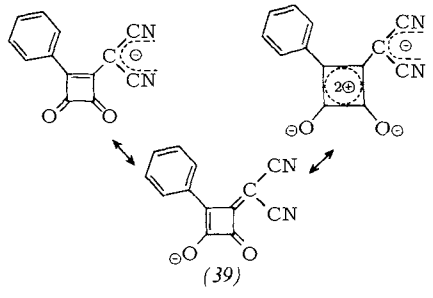


5.1.4. With Carbanions

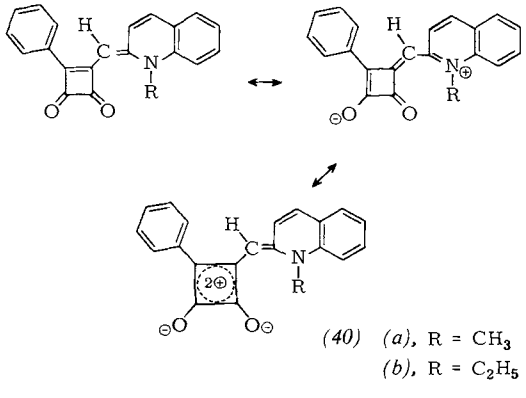
The reactions of methoxyphenylcyclobutenedione *(11)* with active-methylene compounds in the presence of alkalis are particularly interesting[41]. Whereas *(11)* reacts with substituted malonic esters to form the 3-alkyl-4-phenylcyclobutenediones *(36)*, we obtained the hydroxyphenylcyclobutenone *(38)* with diethyl malonate; this result points to a displacement of the equilibrium between the phenylcyclobutenedione *(37)* and its enol form *(38)* in favor of the latter. Under the same conditions, the reaction with malonodinitrile leads to the anion *(39)*.







We obtained compounds having a similar mesomeric four-membered ring system in the reaction of *(11)* with quinaldinium iodides.



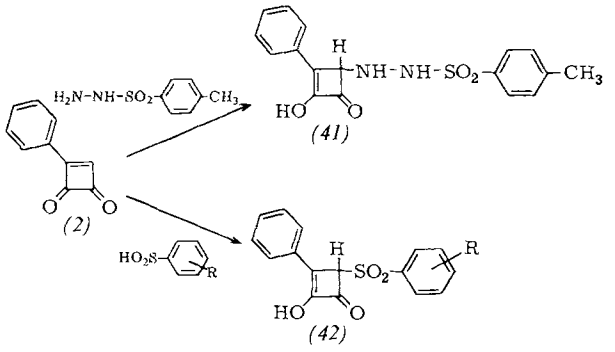
The strong contribution of limiting resonance structures to the ground state of the compounds *(40a)* and *(40b)* can be deduced from their properties. Unlike the phenylcyclobutenediones *(36)*, they are practically insoluble in the common organic solvents. They are also characterized by deep colors and unusually high decomposition points, and are closely related to the dyes synthesized from diethyl squarate and pyridinium, quinolinium, and benzothiazo-

lium iodides[42], though the latter have similar substituents in positions 3 and 4.

5.2. Addition Reactions

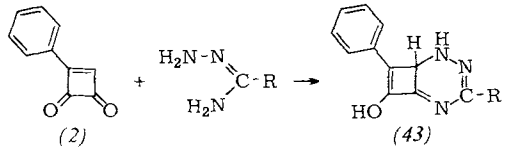
5.2.1. With Tosylhydrazine and Sulfinic Acids

The possibility of additions to phenylcyclobutenedione *(2)* with formation of cyclobutenols is illustrated by the reaction with tosylhydrazine. Instead of tosylhydrazone, the addition product *(41)* was isolated[43].



Phenylcyclobutenedione *(2)* reacts in a similar way with arenesulfinic acids with formation of 4-arenesulfonylcyclobutenols *(42)*[44] and parallels the aldehydes[45] and quinones[46] in its behavior.

The reaction of phenylcyclobutenedione *(2)* with amidrazones includes a condensation step and addition to the four-membered ring system[43].



5.2.2. With Aromatic Compounds

Aromatic compounds add readily to phenylcyclobutenedione *(2)* in the presence of an equimolar quantity of aluminum chloride. It may be assumed that the complex *(44)*, which is a strong electrophile, is formed as an intermediate[47].

Some 3,4-diaryl-2-hydroxy-2-cyclobuten-1-ones *(45)* are listed in Table 5.

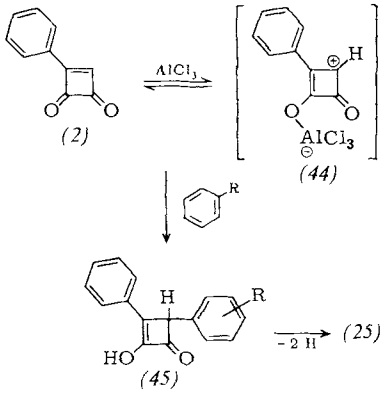


Table 5. 3-Aryl-4-phenyl-2-hydroxy-2-cyclobuten-1-ones *(45)*.

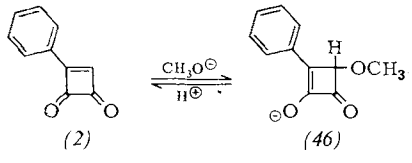
R	M. p. (°C)	Yield (%)
H	198	95
4-CH_3	188	85
2.4-$(CH_3)_2$	191	91
4-F	163	85
4-Cl	172	89
4-Br	175	61
4-OCH_3	198	80
4-$N(CH_3)_2$	220	74

The nucleophilic strength of the aromatic compound is important to the reaction conditions. Weakly nucleophilic aromatic compounds (benzene, halobenzene) are added at boiling point in the absence of solvents, while more strongly nucleophilic aromatic compounds (methoxybenzene) add at lower temperatures in 1,2-dichloroethane. Dialkylanilines can react even in boiling glacial acetic acid[33]. Active-methylene compounds of the malonic acid type have been added to *(2)* in the presence of an equimolar quantity of aluminum chloride[48].

The diarylhydroxycyclobutenones *(45)* can be oxidized with chlorine, bromine or *N*-bromosuccinimide in high yields to form arylphenylcyclobutenediones *(25)*[47], whose preparation by a Friedel-Crafts reaction was described in Section 5.1.2.

5.2.3. With Carbanions

On addition of an equimolar quantity of sodium methoxide to a methanolic solution of phenylcyclobutenedione *(2)*, the equilibrium *(2)* ⇌ *(46)* is established[49].



On the basis of this observation, alkylhydroxyphenylcyclobutenones *(47)* have been obtained from *(2)* and carbanions after the fashion of a Michael addition[48] (see Table 6).

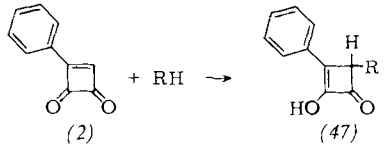
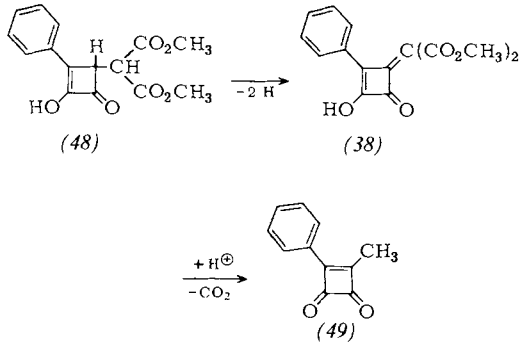


Table 6. Alkylhydroxyphenylcyclobutenones *(47)*.

R	M. p. (°C)	Yield (%)
$C(CO_2C_2H_5)_2CH_2C_6H_5$	174	38
$C(CO_2C_2H_5)_2C_2H_5$	127	30
$C(CO_2CH_3)_2H$	149	54

The hydroxycyclobutenones *(47)* are comparable to the compounds *(45)* in their properties and reactivity. Surprisingly, however, the hydroxycyclobutenone system is retained on oxidation of *(48)*; the product formed is 2-

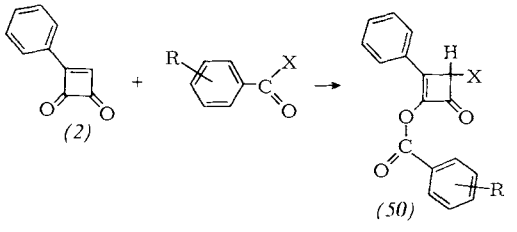
[bis(methoxycarbonyl)methylene]-4-hydroxycyclobutenone *(38)*[41] (see Section 5.1.4), whose hydrolysis and decarboxylation leads to 3-methyl-4-phenylcyclobutenedione *(49)*[50].



(48) *(38)* *(49)*

5.2.4. With Aroyl Halides

The action of aroyl halides on phenylcyclobutenedione *(2)* results in aroylation of the carbonyl group adjacent to the phenyl residue to form the 2-aroyloxy-4-halo-3-phenyl-2-cyclobuten-1-ones *(50)*[51], whose constitution has been demonstrated chemically and spectroscopically as follows:



(2) *(50)*

a) When sulfuric acid is allowed to act for a short time on *(50)*, X = Cl, R = H, *(2)* is formed again, *i. e.* the compound contains a four-membered ring.

b) The bands at 1775 cm^{-1} (with a shoulder at 1800 cm^{-1}) and 1625 cm^{-1} in the IR spectrum of *(50)*, X = Cl, R = H, can be interpreted as the C=O and C=C stretching vibrations of a cyclobutenone system. The UV spectrum (λ_{max} = 294 nm; ε_{max} = 24895 in acetonitrile) also points to a cyclobutenone.

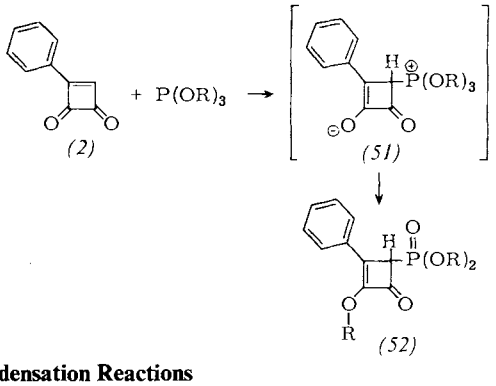
c) The ^{1}H-NMR spectrum of *(50)*, X = Cl, R = H, shows a multiplet at δ = 7.4 to 8.3 (10 H) and a singlet at δ = 5.6 (1 H). The position of the singlet is characteristic of an "allyl proton" in the cyclobutenone system[52, 53].

The nature of the halogen X in the aroyl halides determines how the reaction proceeds. Whereas no reaction takes place with benzoyl bromide and aroyl chlorides, the reaction with benzoyl iodide is complete after a short time. However, aroyl chlorides and aroyl bromides also add smoothly to *(2)* in the presence of Lewis acids[54].

The cyclobutenones *(50)*, which are in the form of white to yellowish-white crystals after recrystallization, are photochromic[55]. The reaction of 3,4-diphenylcyclobutenedione *(5)* with benzoyl bromide in the presence of catalytic quantities of zinc chloride[56] or with thionyl chloride in dimethylformamide[57] leads to 2,2-dihalo-3,4-diphenylcyclobutenones.

5.2.5. With Trialkyl Phosphite

De Selms[58] showed that trialkyl phosphites also add to phenylcyclobutenediones *(2)*. An alkyl group is transferred to the polarized carbonyl group of the hypothetical intermediate *(51)*, and the cyclobutenones *(52)* are formed.



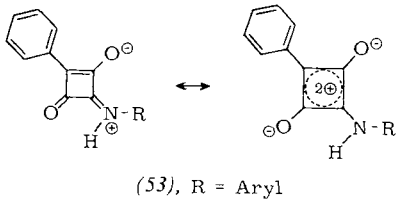
(2) *(51)* *(52)*

5.3. Condensation Reactions

The products formed on reaction of phenylcyclobutenediones with reagents for carbonyl groups have not been extensively studied. Whereas 3,4-diphenylcyclobutenedione *(5)* reacts with tosylhydrazine to give a mixture of mono- and ditosylhydrazones[22], the reaction with 2,4-dinitrophenylhydrazine leads exclusively to the monocondensation product. Monocondensation products are also formed on reaction of *(2)* with 2,4-dinitrophenylhydrazine and with hydroxylamine[7]. There are no reports of investigations on which of the two carbonyl groups of the cyclobutenedione system is attacked or whether a mixture of isomers is formed. Moreover, the occurrence of open-chain products cannot be definitely ruled out[4].

5.3.1. Condensation Reactions of 3-Hydroxy-4-phenylcyclobutenedione

3-Hydroxy-4-phenylcyclobutenedione *(12)* undergoes condensation with primary amines to give derivatives of 2-imonio-3-oxo-4-phenylcyclobuten-1-olate[34, 59] (Table 7), which are similar to the intramolecular salts obtained from squaric acid and amines[42, 60].



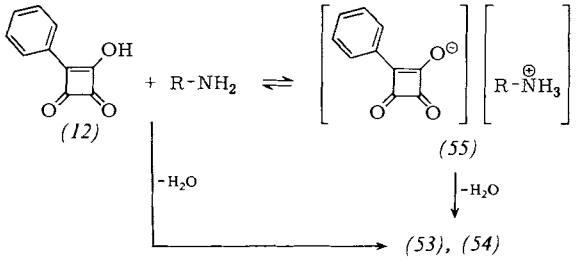
(53), R = Aryl
(54), R = Alkyl

Table 7. Condensation products *(53)* from *(12)* and aromatic amines, and *(54)* from *(12)* and aliphatic amines.

R	M. p. (°C)	Yield (%)
Phenyl	275	72
3-Bromophenyl	280	83
4-Bromophenyl	284	80
3-Nitrophenyl	273	78
4-Aminophenyl	320	72
1-Naphthyl	276	80
2-Naphthyl	262	61
n-Butyl	197—198	89
Benzyl	239—240	64
Cyclohexyl	211—213	65

The compounds *(53)* form yellow to orange-yellow crystals, which are only slightly soluble in solvents of low polarity, but readily soluble in DMF, DMSO, and nitrobenzene. Their decomposition points indicate a high polarity. On the other hand, the compounds *(54)* are yellowish-white and readily soluble. The phenyl residue on the nitrogen atom must thus be responsible for the difference in the properties of the cyclobutenolates.

The reaction of *(12)* with amines under mild conditions leads to the ammonium salts *(55)*, whose stability increases with increasing basicity of the amine. At higher temperatures, the salts *(55)* readily lose water and form the cyclobutenolates *(53)* or *(54)*[59].

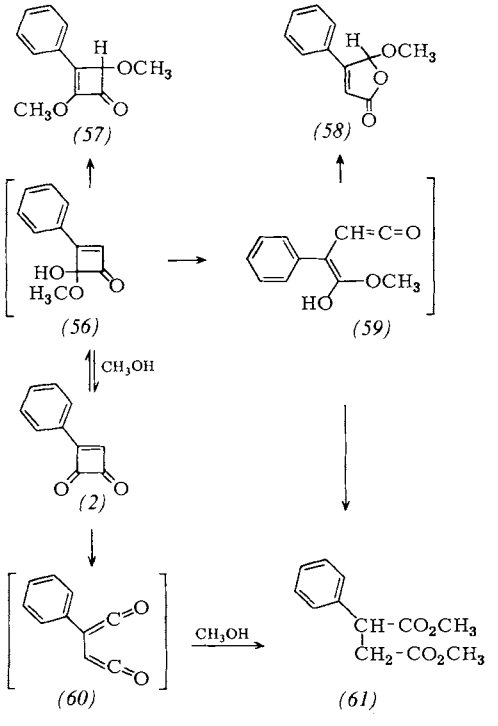


5.4. Ring Cleavage Reactions

5.4.1. With Alcohols

When phenylcyclobutenedione *(2)* is heated in neutral or acidified methanol, three products are formed, the yields of these products being strongly dependent on the reaction conditions, particularly the temperature. They are dimethyl phenylsuccinate *(61)*, 5-methoxy-4-phenyl-2,5-dihydrofuran-2-one *(58)*, and 2,4-dimethoxy-3-phenylcyclobutenone *(57)*[61].

If the temperature is kept below 135 °C, the main product is *(57)*. By acid catalysis, its yield can be increased to a maximum of 49%.

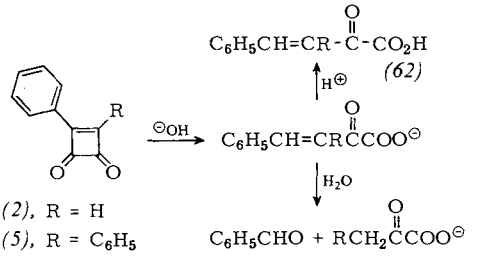


At higher temperatures (150 °C) *(61)* predominates (64%), while *(58)* is formed in a yield of 8%. 4-Hydroxy-4-methoxy-3-phenylcyclobutenone *(56)* existing in equilibrium with phenylcyclobutenedione *(2)* in methanol solution has been postulated as the precursor of the compounds *(57)*, *(58)*, and *(61)*.

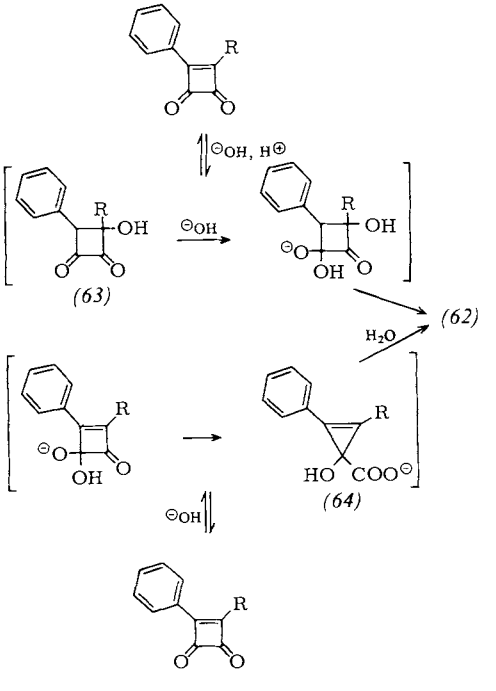
Another path for the formation of *(61)* is offered by the thermal ring cleavage of *(2)* to give the diketene *(60)* and the addition of the latter to methanol. The cleavage of 3,4-diphenylcyclobutenedione *(5)* in ethanol presumably also proceeds *via* a diketene. It leads to a mixture of the meso form and the racemate of diethyl diphenylsuccinate[22].

5.4.2. With Alkalis

Phenylcyclobutenedione *(2)* undergoes ring cleavage when heated in methanolic alkali solution. Benzylidenepyruvic acid *(62)*, R = H, was found as a primary decomposition product. Under the conditions indicated, however, *(62)*, R = H, decomposes mainly into benzaldehyde and pyruvic acid in a reversed aldol reaction[49].



The action of methanolic sodium hydroxide solution on diphenylcyclobutenedione *(5)* similarly yields benzaldehyde and benzylidenephenylpyruvic acid *(62)*, R = C_6H_5, which was isolated as 2,3-diphenyltetrahydrofuran-4,5-dione[62].

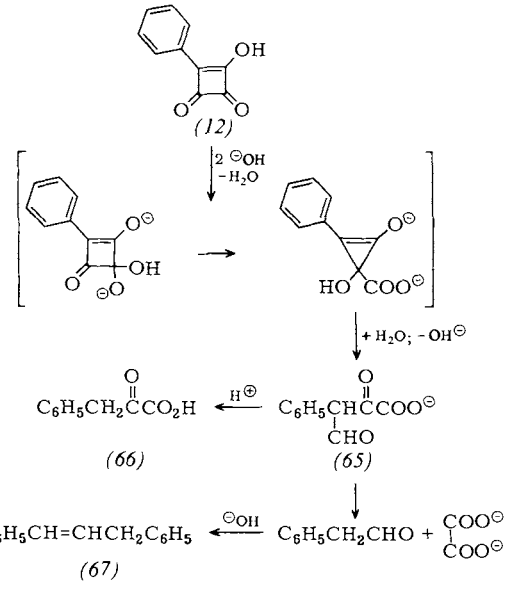


Two mechanisms have been proposed for the alkaline ring cleavage of the phenylcyclobutenediones *(2)* and *(5)*:

1. Addition of a hydroxide ion to the double bond of the cyclobutenedione system followed by uptake of a proton leads to the hydroxycyclobutanedione *(63)*, which is converted into *(62)* by the action of further alkali after the manner of a ring cleavage-elimination reaction[62].

2. Addition of a hydroxide ion to one of the two carbonyl groups of the cyclobutenedione yields a cyclobutenone, which rearranges to give the hydroxyphenylcyclopropenecarboxylic acid *(64)*, and this finally undergoes ring cleavage to form *(62)*[49].

A similar mechanism is thought to occur in the alkaline ring cleavage of hydroxyphenylcyclobutenedione *(12)*, which yields phenylpyruvic acid *(66)*, 1,3-diphenylpropene *(67)*, and oxalic acid[49].

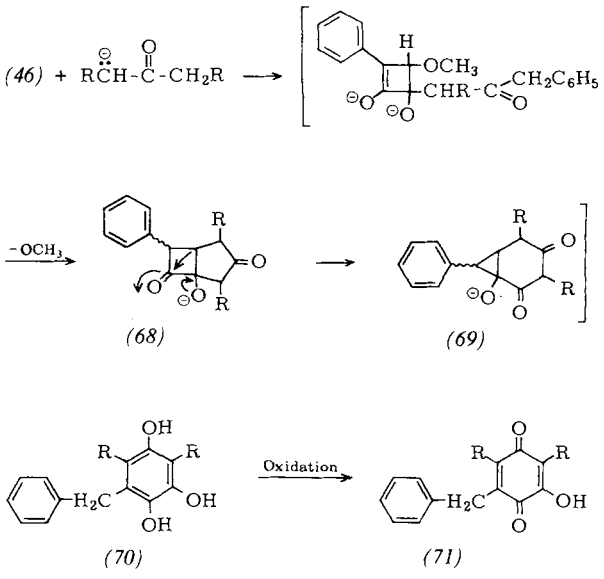


The assumption of 3-formylpyruvic acid *(65)* as the first ring cleavage product[49] was recently confirmed by its isolation[37b].

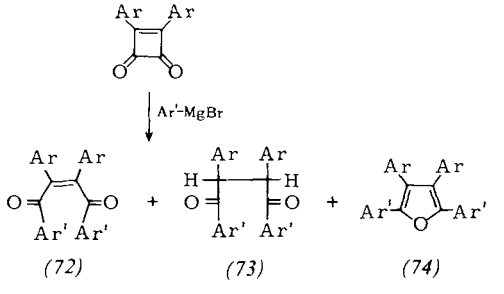
5.4.3. With Carbanions

The reaction of phenylcyclobutenedione *(2)* with dibenzyl ketone in methanolic alkali can be interpreted by a mechanism similar to that proposed by *Roberts* for the alkaline decomposition of 2-hydroxy-3-phenyl-2-cyclobuten-1-one[49]. The reaction leads to 1,2,4-trihydroxy-3,5-diphenyl-6-benzylbenzene *(70)*, which can be oxidized with air to the *p*-quinone *(71)* and isolated in this form[63]. Contraction of the four-membered ring in the bicyclic compound *(68)* and rearrangement of the resulting cyclopropanol system *(69)* are accepted as characteristic reaction steps.

The action of arylmagnesium bromides on diarylcyclobutenediones yields a mixture of the products *(72)* to *(74)*, in which the *cis*-diaroylstilbenes *(72)* form the principal component[64].



Phenylcyclobutenedione *(2)* reacts with phenyllithium at 0 °C and even at −90 °C to form complicated mixtures of products, which have not yet been investigated[65].

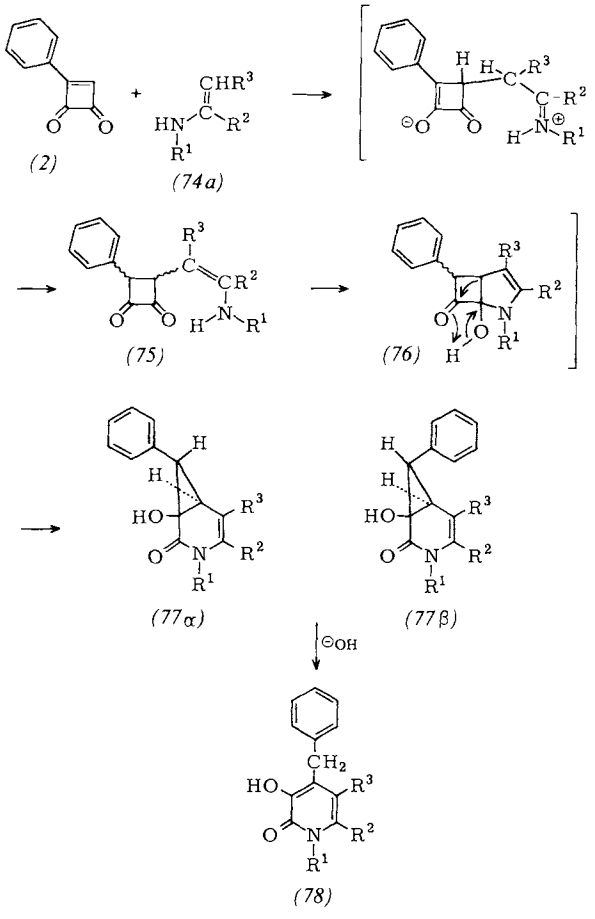


5.4.4. With Enamines

The reaction course described in Section 5.4.3 is supported by the reaction of *(2)* with enamines. The products are azabicyclo[4.1.0]heptenes *(77)*[66], which rearrange smoothly in alkaline media to give the 3-hydroxypyridones *(78)*[67].

It may be assumed that the bicyclic compound *(76)* heteroanalogous to *(68)* is formed *via* the cyclobutane-1,2-dione stage *(75)*; ring contraction then leads to *(77)*. Similar ring contractions have been known in the cyclobutane-1,2-dione series for some time[68]. Behavior of this type has been assumed since 1958 for 2-hydroxy-3-phenyl-2-cyclobuten-1-one[49]. Diarylhydroxycyclobutenones *(45)* also undergo ring contraction under the action of amines and hydrazines to give 2,3-diaryl-1-hydroxycyclopropane-1-carboxamides and -carbohydrazides[69].

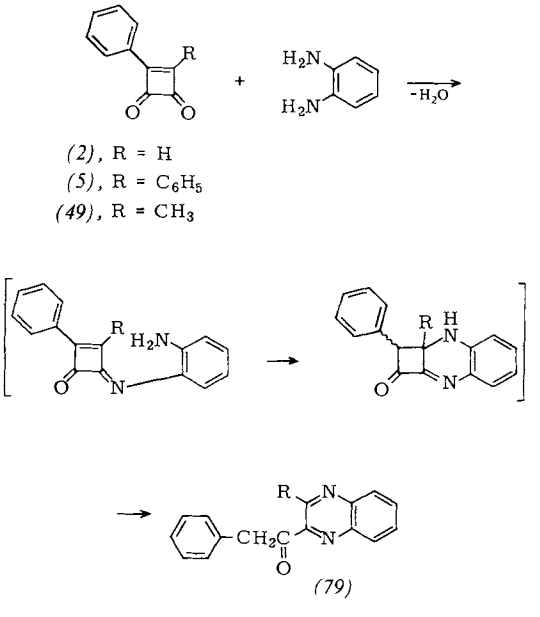
Whereas a bicycloheptene *(77)* having the configuration α was isolated on reaction of *(2)* with ethyl 3-aminocrotonate *(74a)*, $R^1=H$, $R^2=CH_3$, $R^3=CO_2C_2H_5$, the reaction with ethyl *N*-phenyl-3-aminocrotonate *(74a)*, $R^1=C_6H_5$, yields a product having the configuration β. Compounds having the β configuration (65%) and the α configuration (2%) were obtained from a reaction mixture with ethyl *N*-methyl-3-aminocrotonate *(74a)*, $R^1=CH_3$.



(2) (74a) (75) (76) (77α) (77β) (78)

5.4.5. With *o*-Phenylenediamine

Benzocyclobutenedione *(3)*[70] and 1,2-cyclobutanedione[71,68b,c] react with *o*-phenylenediamine to form cyclobuta[*b*]quinoxalines. Phenylcyclobutenedione *(2)*, on the other hand, behaves in an entirely unexpected manner. On fusion of a mixture of *(2)* and *o*-phenylenediamine, *J. D. Roberts et al.*[7] observed the formation of 2-phenylacetylquinoxaline *(79)*, R = H. Diphenylcyclobutenedione *(5)*[62] and methylphenylcyclobutenedione *(49)*[50] react in the same way.



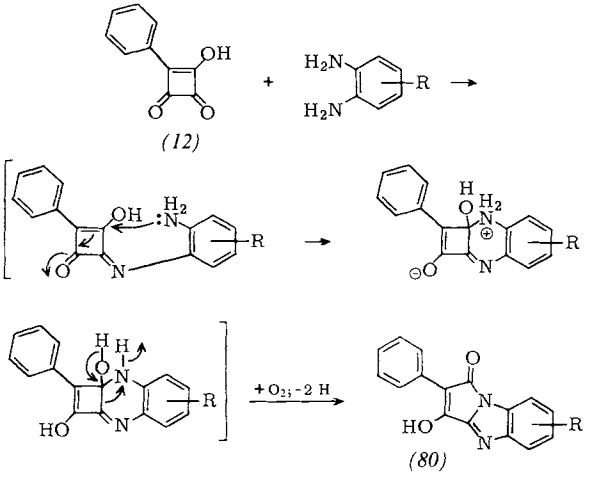
(2), R = H
(5), R = C_6H_5
(49), R = CH_3

(79)

5.5. Reactions with Ring Expansion

5.5.1. With *o*-Phenylenediamine

A new type of reaction has been found in the reaction of *o*-phenylenediamine with hydroxyphenylcyclobutenedione *(12)*. With glacial acetic acid as the solvent and in the presence of atomospheric oxygen, the cyclobutenedione system undergoes ring expansion to give the pyrrolobenzimidazole *(80)*[72,73].

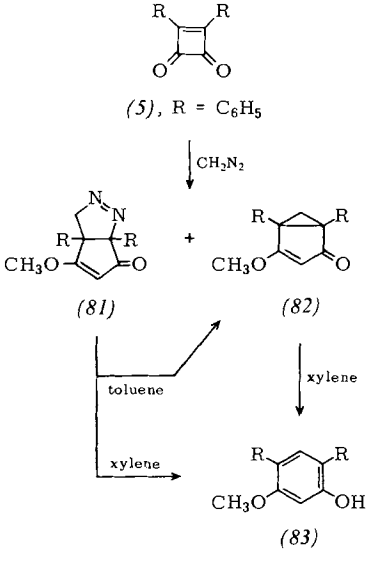


(12) *(80)*

The special position of hydroxyphenylcyclobutenedione *(12)* among the phenylcyclobutenediones, which was observed earlier in the alkaline decomposition, is thus confirmed by its behavior in acids.

5.5.2. With Diazomethane

The action of excess diazomethane on diphenylcyclobutenedione *(5)* leads to cyclopentapyrazole *(81)* and bicyclo[3.1.0]hexenone *(82)* in approximately equal yields.



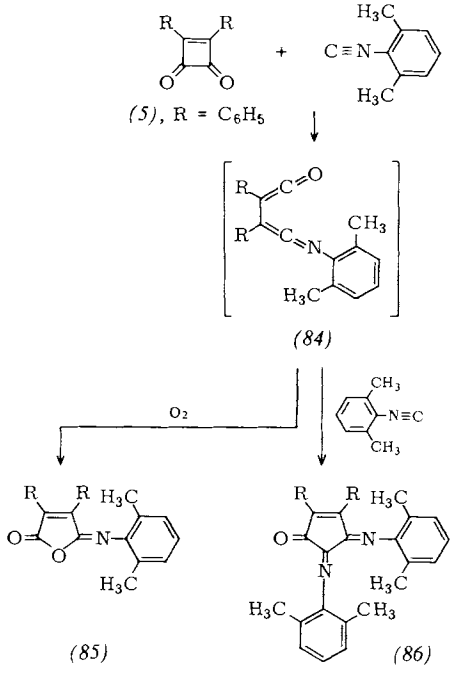
(5), R = C_6H_5
(81) *(82)* *(83)*

When heated in toluene, *(81)* loses N_2 to form *(82)*, which rearranges into 4'-hydroxy-6'-methoxy-*m*-terphenyl *(83)* when heated for 12 hours in xylene[74].

In view of the immediate formation of *(81)* and *(82)* when the reactants are brought together and the behavior of cyclopentadienone[75] and 2,4,5-triphenyl-4-cyclopentene-1,3-dione[76] towards diazomethane, it is possible to rule out a cyclopentenedione as an intermediate. We believe that the first step is a 1,3-dipolar addition of diazomethane to the double bond of the cyclobutenedione, and that a CH_2 group is only then inserted between the carbonyl groups. The reaction is completed by enolization and methylation.

5.5.3. With Isocyanides

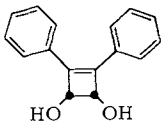
Obata and *Takizawa* found that when diphenylcyclobutenedione *(5)* is heated with 2,6-dimethylphenyl isocyanide, carbon monoxide is eliminated with formation of 4,5-bis-(2,6-dimethylphenylimino)-2,3-diphenylcyclopenten-1-one *(86)* and 5-(2,6-dimethylphenylimino)-3,4-diphenyl-2,5-dihydrofuran-2-one *(85)*[77]. These authors assume that the phenyliminoethyleneketene *(84)* is formed as an intermediate, and reacts with further isocyanide to form *(86)* and with atmospheric oxygen to form *(85)*. Insertion of the isocyanide into the four-membered ring system is ruled out. The authors detected a compound of the type *(84)* on photolysis of *(5)* or its imine derivative[78].



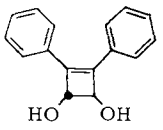
6. Various

6.1. Reduction

Phenylcyclobutenedione *(2)* is extremely resistant to reducing agents. Attempted catalytic hydrogenations were unsuccessful, since *(2)* or a product formed in small quantities acts as a catalytic poison. Heating with catechol in toluene also failed to cause any perceptible change. Polarographic studies show that the reduction of *(2)* is irreversible and pH-dependent. Under the drastic conditions of the Clemmensen reduction, *(2)* is converted into phenylcyclobutane[7]. The reduction of diphenylcyclobutenedione *(5)* with lithium aluminum hydride yields a mixture of 23% of *cis*-3,4-diphenylcyclobutene-1,2-diol *(87)* and 3% of the *trans* compound *(88)*[79].



(87)



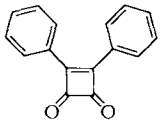
(88)

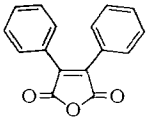
6.2. Oxidation

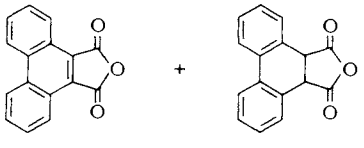
The oxidation of phenylcyclobutenedione *(2)*[7] and of the diphenyl compound *(5)*[22] with permanganate leads to benzoic acid. The action of hydrogen peroxide on *(2)* or *(5)* results in ring expansion after the manner of a Baeyer-Villiger reaction, with formation of substituted maleic anhydrides[7,22].

6.3. Photolysis

The photooxidation of *(5)* in benzene or acetonitrile yields a mixture of phenanthrene-9,10-dicarboxylic anhydride *(89)* and its dihydro derivative *(90)*.


(5)


(91)

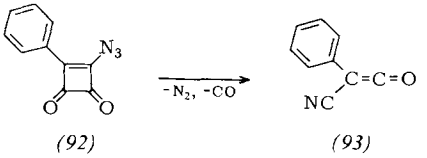


(89) *(90)*

The same products are obtained by the action of light on diphenylmaleic anhydride *(91)*, which is postulated as an intermediate[80]. The photolysis of phenylcyclobutenedione *(2)* in methanol at 60 °C leads in a fast reaction to dimethyl phenylsuccinate *(61)* and a substance whose structure is unknown[61,81].

6.4. Phenylcyanoketene

The action of sodium azide on a solution of halophenylcyclobutenedione *(10a)* or *(10b)* in acetonitrile[82] or



(92) *(93)*

acetone[83] leads to immediate evolution of gas. It must be assumed that the azide *(92)* formed as an intermediate decomposes with liberation of CO and N_2. This leads to phenylcyanoketene *(93)*, which has been intercepted with OH compounds.

We are grateful to the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, the Hermann-Schlosser-Stiftung, and Farbwerke Hoechst AG for their support of our investigations on this topic. W. R. is grateful to the co-workers mentioned in the references for their assistance. A. H. S. is grateful to the Stiftung Stipendien-Fonds des Verbandes der Chemischen Industrie for a Liebig scholarship.

Received: October 18, 1971 [A 919 IE]
revised: August 19, 1972
German version: Angew. Chem. *84*, 1048 (1972)
Translated by Express Translation Service, London

[1] *J. C. Hinshaw*, Chem. Commun. *1971*, 630.

[2] *G. Maahs* and *P. Hegenberg*, Angew. Chem. *78*, 927 (1966); Angew. Chem. internat. Edit. *5*, 888 (1966).

[3] *H. E. Sprenger* and *W. Ziegenbein*, Angew. Chem. *80*, 541 (1968); Angew. Chem. internat. Edit. *7*, 530 (1968).

[4] *M. P. Cava* and *M. J. Mitchell*: Cyclobutadiene and Related Compounds. Academic Press, New York 1967, p. 219.

[5] *J. L. Klundt*, Chem. Rev. *70*, 471 (1970).

[6] *J. D. Roberts*, Rec. Chem. Progr. *17*, 95 (1956), and Ref. [4], p. 128.

[7] *E. J. Smutny, M. C. Caserio*, and *J. D. Roberts*, J. Amer. Chem. Soc. *82*, 1793 (1960).

[8] *E. A. La Lancette*, Dissertation Abstracts *21*, 1760 (1961), cited in Ref. [4], p. 140.

[9] The synthesis of the enols of *(6)*, the simplest hydroxycyclobutenedione, has been reported by *R. W. Hoffmann, U. Bressel, J. Gehlhaus*, and *H. Häuser*, Chem. Ber. *104*, 873 (1971).

[10] *E. J. Smutny* and *J. D. Roberts*, J. Amer. Chem. Soc. *77*, 3420 (1955).

[11] *J. D. Roberts* and *C. M. Sharts*, Org. React. *12*, 8 (1962).

[12] *E. F. Jenny* and *J. Druey*, J. Amer. Chem. Soc. *82*, 3111 (1960).

[13] *Y. Kitahara, M. C. Caserio, F. Scardiglia*, and *J. D. Roberts*, J. Amer. Chem. Soc. *82*, 3106 (1960).

[14] *W. Ried, A. H. Schmidt*, and *V. B. Saxena*, Chem. Ber. *103*, 2709 (1970).

[15] *W. Ried, A. H. Schmidt*, and *W. Kuhn*, Chem. Ber. *104*, 2622 (1971).

[16] *C. M. Sharts* and *J. D. Roberts*, J. Amer. Chem. Soc. *83*, 871 (1961).

[17] *E. V. Dehmlov*, Tetrahedron Lett. *1965*, 2317, 4003; Chem. Ber. *100*, 2779 (1967).

[18] *R. Breslow, L. J. Altman, A. Krebs, E. Mohacsi, J. Murata, R. A. Peterson*, and *J. Posner*, J. Amer. Chem. Soc. *87*, 1326 (1965).

[19] *S. Dixon*, J. Org. Chem. *21*, 400 (1956).

[20] *W. Broser* and *M. Seekamp*, Tetrahedron Lett. *1966*, 6337.

[21] *J. D. Park* and *R. Fontanelli*, J. Org. Chem. *28*, 258 (1963).

[22] *A. T. Blomquist* and *E. A. La Lancette*, J. Amer. Chem. Soc. *83*, 1387 (1961).

[23] *W. Ried, H. Dietschmann*, and *A. H. Schmidt*, unpublished.

[24] *A. H. Schmidt, W. Ried, P. Pustoslemsek*, and *H. Dietschmann*, Angew. Chem. *84*, 110 (1972); Angew. Chem. internat. Edit. *11*, 142 (1972).

[25] *J. F. J. Dippy, S. R. C. Hughes*, and *J. W. Laxton*, J. Chem. Soc. *1956*, 2995.

[26] *S. Cohen, J. R. Lacher*, and *J. D. Park*, J. Amer. Chem. Soc. *81*, 3840 (1959).

[27] The pK_a values given in [26] differ from other literature values. In this connection see: a) *J. D. Park, S. Cohen*, and *J. R. Lacher*, J. Amer. Chem. Soc. *84*, 2919 (1962); b) *S. Cohen* and *S. G. Cohen, ibid. 88*, 1533 (1966).

[28] *J. S. Chickos*, J. Amer. Chem. Soc. *92*, 5749 (1970).

[29] In $CDCl_3$; HMDSO as internal standard; 100 MHz.

[30] *R. M. Silverstein* and *G. C. Bassler*: Spectrometric Identification of Organic Compounds. 2nd Edit. Wiley, New York 1967, p. 140.

[31] *J. E. Thorpe*, J. Chem. Soc. *B 1968*, 1534.

[32] *A. H. Schmidt*, Dissertation, Universität Frankfurt 1970.

[33] *W. Ried* and *W. Kunstmann*, Chem. Ber. *102*, 1431 (1969).

[34] *W. Ried, W. Kunkel*, and *G. Isenbruck*, Chem. Ber. *102*, 2688 (1969).

[35] *W. Ried, A. H. Schmidt*, and *H. Medem*, unpublished.

[36] *W. Ried* and *A. H. Schmidt*, Liebigs Ann. Chem. *742*, 116 (1970).

[37] *W. Ried* and *W. Kunstmann*, a) Angew. Chem. *80*, 121 (1968); Angew. Chem. internat. Edit. *7*, 135 (1968); b) Chem. Ber. *102*, 1422 (1969).

[38] *W. Ried* and *A. H. Schmidt*, Tetrahedron Lett. *1969*, 2435, 3007.

[39] *D. P. Schäfer*, Diplomarbeit, Universität Frankfurt 1968.

[40] *W. Ried* and *F. Bätz*, Liebigs Ann. Chem. *755*, 32 (1972).

[41] *W. Ried, H. Kohl*, and *A. H. Schmidt*, unpublished.

[42] *H.-E. Sprenger* and *W. Ziegenbein*, Angew. Chem. *79*, 581 (1967); Angew. Chem. internat. Edit. *6*, 553 (1967).

[43] *W. Ried* and *P. Schomann*, Liebigs Ann. Chem. *714*, 140 (1968). The cyclobutenedione structure postulated here for the addition product must be replaced by the hydroxycyclobutenone form *(41)*.

[44] *W. Ried, A. H. Schmidt*, and *H. Knorr*, unpublished.

[45] *E. v. Meyer*, J. Prakt. Chem. (2) *63*, 167 (1901); *K. Schank*, Chem. Ber. *99*, 48 (1965).

[46] *O. Hinsberg*, Ber. Dtsch. Chem. Ges. *27*, 3259 (1894).

[47] *W. Ried* and *D. P. Schäfer*, Chem. Ber. *102*, 4193 (1969).

[48] *W. Ried* and *H. Kohl*, Chem. Ber. *104*, 2896 (1971).

[49] *L. Skattebol* and *J. D. Roberts*, J. Amer. Chem. Soc. *80*, 4085 (1958).

[50] *W. Ried* and *H. Kohl*, Synthesis *1971*, 542.

[51] *W. Ried* and *A. H. Schmidt*, Tetrahedron Lett. *1969*, 1443.

[52] *M. C. Caserio, H. E. Simmons, A. E. Johnson*, and *J. D. Roberts*, J. Amer. Chem. Soc. *82*, 3102 (1960).

[53] *W. Ried* and *D. P. Schäfer*, Chem. Ber. *103*, 2225 (1970).

[54] Similar observations were made in the acylation of aldehydes: *R. Adams* and *E. H. Vollweiler*, J. Amer. Chem. Soc. *40*, 1732 (1918).

[55] *W. Ried* and *A. H. Schmidt*, DOS 1958485 (1969).

[56] *W. Ried* and *A. H. Schmidt*, unpublished.

[57] *R. C. De Selms, C. J. Fox*, and *R. C. Riordan*, Tetrahedron Lett. *1970*, 781.

[58] *R. C. De Selms*, Tetrahedron Lett. *1968*, 5545.

[59] *W. Ried, A. H. Schmidt, G. Isenbruck*, and *F. Bätz*, Chem. Ber. *105*, 325 (1972).

[60] *G. Manecke* and *J. Gauger*, Tetrahedron Lett. *1967*, 3509, 1339; *J. Gauger* and *G. Manecke*, Chem. Ber. *103*, 2696 (1970).

[61] *F. B. Mallory* and *J. D. Roberts*, J. Amer. Chem. Soc. *83*, 393 (1961).

[62] *A. T. Blomquist* and *E. A. La Lancette*, J. Amer. Chem. Soc. *84*, 220 (1962).

[63] *W. Ried* and *W. Kunkel*, Liebigs Ann. Chem. *717*, 54 (1968).

[64] *W. Ried* and *R. Lantzsch*, Chem. Ber. *104*, 679 (1971).

[65] *R. E. Hess*, Dissertation, Cornell University 1967.

[66] *W. Ried* and *F. Bätz*, Angew. Chem. *83*, 763 (1971); Angew. Chem. internat. Edit. *10*, 735 (1971).

[67] *W. Ried* and *F. Bätz*, Liebigs Ann. Chem. *725*, 230 (1969).

[68] a) *H. D. Scharf, W. Droste*, and *R. Liebig*, Angew. Chem. *80*, 194 (1968); Angew. Chem. internat. Edit. *7*, 215 (1968); b) *J. J. Bloomfield, J. R. S. Ireland*, and *A. B. Marchand*, Tetrahedron Lett. *1968*, 5647; c) *A. de Groot, D. Oudmann*, and *H. Wynberg, ibid. 1969*, 1529; d) *H. D. Scharf* and *R. Klar*, Liebigs Ann. Chem. *739*, 166 (1970); e) *J. M. Conia* and *J. M. Denis*, Tetrahedron Lett. *1971*, 2845.

[69] *W. Ried, A. H. Schmidt*, and *H. Medem*, unpublished.

[70] a) *M. P. Cava* and *D. R. Napier*, J. Amer. Chem. Soc. *79*, 3606 (1957); b) *M. P. Cava, D. R. Napier*, and *R. J. Pohl, ibid. 85*, 2076 (1963).

[71] *A. Fujino, K. Kasuda*, and *T. Sakan*, Bull. Chem. Soc. Jap. *39*, 160 (1966).

[72] *W. Ried* and *G. Isenbruck*, Angew. Chem. *82*, 807 (1970); Angew. Chem. internat. Edit. *9*, 793 (1970).

[73] *W. Ried* and *G. Isenbruck*, Chem. Ber. *105*, 337 (1972).

[74] *W. Ried, W. Kuhn*, and *A. H. Schmidt*, Angew. Chem. *83*, 764 (1971); Angew. Chem. internat. Edit. *10*, 736 (1971).

[75] *B. Eistert* and *A. Langbein*, Liebigs Ann. Chem. *678*, 78 (1964).

[76] *E. Grens* and *G. Vanags*, Latv. PSR Zinat. Akad. Vestis, Kim. Ser. *2*, 233 (1963); Chem. Abstr. *60*, 443[9] (1964).

[77] *N. Obata* and *T. Takizawa*, Tetrahedron Lett. *1969*, 3403.

[78] *N. Obata* and *T. Takizawa*, Chem. Commun. *1971*, 587.

[79] *A. T. Blomquist* and *E. A. La Lancette*, J. Org. Chem. *29*, 2331 (1964).

[80] *C. W. Bird*, Chem. Commun. *1968*, 1537.

[81] *F. M. Beringer* and *R. E. K. Winter*, Tetrahedron Lett. *1968*, 6183.

[82] *R. C. De Selms*, Tetrahedron Lett. *1969*, 1179.

[83] *A. H. Schmidt* and *W. Ried*, Tetrahedron Lett. *1969*, 2431.

The following articles on this topic have been published since the completion of the present manuscript:

a) The action of bases on ethyl 1-hydroxy-2,3-diphenyl-2-cyclopropene-1-carboxylate leads, after the manner of a reversible benzilic acid rearrangement, to diphenylcyclobutenedione, and offers a new route to the cyclobutenediones. *C. D. De Boer*, Chem. Commun. *1972*, 377.

b) Two novel substitution reactions on phenylcyclobutenedione have been reported by *W. Ried, A. H. Schmidt, W. Kuhn*, and *A. Bierendempfel*, Tetrahedron Lett. *1972*, in press.

c) Trimethyl phosphite and dimethyl phosphite can add to diphenylcyclobutenedione, the four-membered ring system being retained. *P. R. Ortiz de Montellano* and *P. C. Thorstenson*, Tetrahedron Lett. *1972*, 787.

d) The synthesis of a thienocyclobutadiene by reaction of diphenylcyclobutenedione with the di-ylide obtained from dimethyl thioether α,α'-bis(triphenylphosphonium chloride) has been achieved by *P. J. Garrat* and *K. P. C. Vollhardt*, J. Amer. Chem. Soc. *94*, 1022 (1972).

e) The occurrence of a diketene on photolysis of diphenylcyclobutenedione has been confirmed by *O. L. Chapman, C. L. McIntosh*, and *L. L. Barber*, Chem. Commun. *1971*, 1162.

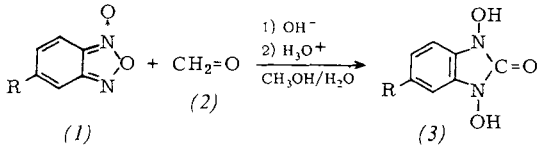
COMMUNICATIONS

Reaction of Benzofuroxan with Formaldehyde

By *Florin Seng* and *Kurt Ley*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

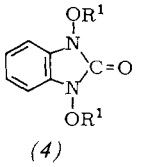
Reaction of formaldehyde *(2)* with benzofuroxan *(1)* in the presence of alkali proceeds exothermally to give the hitherto unknown 1,3-dihydroxybenzimidazolin-2-ones *(3)*.



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

(3), R =	Dec. pt. [°C]	Color	Yield [%]
H	227	pale yellow	91
Cl	206	brownish red	65
CH_3	209	yellow	80
CH_3O	153	yellow	62
COOH	260	yellow	76
H_2NCO	220	yellowish brown	67

Reduction of *(3)* by sodium dithionite leads to benzimidazolinones. Numerous reactions can be effected at the hydroxyl groups (alkylation, acetylation, addition of isocyanates and acrylonitrile). Compounds of type *(4)* are thus obtained.



(4)

(a), $R^1 = CH_3$; m.p. 99 °C
(b), $R^1 = COCH_3$; m.p. 91 °C
(c), $R^1 = CONHC_6H_5$; m.p. 183 °C
(d), $R^1 = CH_2CH_2CN$; m.p. 192 °C.

Oxidation of *(3)* with PbO_2 or irradiation in tetrahydrofuran yields a radical with the following splitting parameters $a_N = 5.96$ G; $a_{H_{2,3}} = 0.92$ G; $a_{H_{1,4}} = 2.76$ G; $(= 3 \times a_{H_{2,3}})$; $a_{H_{OH}} = 0.18$ G: $a_{N'} = 0.92$ G $(= a_{H_{2,3}})$

1,3-Dihydroxybenzimidazolin-2-one (3), R = H:

Benzofuroxan (136 g, 1 mol) is suspended in methanol (500 ml) and water (500 ml) and treated with 30% aqueous formaldehyde (100 g, 1 mol). Then a solution of potassium hydroxide (114 g, 2 mol) in water (100 ml) and methanol (100 ml) is added dropwise, the temperature being kept at 40–50 °C by cooling. After the main reaction the solution is stirred for 1 h. The deep red solution is then treated with water (1 l) and acidified with 10% hydrochloric acid. Pale yellow crystals of *(3)*, R = H, then separate (150 g, 91%), which after recrystallization from water melt at 227 °C with violent decomposition. If the solution is acidified with acetic acid, the colorless monopotassium salt (decomp. 204 °C) is obtained.

Received: May 23, 1972 [Z 680a IE]
German version: Angew. Chem. *84*, 1060 (1972)
Publication delayed at authors' request

[*] Prof. Dr. K. Ley and Dr. F. Seng
Wissenschaftliches Hauptlaboratorium der Farbenfabriken
Bayer AG
509 Leverkusen-Bayerwerk (Germany)

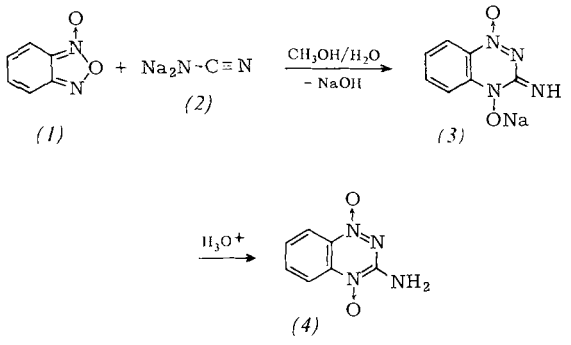
Simple Synthesis of 3-Amino-1,2,4-benzotriazine 1,4-Dioxide

By *Florin Seng* and *Kurt Ley*[*]

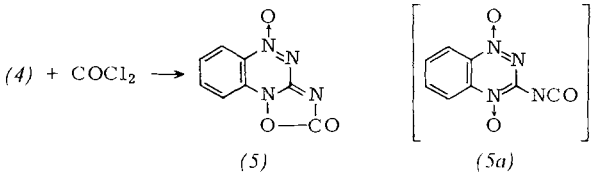
Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

Disodiocyanamide *(2)* adds exothermally to benzofuroxan *(1)* with formation of the sodium salt *(3)*, which on acidification is transformed into 3-amino-1,2,4-benzotriazine 1,4-dioxide *(4)*.

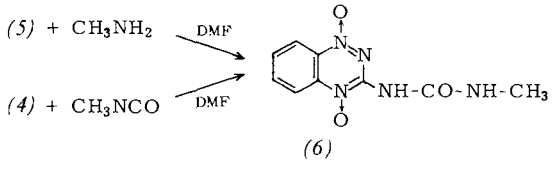
[*] Prof. Dr. K. Ley and Dr. F. Seng
Wissenschaftliches Hauptlaboratorium der Farbenfabriken
Bayer AG
509 Leverkusen-Bayerwerk (Germany)



Treating *(4)* with phosgene in toluene at 90 °C gives *(5)*, which behaves like the isocyanate *(5a)* towards nucleophiles.



The structure of *(5)* is proved by its reaction with methylamine to give the urea *(6)* that is also obtained from *(4)* and methyl isocyanate.



3-Amino-1,2,4-benzotriazine 1,4-dioxide (4):

Benzofuroxan (136 g, 1 mol) is suspended in methanol (400 ml) and water (400 ml) and treated with disodiocyanamide (172 g, 2 mol). The temperature rises to 50—60 °C and the solution becomes bluish-violet. After 10 min a further portion of disodiocyanamide (86 g, 1 mol) is added, and 15 min later *(3)* separates as a bluish-violet precipitate. This is filtered off and dissolved in water, the solution is filtered and the filtrate is acidified with acetic acid. *(4)* (144 g, 81%) then separates as reddish-yellow crystals that melt with decomposition at 220 °C (Ref. [1], 220 °C).

Reaction of (4) with phosgene:

(4) (35.6 g, 0.2 mol) is suspended in toluene (200 ml). A vigorous stream of phosgene is passed into this suspension at 90 °C. After 4 h, filtration gives *(5)* as yellowish-brown crystals (34 g, 84%), which after recrystallization from acetonitrile melt at 262 °C with decomposition.

Received: May 23, 1972 [Z 680b IE]
German version: Angew. Chem. *84*, 1061 (1972)
Publication delayed at authors' request

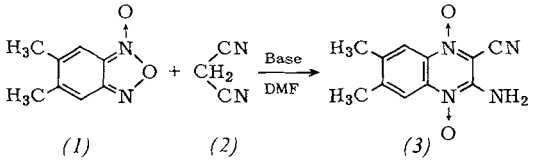
[1] *I. C. Mason* and *G. I. Tennant*, J. Chem. Soc. *B 1970*, 911.

A New Synthesis of Lumichrome

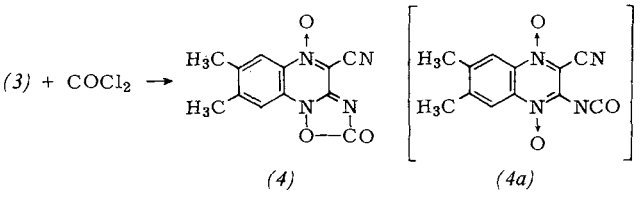
By *Florin Seng* and *Kurt Ley*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

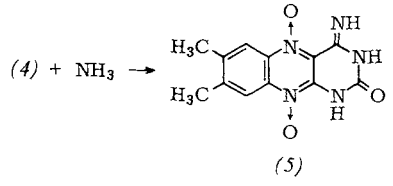
Benzofuroxans add malonodinitrile *(2)* in the presence of bases, yielding 2-amino-3-cyanoquinoxaline 1,4-dioxides[1,2]. This type of synthesis provides a very simple route to lumichrome[3].



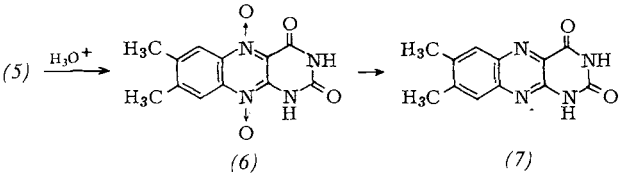
5,6-Dimethylbenzofuroxan *(1)*[4] is converted by *(2)* into the dioxide *(3)*. Intramolecular ring closure of *(3)* with phosgene in chlorobenzene at 90 °C leads to 4-cyano-7,8-dimethyl-2-oxo-1,2,4-oxadiazolo[2,3-*a*]quinoxaline 5-oxide *(4)*, which behaves like the isocyanate *(4a)* on treatment with nucleophiles.



Thus reaction with ammonia leads to the iminobenzopteridine 5,10-dioxide *(5)* by addition and simultaneous ring closure involving the nitrile group.



Acid hydrolysis of *(5)* to give *(6)*, and reduction of the latter, afford lumichrome *(7)* in high yield.



The structures of the new compounds *(3)* to *(6)* were proved by analysis and spectroscopy.

2-Amino-3-cyano-6,7-dimethylquinoxaline 1,4-dioxide (3):

5,6-Dimethylbenzofuroxan *(1)* (164 g, 1 mol) and malonodinitrile (70 g, 1.05 mol) are dissolved in dimethylformamide

[*] Prof. Dr. K. Ley and Dr. F. Seng
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG
509 Leverkusen-Bayerwerk (Germany)

(750 ml), and triethylamine (25 g, 0.25 mol) is added dropwise over 30 min. The temperature is kept at 25—30 °C by cooling in ice. After 1.5 h the precipitate is filtered off, affording *(3)* (160 g, 70%) as golden-red crystals, which after recrystallization from dimethylformamide melt at 253 °C with decomposition.

4-Cyano-7,8-dimethyl-2-oxo-1,2,4-oxadiazolo[2,3-a]-quinoxaline 5-oxide (4):

(3) (230 g, 1 mol) is suspended in chlorobenzene (2 l), and a vigorous stream of phosgene is passed through the suspension at 80—90 °C, whereupon the color changes from red to yellow. The reaction is complete when addition of a sample of the yellow precipitate to water no longer produces a red color. On filtration, yellow crystals of *(4)* (239 g, 93%) are obtained, which after recrystallization from DMSO melt at 228 °C with decomposition.

4-Imino-7,8-dimethylbenzopteridine 5,10-dioxide (5):

(4) (25.6 g, 0.1 mol) is suspended in dimethylformamide (150 ml) and treated with concentrated ammonia solution (20 g). After 8 h, filtration affords yellowish-brown crystals of *(5)* (25 g, 92%), which after recrystallization from dimethylformamide melt at 360 °C with decomposition.

7,8-Dimethylbenzopteridine 5,10-dioxide (6):

(5) (27.3 g, 0.1 mol) is stirred in 20% sulfuric acid (300 ml) for 8 h at 80 °C. Filtration then affords yellow crystals of *(6)* (21.5 g, 77%).

7,8-Dimethylbenzopteridine (7), lumichrome:

(6) (27.4 g, 0.1 mol) is suspended in methanol (200 ml) and treated at 70 °C dropwise with a solution of sodium dithionite (60 g) in water (210 ml). After 5 h the mixture is cooled and filtered. The precipitate isolated is stirred with water, thus affording lumichrome *(7)* as yellow crystals that, after recrystallization from glacial acetic acid, melt with decomposition at 354 °C (Ref. [3], 360 °C).

Received: May 23, 1972 [Z 680c IE]
German version: Angew. Chem. *84*, 1061 (1972)
Publication delayed at authors' request

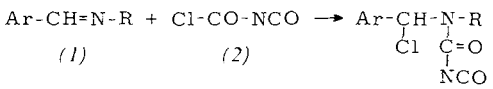
[1] *K. Ley, F. Seng, R. Nast, U. Eholzer*, and *R. Schubart*, Angew. Chem. *81*, 569 (1969); Angew. Chem. internat. Edit. *8*, 596 (1969).
[2] *F. Seng, R. Nast*, and *K. Ley*, Ger. Pat. Appl. P 16-70-743,0 (Aug. 26, 1966); DOS 1670743.
[3] *R. Kuhn*, Chem. Ber. *67*, 1826 (1934).
[4] *F. B. Mallory, S. L. Manatt*, and *C. S. Wood*, J. Amer. Chem. Soc. *87*, 5433 (1965).

N-Carbonylureas from Azomethines and *N*-Chlorocarbonyl Isocyanate

By *Hermann Hagemann* and *Kurt Ley*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

Although it is known that carboxamides[1], carbamidic esters[2], and carbamidamides[3] are converted by oxalyl chloride or phosgene into the corresponding isocyanates, the analogous reaction with ureas has not previously been recorded. We have now prepared isocyanates of type *(3)* (water-clear distillable liquids) by a simple method, namely addition of *N*-chlorocarbonyl isocyanate *(2)*[4] to Schiff bases *(1)*.



$$\mathrm{Ar\text{-}CH{=}N\text{-}R} + \mathrm{Cl\text{-}CO\text{-}NCO} \longrightarrow \mathrm{Ar\text{-}\underset{\displaystyle Cl}{\underset{|}{CH}}\text{-}\overset{\displaystyle C{=}O}{\overset{|}{N}}\text{-}R}$$

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

(3)	Ar	R	B.p. [°C/torr]	Yield [%]
(a)	C_6H_5	CH_3	112/0.05	66
(b)	C_6H_5	$i\text{-}C_3H_7$	115/0.15	65
(c)	C_6H_5	Cyclohexyl	142/0.07	15
(d)	C_6H_5	C_6H_5	152/0.1	70
(e)	$p\text{-Cl—}C_6H_4$	CH_3	115/0.1	86

In *(3)* the basic character of the amide nitrogen is weakened by the neighboring chlorine atom, which would be expected to contribute significantly to the stability of such *N*-carbonylureas. The reactivity towards acylatable compounds is comparable with that of alkoxycarbonyl isocyanates[2].

The structures of the compounds obtained are proved by their IR spectra [stretching vibrations at 1700 cm^{-1} (C=O) and 2242 cm^{-1} (N=C=O)], NMR spectra, results of elemental analysis, and chemical reactions.

Experimental:

N-Chlorocarbonyl isocyanate *(2)* (105.5 g, 1 mol) in chlorobenzene (250 ml) is treated dropwise over 45 min at 15—30 °C with the Schiff base (119 g, 1 mol) from benzaldehyde and methylamine. The whole is stirred at *ca.* 25 °C for 3 h, then the chlorobenzene is removed at water-pump pressure and the residue is distilled at oil-pump vacuum. This affords *(3a)* (148 g, 66%) as a colorless oil of b.p. 112 °C/0.05 torr.

Received: May 23, 1972 [Z 680d IE]
German version: Angew. Chem. *84*, 1062 (1972)
Publication delayed at authors' request

[1] *A. J. Speziale* and *L. R. Smith*, J. Org. Chem. *27*, 3742 (1962).
[2] *A. J. Speziale, L. R. Smith*, and *J. E. Fedder*, J. Org. Chem. *30*, 4306 (1965); *W. Klebert* and *E. Müller*, DOS 1518806 (Aug. 21, 1969), Farbenfabriken Bayer AG.
[3] *L. J. Samaraj, N. A. Bondor*, and *G. J. Derkatsch*, Angew. Chem. *79*, 897 (1967); Angew. Chem. internat. Edit. *6*, 864 (1967).
[4] *H. Hagemann*, Angew. Chem. *83*, 906 (1971); Angew. Chem. internat. Edit. *10*, 832 (1971).

Cyclization of Azomethines by *N*-Chlorocarbonyl Isocyanate

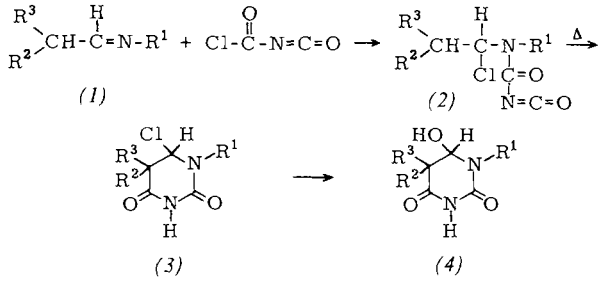
By *Hermann Hagemann* and *Kurt Ley*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

Schiff bases from aromatic aldehydes add *N*-chlorocarbonyl isocyanate[2] with retention of the isocyanate group[1]. The products, of type *(2)*, are formed also on treatment of azomethines *(1)* with *N*-chlorocarbonyl isocyanate.

[*] Dr. H. Hagemann and Prof. Dr. K. Ley
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG
509 Leverkusen-Bayerwerk (Germany)

[*] Dr. H. Hagemann and Prof. Dr. K. Ley
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG
509 Leverkusen (Germany)



(1) (2) (3) (4)

within wide limits[1]. Only little is known about six-membered representatives of this class of compound[2]. We obtained *(3)*, a derivative of imidodicarboxylic acid, by treatment of *N*-chlorocarbonyl isocyanate[3] with trisubstituted thioureas *(1)* and dehydrochlorination of the salt-like compounds *(2)* first formed.

Reservations may be made about the aromatic character of *(3)*, as for the five-membered mesoionic aromatic compounds of type *(4)*[4,1]. The photoelectron spectra[5] of *(3)*

	R^1	R^2	R^3	*(3)*, m.p. [°C]	*(3)*, yield [%]	*(4)*, m.p. [°C]	*(4)*, yield [%]
(a)	cyclohexyl	CH_3	CH_3	198	92	213	92
(b)	cyclohexyl	$-CH_2-CH=CH-(CH_2)_2-$		211	91	213	98
(c)	CH_3	CH_3	CH_3	205—207	57	180	66
(d)	CH_3	$-CH_2-CH=CH-(CH_2)_2-$		190	44	192	60
(e)	benzyl	CH_3	CH_3	86—88	70	204	39
(f)	i-C_3H_7	CH_3	CH_3	161—163	78	203	92

The reaction of derivatives of disubstituted acetaldehyde does not stop at the isocyanates *(2)*, but on gentle warming (*ca.* 90 °C) a rapid cyclization occurs, yielding 6-chloropyrimidine-2,4-diones *(3)*.

Like the open-chain analogs[3], these heterocycles are readily substituted by nucleophiles at carbon atom 6: heating with water or aqueous ethanol leads smoothly to *(4)*.

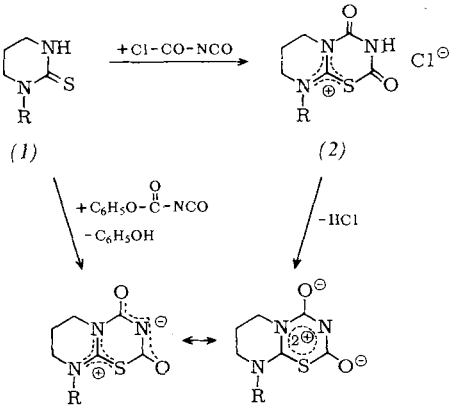
The structures of the products are proved by IR and NMR spectra and the results of elemental analysis.

Experimental:

A solution of the aldimine (153 g, 1 mol) from isobutyraldehyde and cyclohexylamine in chlorobenzene (600 ml) is added dropwise at 20—30 °C (cooling) to a solution of *N*-chlorocarbonyl isocyanate (105.5 g, 1 mol) in chlorobenzene (200 ml). The mixture is kept at room temperature for 2 h, then stirred for a further hour with gradual warming to 90 °C. Most of the product then separates. After cooling, compound *(3a)* is obtained as colorless crystals (190 g), melting at 198 °C. A further crop (47 g) of *(3a)* can be isolated from the mother liquor.

(3f) (100 g, 0.46 mol) is recrystallized from water (500 ml). This affords the dihydrobarbiturate *(4f)* (84 g, 92%) melting at 203 °C.

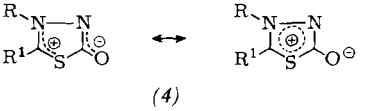
Received: May 23, 1972 [Z 680e IE]
German version: Angew. Chem. *84*, 1063 (1972)
Publication delayed at authors' request



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

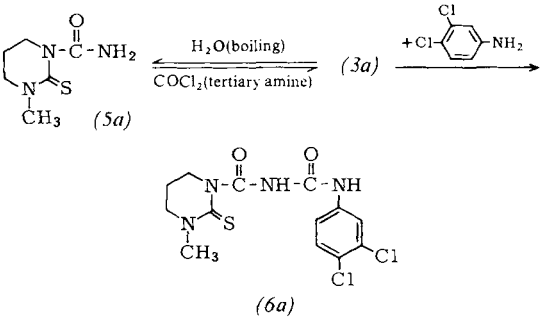
(3a), R = CH_3, m.p. 210—211 °C
(3b), R = i-C_3H_7, m.p. 190 °C
(3c), R = n-C_4H_9, m.p. 114 °C
(3d), R = cyclohexyl, m.p. 208 °C

show two signals for the three N atoms in the intensity ratio 2 : 1 [= (number of N atoms with positive partial charge) : (number of N atoms with negative partial charge)], whereas the four nitrogen atoms of a monothiotriuret of type *(6a)* give only one signals. This finding shows the strong charge separation typical of mesoionic heterocycles.



(4)

Heating an aqueous solution of *(3a)* to the boiling point leads, with ring opening, to the monothiobiuret *(5a)*, m.p.



(5a) *(6a)*

[1] *H. Hagemann* and *K. Ley*, Angew. Chem. *84*, 1062 (1972); Angew. Chem. internat. Edit. *11*, 1011 (1972).
[2] *H. Hagemann*, Angew. Chem. *83*, 906 (1971); Angew. Chem. internat. Edit. *10*, 832 (1971).
[3] a) *E. Cherbuliez* and *E. Feer*, Helv. Chim. Acta *5*, 678 (1922); b) *H. Hellmann*, Angew. Chem. *69*, 466 (1957).

Six-Membered Mesoionic "Aromatic" Compounds

By *Hermann Hagemann* and *Kurt Ley*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

The position and nature of the hetero atoms in five-membered mesoionic compounds of sydnone type can be varied

[*] Dr. H. Hagemann and Prof. Dr. K. Ley
Wissenschaftliches Hauptlaboratorium der Farbenfabriken Bayer AG
509 Leverkusen-Bayerwerk (Germany)

152—155 °C, which is recyclized to *(3a)* by phosgene in the presence of a tertiary amine. 3,4-Dichloroaniline reacts with *(3a)* even at *ca.* 20 °C, giving the monothiotriuret *(6a)*, m.p. 163 °C. *(3a)* can be prepared from *(1a)* and phenoxycarbonyl isocyanate in boiling toluene even in absence of a tertiary base.

Experimental:

A solution of *(1a)* (11.6 g, 0.1 mol) in methylene chloride (40 ml) is added, with cooling, to one of *N*-chlorocarbonyl isocyanate (10.5 g, 0.1 mol) in methylene chloride (60 ml). The white precipitate of *(2a)* that is immediately formed is filtered off and dried. M. p. 222 °C. Yield 19.5 g (95%).

A solution of *(2a)* (22.15 g, 0.1 mol) in water (50 ml) is added dropwise with cooling, to one of *N,N*-dimethylaniline (12.1 g, 0.1 mol) in methanol (50 ml). The white precipitate is filtered off and washed with water, giving 70% (13 g) of *(3a)*, m.p. 210—211 °C.

Received: May 23, 1972 [Z 680f IE]
German version: Angew. Chem. *84*, 1063 (1972)
Publication delayed at authors' request

[1] *M. Ohta* and *H. Kato* in *J. P. Snyder*: Nonbenzenoid Aromatics. Academic Press, New York, London 1969, Vol. 1.

[2] a) *Th. Kappe* and *N. Lube*, Angew. Chem. *83*, 967 (1971); Angew. Chem. internat. Edit. *10*, 925 (1971); b) *Th. Kappe* and *N. Lube*, Mh. Chem. *102*, 781 (1971); c) *R. M. Moriarty, J. M. Kliegman*, and *R. B. Desai*, Chem. Commun. *1967*, 1045.

[3] *H. Hagemann*, Angew. Chem. *83*, 906 (1971); Angew. Chem. internat. Edit. *10*, 832 (1971).

[4] *R. Grashey, M. Baumann*, and *N. D. Lubos*, Tetrahedron Lett. *1968*, 5877.

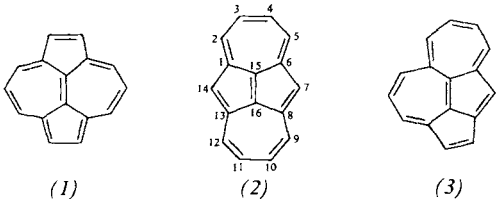
[5] *H. G. Fitzky, D. Wendisch*, and *R. Holm*, Angew. Chem. *84*, 1037 (1972); Angew. Chem. internat. Edit. *11*, 979 (1972).

Dicyclohepta[*cd,gh*]pentalene—A New Pyrene Isomer[**]

By *Henning Reel* and *Emanuel Vogel*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

HMO calculations[1] on the three non-alternant pyrene isomers consisting only of five- and seven-membered rings dicyclopenta[*ef,kl*]heptalene *(1)*, dicyclohepta-[*cd,gh*]pentalene *(2)*, and pentaleno[2,1,6-*def*]heptalene *(3)* which, like pyrene, have Kekulé structures with a peripheral 14π Hückel system and a central double bond yield the relatively high resonance energies (R_E) of 6.05 β, 6.03 β, and 5.95 β respectively (pyrene: $R_E = 6.51$ β). Accordingly, compound *(1)* which has very recently been synthesized by two independent routes[2] and the longer known 9-methyl derivative of *(3)*[3] are thermodynamically



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

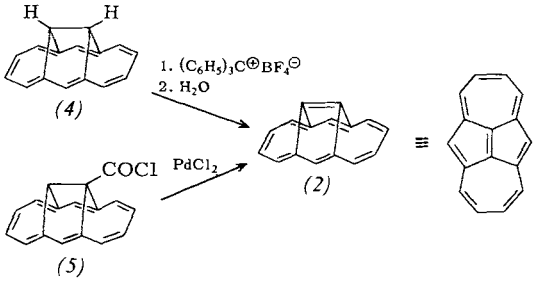
[*] Dr. H. Reel and Prof. Dr. E. Vogel
Institut für Organische Chemie der Universität
5 Köln 1, Zülpicher Strasse 47 (Germany)

[**] To facilitate comparison, the numbering chosen for *(2)* corresponds to that of bridged [14]annulenes having an anthracene perimeter.

stable hydrocarbons deserving the designation aromatic. The hitherto elusive pyrene isomer *(2)*—which has long been the goal of synthetic efforts[4] and the subject of quantum mechanical calculations[1,4-8]—has now been prepared in our laboratory.

Dicyclohepta[*cd,gh*]pentalene *(2)* attracted our interest since it is to be regarded as the parent of the bridged [14]annulenes possessing an anthracene perimeter: 1,6;8,13-ethanediylidene[14]annulene *(4)*[9], 1,6;8,13-propanediylidene[14]annulene[10], 1,6;8,13-butanediylidene-[14]annulene[11] *etc.*[8,12].

As can be readily seen, this series of [14]annulenes is derived from the above Kekulé structure of *(2)* by replacement of its formal central double bond by the >CH—$(CH_2)_n$—CH< grouping with $n = 0,1,2$, *etc.* The recently described 1,6;8,13-ethanediylidene[14]annulene *(4)*[9] thus represents the *cis*-15,16-dihydro derivative of *(2)*. This relationship prompted experimental efforts to convert *(4)* into *(2)* by dehydrogenation.



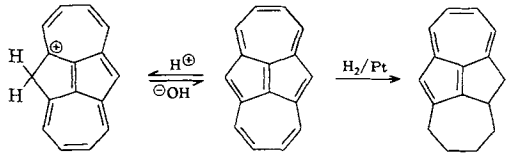
Contrary to expectation, dehydrogenation of *(4)* by the usual methods ran into difficulties; either no reaction took place (with noble metal catalysts in boiling decalin!) or decomposition occurred (with 2,3-dichloro-5,6-dicyanobenzoquinone). The desired transformation eventually became possible when we observed that a bridge hydrogen is abstracted as hydride ion when *(4)* is treated with triphenylmethyl tetrafluoroborate in acetonitrile (at *ca.* 50 °C). Treatment of the resulting stable carbenium ion, *i.e.* protonated *(2)*, with water effects deprotonation to give *(2)* [yield 70% based on *(4)*][13]. The interesting question whether the aforementioned carbenium ion intermediate is the primary product of hydride abstraction [*(2)* protonated in position 15] or the hydride-shift product *(6)*[4] is still open since the poor solubility of the ion has so far hampered NMR studies.

The hydrocarbon *(2)* was subsequently found to be more readily accessible by degradation of 1,6;8,13-ethanediylidene[14]annulene-15-carboxylic acid[9] than by the two-step dehydrogenation of *(4) viz.* a) by heating the acyl chloride *(5)* with palladium chloride in decalin to 170—180 °C (yield 25%) and b) by reaction of *(5)* with sodium azide in acetone/water and subsequent heating of the resulting carbonyl azide in ethanol (yield 50%)[14]. Compound *(2)* is relatively stable towards air and crystallizes from cyclohexane (yellowish-brown solution) as greenish black needles of m.p. 141—142 °C (partial decomposition).

The NMR spectrum of the pyrene isomer *(2)* (0.35 mol in CS_2/TMS) consists only of an AA'BB' system at $\tau_A = 1.34$ (H^2,H^5,H^9,H^{12}) and $\tau_B = 1.92$ (H^3,H^4,H^{10},H^{11}) with the coupling constants $J_{2,3} = 9.91$ Hz, $J_{2,4} = 0.44$ Hz, $J_{2,5} = 0.80$ Hz, and $J_{3,4} = 10.23$ Hz, and a singlet at $\tau = 1.94$ (H^7,H^{14})[15]. The shape and coupling constants of the spectrum thus correspond to those of the spectra

of the bridged [14]annulenes derived from *(2)*. The pronouncedly downfield position of the proton resonances can be rationalized by assuming an important contribution by the Kekulé structures with a peripheral 14π system—as inferred from the theoretically determined bond orders in *(2)*[4]. An alternative interpretation of the observed chemical shifts derives from ring-current calculations by *Jung*[6], which predict diamagnetic ring currents in the five- and seven-membered rings of *(2)* and of the isomers *(1)* and *(3)*. Support for the conclusions drawn from the NMR spectrum and MO calculations regarding the π-electron structure of *(2)* should come from an X-ray structural analysis of the hydrocarbon that is currently in progress[16].

The absorption bands of the UV spectrum of *(2)* [(in cyclohexane): $\lambda_{max}=235$ ($\varepsilon=27000$, sh), 284 (181300), 296 (33750 sh), 310 (26500), 321 (6950, sh), 363 (6200, sh), 367 (8700), 374 (4750, sh), 383 (6780), 387 (12200), 427 (720, sh), and 486 nm (4660)] are in satisfactory agreement with the values calculated by a simplified Pariser-Parr-Pople method[5].



(6) *(2)* *(7)*

The prediction, based on HMO calculations[4], that electrophiles will preferentially attack *(2)* in position 7 (or 14) has meanwhile been confirmed for protonation. *(2)* dissolves in trifluoroacetic acid or in 50% sulfuric acid to form the stable carbenium ion *(6)* [NMR spectrum (in CF_3COOH): complex multiplet at $\tau=0.52-1.58$ (9H) and singlet at 4.30 (2H)], from which the hydrocarbon can be regenerated, albeit with some losses, by addition of dilute sodium hydroxide solution at 0°C.

By analogy with the catalytic hydrogenation of the 9-methyl derivative of *(3)*[3], treatment of *(2)* with Pt/H_2 in ethanol yields an azulene derivative (together with other hydrogenation products); the compound designated structure *(7)* has so far become available in only very small quantities so that its characterization has been limited to UV and mass spectrometry.

Received: October 3, 1972 [Z 718 IE]
German version: Angew. Chem. *84*, 1064 (1972)

[1] *R. Zahradník, J. Michl*, and *J. Pancíř*, Tetrahedron *22*, 1355 (1966); see also *A. Streitwieser, Jr.*, and *J. I. Braumann*: Supplemental Tables of Molecular Orbital Calculations. Vol. 1, Pergamon-Press, Oxford 1965; *R. Zahradník*, Angew. Chem. *77*, 1097 (1965); Angew. Chem. internat. Edit. *4*, 1039 (1965).

[2] *A. G. Anderson, Jr., A. A. MacDonald*, and *A. F. Montana*, J. Amer. Chem. Soc. *90*, 2993 (1968); *C. Jutz* and *E. Schweiger*, Angew. Chem. *83*, 886 (1971); Angew. Chem. internat. Edit. *10*, 808 (1971).

[3] *K. Hafner, R. Fleischer*, and *K. Fritz*, Angew. Chem. *77*, 42 (1965); Angew. Chem. internat. Edit. *4*, 69 (1965); unsubstituted compound *(3)* has meanwhile been synthesized by *K. Hafner* and *F. Bauer*. We thank Professor *Hafner* for this personal communication.

[4] *E. R. Hanna, K. T. Finley, W. H. Saunders, Jr.*, and *V. Boekelheide*, J. Amer. Chem. Soc. *82*, 6342 (1960).

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

[6] *D. E. Jung*, Tetrahedron *25*, 129 (1969).

[7] *A. Dasgupta* and *N. K. Dasgupta*, Tetrahedron *28*, 3587 (1972).

[8] A study of the orbital interaction between the peripheral 14π Hückel system and the π system of the C^{15}—C^{16} bridge of *(2)* carried out by *K. Müllen* and *H. Reel* appears to justify our regarding *(2)* as perturbed [14]annulene; Helv. Chim. Acta, in press.

[9] *E. Vogel* and *H. Reel*, J. Amer. Chem. Soc. *94*, 4388 (1972).

[10] *E. Vogel, A. Vogel, K.-H. Kübbeler*, and *W. Sturm*, Angew. Chem. *82*, 512 (1970); Angew. Chem. internat. Edit. *9*, 514 (1970).

[11] *E. Vogel, W. Sturm*, and *H.-D. Cremer*, Angew. Chem. *82*, 513 (1970); Angew. Chem. internat. Edit. *9*, 516 (1970).

[12] The [14]annulene series 1,6;8,13-ethanediylidene-, 1,6;8,13-propanediylidene-, and 1,6;8,13-butanediylidene-[14]annulene has now been supplemented on the left-hand side—*i.e.*, in the direction of increasing planarity of the [14]annulene ring—by the synthesis of 1,6;8,13-cyclopropanediylidene[14]annulene ("15,16-methylene-1,6;-8,13-ethanediylidene[14]annulene") (permanganate-colored crystals of m.p. 169—170°C).

[13] This two-step dehydrogenation is analogous to the conversion of dihydroheptalene into heptalene: *H. J. Dauben, Jr.*, and *D. J. Bertelli*, J. Amer. Chem. Soc. *83*, 4659 (1961).

[14] *E. Vogel* and *W. Wagemann*, unpublished.

[15] We are grateful to Dr. *K. Müllen* for the analysis of the NMR spectrum. Assignment of the AA'BB' system was based on the conditions prevailing in the bridged [14]annulenes having an anthracene perimeter.

[16] Professor *M. Simonetta*, Milan, is currently engaged with the X-ray structure analysis of *(2)*.

Unusual Oxidation States of Metalloporphyrins: Octaethylporphinatosilver(III) Perchlorate[**]

By *Karl Kadish, Donald G. Davis*, and *Jürgen H. Fuhrhop*[*]

During a comprehensive survey of the redox potentials of some 30 different metalloporphyrin compounds certain anomalies were noticed which indicated the formation of some unusual oxidation states of the central metal ion. It has been shown that for the case of a simple derivative, such as tetraphenylporphinatozinc(II) or the corresponding etioporphyrin compound, the porphyrin ring can be oxidized in two successive, reversible, one-electron steps[1-3] (yielding π cation radicals and dications) and reduced in two successive, reversible, one-electron steps[4-6] (yielding π anion radicals and dianions). In several metalloporphyrins, such as those involving Mn, Co, and Fe, the central metal ion itself may undergo an oxidation state change $M^{II} \rightleftarrows M^{III}$. The decision as to whether a given reaction is that of the ring or the metal ion can often be made on the basis of visible and/or ESR spectra[1, 3, 5, 6].

Another criterion for differentiating between metal and ring reactions is provided by electrochemical potentials. During a cyclic voltammetric study[7] we observed that the absolute redox potentials of ring oxidations and reductions fall into well defined patterns: the numerical difference between the half-wave potential ($E_{\frac{1}{2}}$) for the first ring oxidation (in butyronitrile) and the first ring reduction (in dimethyl sulfoxide) remained constant at $E_{\frac{1}{2}ox}-E_{\frac{1}{2}red}=2.25\pm0.15$ V, regardless of the charge on the central metal ion. This was true for the M^{2+} ions of Mg, Ca, Cu, Ni, Pd,

[*] Dr. K. Kadish and Dr. D. G. Davis
Department of Chemistry
Louisiana State University
New Orleans, Louisiana 70122 (USA)
Dr. J.-H. Fuhrhop
Gesellschaft für Molekularbiologische Forschung
3301 Stockheim über Braunschweig (Germany)

[**] The support of the National Science Foundation (GP-19749) and the Deutsche Forschungsgemeinschaft is gratefully acknowledged. The Deutsches Bundesministerium für Bildung und Wissenschaft also supported this work within its technology program.

Zn, Cd; the M^{3+} ions of Al, Ga, In, Tl, Sc, Cr, and Fe; and the M^{4+} ions of Si, Sn, Ge, Ti, and V. Intermediate changes in the metal oxidation state appeared to have little effect on the observed value of 2.25 V. The only exceptions were Mn and Mo, which is probably due to an interaction of metal d orbitals with the porphyrin $e_g(\pi)$ orbitals. Further correlations also indicated that the difference between the first and second ring oxidation ($\Delta E_{\frac{1}{2}\,ox}$) was 0.29 ± 0.05 V, while that between the first and second ring reduction ($\Delta E_{\frac{1}{2}\,red}$) was 0.42 ± 0.05 V. These values agree well with the average values of 0.30 and 0.44 V, respectively, from the data available for a number of tetraphenylporphyrin-metal chelates[2, 5].

Constancy of these ΔE values over a wide range of central metal ions is a good indication that the electron transfers involve the porphyrin ring and not the metal. Conversely, apparent deviations can be regarded as an indication that the reaction possibly involves an originally unsuspected change in metal oxidation state. Visible and ESR spectroscopy can then be used to fully elucidate the situation.

For example, the $\Delta E_{\frac{1}{2}\,ox}$ for octaethylporphinatoiron(III) is 0.24 V and thus agrees well with the value expected for two consecutive ligand oxidations. This finding appears not to support the contention that the oxidation of porphyrin-Fe^{III} compounds produces Fe^{IV} complexes[8]. However, the difference between the first reduction at -1.33 V and the closest oxidation at -0.24 V is much smaller than the 2.25 V expected, and one can reasonably postulate that the latter process involves an $Fe^{III} \rightleftarrows Fe^{II}$ transition; this reaction is well confirmed and generally accepted in the literature. Assignment of the first ring reduction to the reaction at -1.33 V yields a resonable value for $E_{\frac{1}{2}\,ox} - E_{\frac{1}{2}\,red}$ of 2.33 V. In a similar manner the $\Delta E_{\frac{1}{2}\,ox} = 0.28$ V for octaethylporphinatomanganese(III) fits for two consecutive ligand oxidations but the closest reduction at -0.42 V is "too oxidizing" for a ring reduction and can be regarded as the known $Mn^{III} \rightarrow Mn^{II}$ transition.

The case of octaethylporphinatosilver(II) *(1)* is of special interest. It is well established[9] that when silver is inserted into the porphyrin ring it is simultaneously oxidized to Ag^{2+}. The $\Delta E_{\frac{1}{2}\,red}$ of 0.55 V is in fair agreement with two ring reductions, but the oxidation which occurs at 0.44 V is only 1.73 V more oxidizing than the first ring reduction — far less than our observed 2.25 V. We therefore assign the oxidation at 0.44 V to the formation of an octaethylporphinatosilver(III) complex *(2)*, an assignment which has not been previously reported.

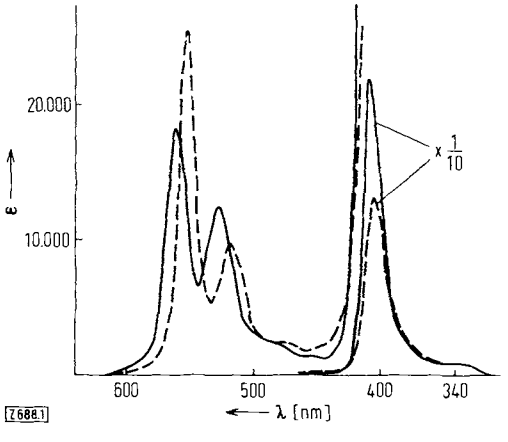


Fig. 1. The spectra of octaethylporphinatosilver(II) *(1)* (——) and octaethylporphinatosilver(III) perchlorate (– – –) in chloroform/methanol.

(1) is paramagnetic and has similar properties to the analogous copper complex, but on oxidation, either electrochemically or chemically, it does not yield a porphyrin cation radical as the latter does[1, 3]. Oxidation of *(1)* with $Fe(ClO_4)_3$ in chloroform/methanol solution produces the spectral changes shown in Figure 1. The new spectrum is typical for metalloporphyrins with no single electron in the ligand orbitals. The Ag^{II} complex *(1)* also yields a typical ESR spectra (nine lines with a $g_{\parallel}$ of 2.1060 and a $g_{\perp}$ of 2.0304 in acetone solution)[10]. This spectrum disappears on oxidation with Fe^{III} salts. Octaethylporphinatosilver(III) perchlorate *(2)* was also obtained in crystalline form and magnetic measurements on a Gouy balance confirmed it to be diamagnetic as would be expected for a d^8 square-pyramidal complex. Elemental analyses of *(1)* and *(2)* were satisfactory. To our knowledge the only other complexes of Ag^{III} reported are guanidine derivatives[11, 12] obtained by oxidation with persulfates. No oxidation potentials have been reported. The porphyrin-like square planar arrangement of four nitrogens is also probable in these systems and can explain the extraordinary stabilization of d^8 ions in these two ligand fields. Another interesting fact is that *(2)* is unusually hard to oxidize further. The complex is stable up to 1.4 V and remains unoxidized after treatment with *N*-bromosuccinimide. A second oxidation step reported by *Stanienda* and *Biebl*[12] at 0.9 V could not be confirmed by us.

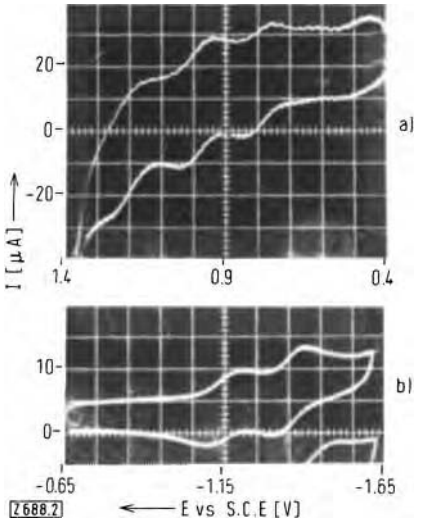


Fig. 2. Cyclic voltammogram of a) the oxidation of octaethylporphinatochromium(III) hydroxide *(3)* in butyronitrile (scan rate 1.54 V/s, 0.1 M $[Bu_4N]ClO_4$ as electrolyte) and b) the reduction of *(3)* in dimethyl sulfoxide (scan rate 0.60 V/s, 0.1 M $[Bu_4N]ClO_4$ as electrolyte).

Another case to be considered is that of octaethylporphinatochromium(III) hydroxide *(3)*. A typical set of cyclic voltammograms is shown in Fig. 2; five sets of peaks may be seen with $E_{\frac{1}{2}}$'s at 1.22, 0.99, 0.79, -1.14, and -1.35 V. A comparison of these potentials with the redox patterns found for normal porphyrins suggests that the two most oxidizing steps at 1.22 and 0.99 V can be assigned to ring oxidations since $\Delta E_{\frac{1}{2}\,ox}$ is close to the expected 0.29 ± 0.05 V. In addition, since there is another one-electron oxidation between the starting material *(3)* and the standard ring oxidation at 0.79 V, it is concluded that the Cr^{IV} complex is being produced. Unfortunately our initial attempts to produce pure solutions of this complex for the purpose of recording visible and ESR spectra were unsuccessful, owing

to instability of the complex at longer than polarographic time spans. Although reports on this oxidation state are rare (*e.g.*[14]) it has been invoked to explain the properties of hydroxy-bridged dimeric complexes of Cr^{III}[13]. The reaction at −1.14 V is believed to be the reduction of *(3)* to the Cr^{II} complex, with the second reduction at −1.35 V being attributed to the ring. Either of the values of −1.14 or −1.35 V satisfies the criterion of $E_{\frac{1}{2}\,ox} - E_{\frac{1}{2}\,red} = 2.25 \pm 0.15$ V. However the $\Delta E_{\frac{1}{2}\,red}$ of all octaethylporphyrin chelates is about 0.42 V. In the case at hand this difference would be only 0.21 V if the first reduction were that of the ring. The existence of a stable Cr^{II} complex[15] supports a $Cr^{III} \rightarrow Cr^{II}$ transition.

Received May 3, 1972 [Z 688 IE]
German version: Angew. Chem. *84*, 1072 (1972)

[1] *J.-H. Fuhrhop* and *D. Mauzerall*, J. Amer. Chem. Soc. *91*, 4174 (1969).

[2] *A. Stanienda* and *G. Biebl*, Z. Phys. Chem. (Frankfurt) *52*, 254 (1967).

[3] *J. Manassen* and *A. Wolberg*, J. Amer. Chem. Soc. *92*, 2982 (1970).

[4] *D. W. Clark* and *N. S. Hush*, J. Amer. Chem. Soc. *87*, 4238 (1955).

[5] *R. H. Felton* and *H. Linschitz*, J. Amer. Chem. Soc. *88*, 1113 (1966).

[6] *R. H. Felton, J. Fajer, D. C. Borg, A. Forman*, and *D. Dolphin*, J. Amer. Chem. Soc. *92*, 3451 (1970).

[7] *J.-H. Fuhrhop, K. Kadish*, and *D. G. Davis*, in preparation.

[8] *R. H. Felton, G. S. Owen, D. Dolphin*, and *J. Fajes*, J. Amer. Chem. Soc. *93*, 6332 (1971).

[9] *J. E. Falk*: Porphyrins and Metalloporphyrins. Elsevier, New York 1964.

[10] *A. MacCragh, C. B. Storm*, and *W. S. Koski*, J. Amer. Chem. Soc. *87*, 1470 (1965).

[11] *D. Sen, P. Ray*, and *N. N. Ghosh*, J. Indian Chem. Soc. *27*, 619 (1950).

[12] *S. Sailendra* and *N. G. Podder*, J. Indian Chem. Soc. *47*, 39 (1970).

[13] *L. Anghileri*, Z. Naturforsch. *B 25*, 288 (1970).

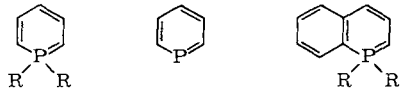
[14] *V. E. Huss* and *W. Klemm*, Z. Anorg. Allg. Chem. 262, 25 (1950).

[15] *M. Tsutsui, A. Velapoldi, K. Syzuki, F. Vohwinkel, M. Ichikawa*, and *T. Koyano*, J. Amer. Chem. Soc. *91*, 6262 (1969).

1,1-Dibenzyl-2-phenyl-1-phosphanaphthalene

By *Gottfried Märkl* and *Karl-Heinz Heier*[*]

1,1-Disubstituted phosphabenzenes *(1)* have been prepared by total synthesis[1], from pyrylium salts[2], and from phosphabenzene *(2)* by radical or ionic additions to the heteroatom[3].



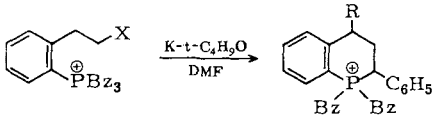
(1) *(2)* *(3)*

The question of the bonding relations in these systems with a formal $3d\pi - 2p\pi$ double bond has been discussed by *Mason*[4], *Fukui*[5], and *Vilceanu*[6]; *Schweig*'s assumption[7] of a delocalized π-electron system for *(1)* agrees with the results of ^{1}H-NMR spectroscopy[8] and of X-ray structure analysis[9].

These facts made it of interest to enquire whether the mesomerism of the benzene ring in 1,1-disubstituted phosphanaphthalenes *(3)* would prevent conjugation in the heterocycle and thus destabilize the system or whether the π-electron systems of both "halves" of the molecule would participate in naphthalene mesomerism.

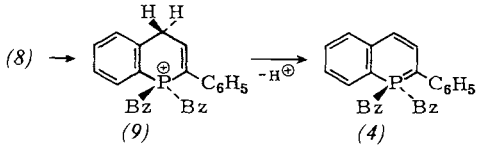
A successful synthesis of 1,1-dibenzyl-2-phenyl-1-phosphanaphthalene *(4)* has provided us with the first crystalline derivative of *(3)*[10].

Tribenzylphosphane[11] was arylated by *o*-bromophenylethyl methyl ether in methanol in presence of anhydrous $NiBr_2$[12], yielding the quaternary salt *(5)* in 60% yield (perchlorate, m.p. 121—123 °C). The bromide *(6)* (m.p. 136—137 °C) obtained by fission of this ether with HBr in glacial acetic acid (78% yield) cyclized on treatment with K-*tert*-butoxide in DMF by intramolecular *C*-alkylation[13] of the intermediate alkylidenephosphane, thus giving 1,1-dibenzyltetrahydro-2-phenylphosphonianaphthalene perchlorate *(7)* (80% yield) as colorless needles, m.p. 160—161 °C [^{1}H-NMR spectrum ($CDCl_3$): benzyl-CH_2: τ = 6.02 (d, 2H); 6.34 (d, 2H); $^2J_{P-H} = 13.5$ Hz].



(5), X = OCH_3 *(7)*, R = H
(6), X = Br *(8)*, R = Br

The 4-bromo derivative *(8)* prepared from *(7)* by *N*-bromosuccinimide (yield 77%; m.p. 180—181 °C) was dehydrobrominated when heated in 100% H_3PO_4 and simultaneously isomerized to the perchlorate of *(9)* [yield 96%; m.p. 151—152 °C; ^{1}H-NMR spectrum ($CDCl_3$): benzyl-CH_2: τ = 5.66 (m, 4H); H_γ: τ = 6.81 (m, 2H)].



(9) *(4)*

Deprotonation of *(9)* by dilute sodium hydroxide solution gave 1,1-dibenzyl-2-phenyl-1-phosphanaphthalene *(4)* which was moderately stable in solution and very stable in the solid state [yield 80%; shiny red leaflets, m.p. 123 °C (from ethanol/ethyl acetate).—IR spectrum (KBr): characteristic double band at 1285 cm^{-1} and 1295 cm^{-1}[14]. —UV spectrum (CH_3CN): λ_{max} (ε) = 470 (7400), 420 sh (4000), 310 nm (5600).—Mass spectrum: *m/e* = 404, rel. intensity 65% (M); 313, 100% (M − C_7H_7); 91, 54% (C_7H_7)].

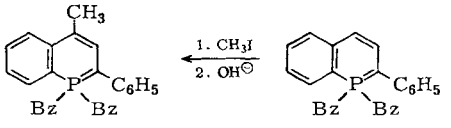
An increase in the π-electron density at positions 2, 4, and 6 (ylide character) of 1,1-disubstituted phosphabenzenes has been observed experimentally[8] and confirmed by *Schweig* by CNDO/2 calculations[7], which leads one to expect nucleophilic reactivity for *(4)* at positions 2 and 4. In agreement with this, *(4)* undergoes smooth alkylation and acylation:

With methyl iodide, *(4)* forms a phosphonium salt, deprotonation of which by aqueous NaOH gives 1,1-dibenzyl-4-methyl-2-phenyl-1-phosphanaphthalene *(10)* [yield 50%; carmine-red crystals (from ethanol/ethyl acetate), m.p. 109—111 °C.—UV spectrum: λ_{max} = 480

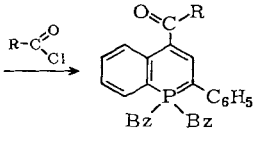
[*] Prof. Dr. G. Märkl and Dipl.-Chem. K.-H. Heier
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

nm (ε = 8000).—Mass spectrum: $m/e = 418$, rel. intensity 33% (M); 327, 100% ($M - C_7H_7$); 91, 94% (C_7H_7)].

Treating *(4)* with benzoyl chloride leads directly to 4-benzoyl-1,1-dibenzyl-2-phenyl-1-phosphanaphthalene *(11)*. The phosphonium salt first formed is immediately deprotonated by the more strongly basic *(4)* (transylidation).—*(11)*: yield 68%; shiny yellow needles, m. p.



(10) *(4)*

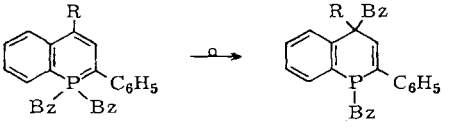


(11), R = C_6H_5
(12), R = OC_2H_5

186—188 °C (from ethanol/ethyl acetate).—IR spectrum (KBr): $\nu_{C=O} = 1500$ cm^{-1} (for comparison: for $(C_6H_5)_3P{=}CH{-}CO{-}C_6H_5$ $\nu_{C=O}$ is at 1527 cm^{-1} [15]); characteristic double band at 1270 and 1290 cm^{-1} [14].—^{1}H-NMR spectrum ($CDCl_3$): benzyl-CH_2: $\tau = 6.21$ (m, 4H) (ABX spectrum).—UV spectrum (ethanol): λ_{max} (ε) = 395 (26000); 275 nm (8200, sh).—Mass spectrum: $m/e = 508$, rel. intensity 68% (M); 417, 44% ($M - C_7H_7$); 91, 100% (C_7H_7).

(4) also reacts with ethyl chloroformate. The yellow ethyl 1,1-dibenzyl-2-phenyl-1-phosphanaphthalene-4-carboxylate *(12)* has not yet been obtained crystalline.—*(12)*: IR spectrum (KBr): $\nu_{C=O} = 1640$ cm^{-1}.—UV spectrum (ethanol): λ_{max} (ε) = 415 (10400); 375 (9500); 312 (10900).—Mass spectrum: $m/e = 476$, rel. intensity 40% (M), 385, 49% ($M - C_7H_7$); 91, 100% (C_7H_7).

Thermolysis of the 1,1-dibenzylphosphanaphthalenes proceeded in a surprising manner. Whereas 1,2-dibenzyldihydro-2,4,6-triphenylphosphabenzene rearranges at 180 °C to the 1,1-dibenzyl compound, which in turn decomposes to 2,4,6-triphenylphosphabenzene and bibenzyl at 220 °C [8], the 1,1-dibenzylphosphanaphthalenes *(4)* and *(10)* rearrange at 230—250 °C with migration of the benzyl group to position 4, yielding the 1,4-dibenzyl-1,4-dihydrophosphanaphthalenes *(13)* and *(14)*, respectively.—*(13)*: m.p. 126—128 °C, pale yellow crystals.—



(4), R = H
(10), R = CH_3

(13), R = H
(14), R = CH_3

UV spectrum (ethanol): λ_{max} (ε) = 265 (6500); 220 nm (48000, sh).—Mass spectrum: $m/e = 404$, rel. intensity 19% (M); 91, 100% (C_7H_7).—*(14)*: m. p. 131—134 °C, colorless crystals.—UV spectrum (ethanol): λ_{max} (ε) = 268 (5200); 215 nm (38000, sh).—Mass spectrum: $m/e = 418$, rel. intensity 50% (M); 91, 100% (C_7H_7).

Unlike the phosphabenzenes, 1,4-dihydrophosphanaphthalenes, as tertiary phosphanes, are clearly favored energetically over the phosphanaphthalenes with ter- or quinque-valent phosphorus.

Received: July 31, 1972 [Z 699a IE]
German version: Angew. Chem. *84*, 1066 (1972)

[1] *G. Märkl*, Angew. Chem. *75*, 669 (1963); Angew. Chem. internat. Edit. *2*, 479 (1963).

[2] *G. Märkl, A. Merz*, and *H. Rausch*, Tetrahedron Lett. *1971*, 2989.

[3] *G. Märkl* and *A. Merz*, Tetrahedron Lett. *1968*, 3611; *1969*, 1231; *K. Dimroth* and *W. Städe*, Angew. Chem. *80*, 966 (1968); Angew. Chem. internat. Edit. *7*, 881 (1968); *A. Hettche* and *K. Dimroth*, Tetrahedron Lett. *1972*, 829, *K. Dimroth, A. Hettche, H. Kanter*, and *W. Städe*, ibid. *1972*, 835.

[4] *S. F. Mason*, Nature *205*, 495 (1965).

[5] *K. Fukui, K. Morokuma*, and *Ch. Nagata*, Bull. Chem. Soc. Jap. *33*, 1214 (1961).

[6] *R. Vilceanu, A. Balint*, and *Z. Simon*, Nature *217*, 61 (1968).

[7] *H. Oehling* and *A. Schweig*, Tetrahedron Lett. *1970*, 4941.

[8] *G. Märkl* and *A. Merz*, Tetrahedron Lett. *1971*, 1215; *A. Merz*, Dissertation, Universität Würzburg 1969.

[9] *J. J. Daly* and *G. Märkl*, Chem. Commun. *1969*, 1057.

[10] *G. Märkl*, Angew. Chem. *75*, 168 (1963); Angew. Chem. internat. Edit. *2*, 153 (1963).

[11] *R. C. Hinton* and *F. G. Mann*, J. Chem. Soc. *1959*, 2835.

[12] *Y. Hirusawa, M. Oku*, and *K. Yamamoto*, Bull. Chem. Soc. Jap. *30*, 667 (1957); *L. Horner, G. Mummenthey, H. Moser*, and *P. Beck*, Chem. Ber. *99*, 2782 (1966).

[13] *G. Märkl*, Z. Naturforsch. *18b*, 84 (1963).

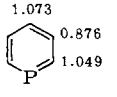
[14] All the 1,1-disubstitued-phosphabenzenes studied show this pair of bands.

[15] *F. Ramirez* and *S. Dershowitz*, J. Org. Chem. *22*, 41 (1957).

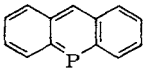
2-Phenyl-1-phosphanaphthalene

By *Gottfried Märkl* and *Karl-Heinz Heier* [*]

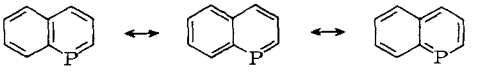
According to the results of spectroscopy [1], X-ray structure analysis [2], and CNDO/2 calculations [3], there exist in the phosphabenzoles *(1)* Hückel-aromatic systems with a π-electron density distribution differing from that in the pyridine system. As a result of the reactivity at positions 9



(1)



(3)



(2)

and 10 arising from the π-electron density distribution in anthracene itself, the dibenzannelated phospha compound 9-phosphaanthracene *(3)* [4] is less stable and cannot be isolated in the solid state; only the 10-phenyl derivative [5] is relatively stable, owing to reduction of the reactivity by steric shielding.

There arise the questions whether the decreasing stability would be observable also with the singly benzannelated

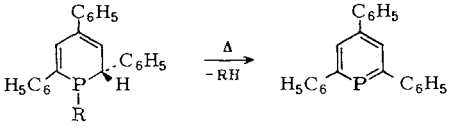
[*] Prof. Dr. G. Märkl and Dipl.-Chem. K.-H. Heier
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

phosphabenzenes, the phosphanaphthalenes *(2)*, whether bond fixation with support for the Kekulé structure by benzene mesomerism would result, or whether a delocalized 10π electron system incorporating the P=C $3p\pi-2p\pi$ double bond would be formed.

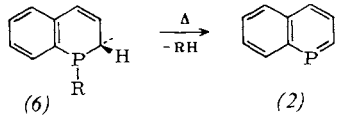
We now report the first synthesis of a phosphanaphthalene not carrying a substituent on the P atom, namely 2-phenyl-1-phosphanaphthalene *(4)*. Since we also describe 1,1-dibenzyl-2-phenyl-1-phosphanaphthalene[6] we can compare phosphanaphthalenes with tri- and quinquevalent phosphorus.

Unlike 1,1-dibenzyl-2,4,6-triphenylphosphabenzene which decomposes smoothly at 220°C to 2,4,6-triphenylphosphabenzene and bibenzyl, the benzyl groups at position 1 acting as protecting groups, the 1,1-dibenzyl-1-phosphanaphthalenes isomerize to 1,4-dihydrophosphanaphthalenes with migration of a benzyl group[6].

1-Alkyl-1,2-dihydro-2,4,6-triphenylphosphabenzenes *(5)* also undergo smooth thermal cleavage to the phosphabenzenes[7] [*(5a)* at 220°C, *(5b)* at 120°C]. 1-Alkyl-1,2-dihydrophosphanaphthalenes *(6)* should yield phosphanaphthalenes *(2)* analogously on thermolysis.

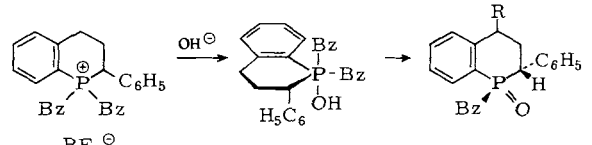


(5a), R = $CH_2C_6H_5$
(5b), R = $C(CH_3)_3$



(6) *(2)*

For the preparation of 1-benzyl-1,2-dihydro-2-phenylphosphanaphthalene, 1,1-dibenzyltetrahydro-2-phenylphosphonianaphthalene tetrafluoroborate *(7)* was hydrolyzed by alkali. Since in the pentacoordinated transition state of the hydrolysis[8] the diequatorial attachment of the ring to phosphorus is favored, the degradation proceeds smoothly, yielding 1-benzyltetrahydro-2-phenylphosphanaphthalene 1-oxide *(8)* [m.p. 209—211°C; yield 100%; mass spectrum: $m/e=332$ (M)].



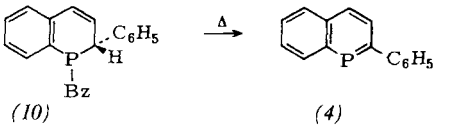
(7)

(8), R = H
(9), R = Br

Bromination of the oxide *(8)* by *N*-bromosuccinimide to give the 4-bromotetrahydrophosphanaphthalene 1-oxide *(9)* is effected in 50% yield[9]. The product crystallizes with 1 mol of ethanol [M.p. 120—122°C; mass spectrum: $m/e=410$ ($^{79}Br-M$); 412 ($^{81}Br-M$); 330, rel. intensity 100% (M−HBr)].

On dehydrobromination of *(9)* by LiBr in DMF at 150°C 1-benzyl-1,2-dihydrophosphanaphthalene 1-oxide is formed in 42% yield[9] (m.p. 143—144°C) and its reduction by trichlorosilane in boiling benzene smoothly affords the free phosphane *(10)*.

The 1-benzyl-2-phenyl-1,2-dihydrophosphanaphthalene *(10)* was heated at 260—300°C without purification. The pale yellow oil that distills off through an upright air-condenser soon crystallizes, yielding 2-phenyl-1-phosphanaphthalene *(4)* as shiny, pale yellow leaflets, m.p. 101—102°C (from ethanol), that are stable in air.—



(10) *(4)*

Mass spectrum: $m/e=222$, rel. intensity 100% (M); 189, 19% (M−PH_2); 178, 14% (M−HCP); 110, 18% ($C_6H_5PH_2$).—The ^{1}H-NMR spectrum (Fig. 1), with a

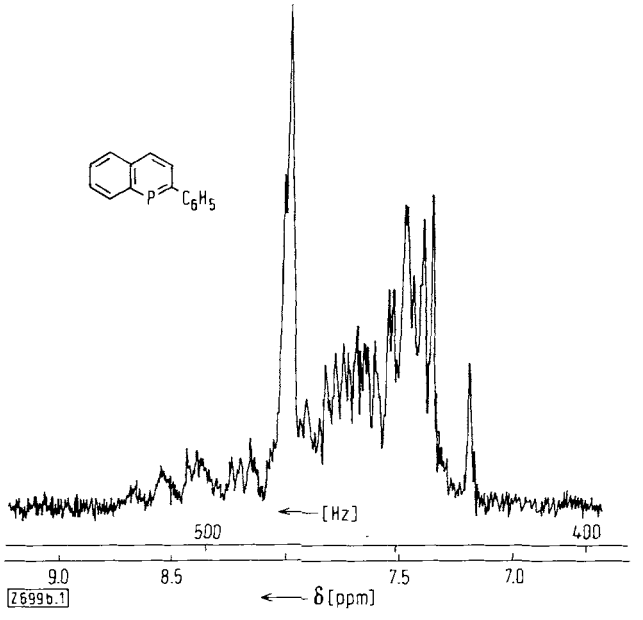


Fig. 1. ^{1}H-NMR spectrum of 2-phenyl-1-phosphanaphthalene *(4)* in $CDCl_3$.

multiplet at $\tau=1.34$ to 2.80, has much more fine structure than has that of 2-phenylquinoline ($\tau=1.50$—2.83), owing to the P coupling.—In the ^{31}P-NMR spectrum (H_3PO_4 as external standard) the resonance signal is at extremely low field (−197 ppm) as a doublet with unresolved fine structure; comparison of the chemical shift with that of simple tertiary phosphanes (Table 1) clearly shows the unusual electronic situation at the trivalent P atom with coordination number 2.—UV spectrum: λ_{max} (ε) = 332 (9300); 271 nm (49800); for comparison: 2-phenyl-

Table 1. Chemical shifts in the ^{31}P-NMR spectra of phosphorins and tertiary phosphanes (H_3PO_4 as external standard).

2,4,6-Triphenylphosphabenzene	−178.0 ppm
2-Phenylphosphanaphthalene	−197.0 ppm
Triphenylphosphane	+ 7.0 ppm
Triethylphosphane	+ 20.4 ppm

quinoline: 322 (6600); 256 nm (31600). If the still unconfirmed assignments are accepted, it appears that both the long-wave α-(^1L_b) band at 332 nm and the β-(^1B_b)

band at 271 nm are shifted bathochromically by 10 and 15 nm, respectively, relative to the corresponding bands of 2-phenylquinoline with simultaneous pronounced increases in the molar extinctions.

Received: July 31, 1972 [Z 699b IE]
German version: Angew. Chem. *84*, 1067 (1972)

[1] *G. Märkl*, Angew. Chem. *78*, 907 (1966); Angew. Chem. internat. Edit. *5*, 846 (1966); *G. Märkl, F. Lieb*, and *A. Merz*, Angew. Chem. *79*, 475, 947 (1967); Angew. Chem. internat. Edit. *6*, 458, 944 (1967); *K. Dimroth, N. Greif, W. Städe*, and *F. W. Steuber*, Angew. Chem. *79*, 725 (1967); Angew. Chem. internat. Edit. *6*, 711 (1967).

[2] *J. C. J. Bart* and *J. J. Daly*, Angew. Chem. *80*, 843 (1968); Angew. Chem. internat. Edit. *7*, 811 (1968).

[3] *H. Oehling* and *A. Schweig*, Tetrahedron Lett. *1970*, 4941.

[4] *P. de Koe* and *F. Bickelhaupt*, Angew. Chem. *79*, 533 (1967); Angew. Chem. internat. Edit. *6*, 567 (1967).

[5] *P. de Koe* and *F. Bickelhaupt*, Angew. Chem. *80*, 912 (1968); Angew. Chem. internat. Edit. *7*, 889 (1968).

[6] *G. Märkl* and *K. H. Heier*, Angew. Chem. *84*, 1066 (1972); Angew. Chem. internat. Edit. *11*, 1016 (1972).

[7] *G. Märkl* and *A. Merz*, Tetrahedron Lett. *1971*, 1215.

[8] *L. Horner, H. Winkler*, and *A. Rapp*, Tetrahedron Lett. *1961*, 161; *L. Horner*, Pure Appl. Chem. *9*, 225 (1964).

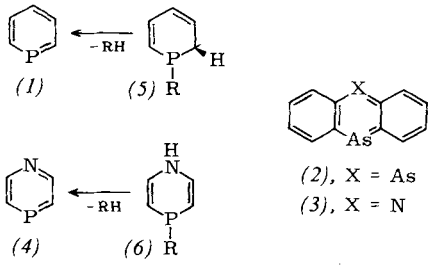
[9] Isomeric oils formed alongside the crystalline product were also used in the preparation of *(4)*.

2,6-Diphenyl-1-aza-4-phosphabenzene

By *Gottfried Märkl* and *Dieter Matthes*[*]

Our knowledge of six-membered aromatic phosphorus heterocycles containing trivalent phosphorus with coordination number 2 was until recently confined to the phosphabenzene system *(1)*[1].

It was not previously possible to prove that —P=N— or —P=P— double bonds to trivalent phosphorus could exist either as isolated double bonds or in systems stabilized by mesomerism[2]; fundamentally, however, there is no argument against the existence of six-membered phosphaheteroaromatic compounds containing heteroatoms of the fifth main group in positions 4 or 3,5 of the phosphabenzene ring.



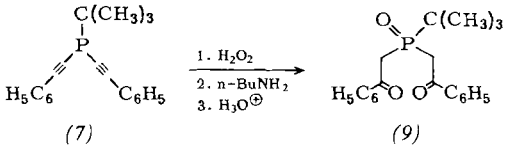
(1) *(5)* R *(2)*, X = As *(3)*, X = N *(4)* *(6)* R

The fact that diarsaanthracene *(2)* (as a 1,4-diarsabenzene derivative[3]) and azaarsaanthracene *(3)* (as a 1-aza-4-arsabenzene derivative[4]) occur as non-aromatic dimers[5] could be ascribable to destabilization of these systems by the dibenzannelation.

A basis for our envisaged preparation of 1-aza-4-phosphabenzenes *(4)* was offered by the synthesis[6] of 3,5-disubstituted 4-phenyl-1-aza-4-phosphacyclohexa-2,5-diene 4-oxides. It should be possible to extend the principle of thermolysis of 1,2-dihydrophosphabenzenes *(5)* to phosphabenzenes[7] to cover the aza system *(6)* if there were suitable leaving groups R[—$CH_2C_6H_5$ or —$C(CH_3)_3$] on the phosphorus.

For the synthesis of 4-*tert*-butyl-1,4-dihydro-2,6-diphenyl-1-aza-4-phosphabenzene *(11)*, *tert*-butylbis(phenylethynyl)phosphane *(7)* (obtained from *tert*-butyldichlorophosphane and C_6H_5—C≡C—MgBr, yield 75%; m.p. 84 °C; $\nu_{C\equiv C} = 2160\ cm^{-1}$) was converted into its oxide *(8)* (yield 98%; m.p. 82 °C; $\nu_{C\equiv C} = 2180\ cm^{-1}$, $\nu_{P=O} = 1230\ cm^{-1}$), whose *n*-butylamine adduct was hydrolyzed to the diketone *(9)* by *Aguiar*'s method[6].

(9): yield 56%, m.p. 108 °C (from ether/light petroleum; $\nu_{C=O} = 1665\ cm^{-1}$.—^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: τ = 1.85—2.8 (10 H, m); —CH_2—: τ = 6.2 (4 H, d), $^2J_{P-H} = 7$ Hz; *tert*-butyl: τ = 8.71 (9 H, d), $^3J_{P-H} = 8$ Hz.

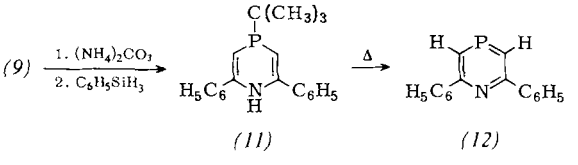


(7) *(9)*

The diketone *(9)* reacts with $(NH_4)_2CO_3$ during 24 h in a bomb-tube at 100 °C, giving a 65% yield of 4-*tert*-butyl-2,6-diphenyl-1-aza-4-phosphacyclohexa-2,5-diene 4-oxide *(10)*.

(10): m.p. 360—362 °C (from ethanol/water), $\nu_{NH} = 3250\ cm^{-1}$ (w), $\nu_{C=C} = 1620\ cm^{-1}$ (s).—^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: τ = 2.87 (10 H, s); vinyl-H: τ = 4.7 (2 H, dd), $^2J_{P-H} = 4$ Hz, $^4J_{NH-H} = 1$ Hz; *tert*-butyl: τ = 9.03 (9 H, d), $^3J_{P-H} = 10$ Hz; NH: τ = 1.73.

Phenylsilane reduces the oxide in boiling toluene during 72 h to the free dihydroazaphosphorin *(11)*.



(11) *(12)*

(11): yield 74%; m.p. 258—261 °C (dec); $\nu_{C=C} = 1620\ cm^{-1}$ (s).—Mass spectrum: *m/e* = 307, rel. intensity 13.5% (M); 250, 100% (M − C_4H_9); 219, 5.4% (M − C_4H_9P).—^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: τ = 2.6 (10 H, s); vinyl-H: τ = 4.92 (2 H, dd), $^2J_{P-H} = 7$ Hz, $^4J_{NH-H} = 1$ Hz; *tert*-butyl: τ = 8.8 (9 H, d), $^3J_{P-H} = 10$ Hz.

Methiodide of *(11)*: yield 68%, m.p. 229—230 °C.—^{1}H-NMR spectrum ($CDCl_3$): CH_3: τ = 8.04 (d), $^2J_{P-H} = 6.5$ Hz.

As expected, the azaphosphorin *(11)* was cleaved smoothly and quantitatively at 260—280 °C, 2,6-diphenyl-1-aza-4-phosphabenzene *(12)* distilling off *in vacuo* as a pale yellow, viscous oil.

(12): mass spectrum: *m/e* = 249, rel. intensity 100% (M), 172, 23% (M − C_6H_5); 146, 19% (M − C_6H_5CN); 102, 27% (C_6H_5—C≡C).—^{1}H-NMR spectrum (Fig. 1): phenyl-H: τ = 1.84—3.0 (m); H_α: τ = 1.34 (d), $^2J_{P-H} = 18$ Hz.—The position of the signal of the H_α ring protons of *(12)* corresponds to the position of the signals of the α-protons in the phosphabenzenes *(e.g.* τ = 1.2 for 3,4,6-triphenylphosphabenzene, $^2J_{P-H} = 38$ Hz[8]), but the P—H coupling is distinctly smaller. This shows *(12)* to be a heteroaromatic compound, an assumption that is supported by the ^{31}P-

[*] Prof. Dr. G. Märkl and D. Matthes
Fachbereich Chemie der Universität
84 Regensburg, Universitätsstrasse 31 (Germany)

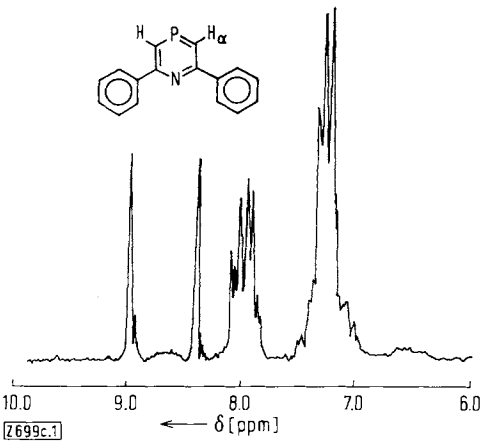
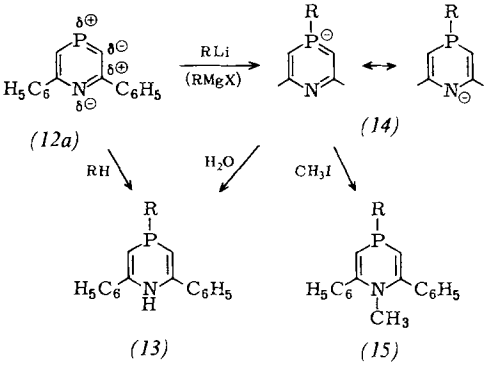


Fig. 1. ^{1}H-NMR spectrum of 2,6-diphenyl-1-aza-4-phosphabenzene *(12)*.

NMR spectrum: $\delta = -245.4$ ppm (t), $^2J_{H-P} = 18$ Hz (H_3PO_4 as external standard). The signal lies at even lower field than that for 2,4,6-triphenylphosphabenzene [$\delta = -178$ ppm (m)].

The chemistry of *(12)* is surprising and clearly shows the influence of aza substitution. The phosphabenzene ring system exhibits no nucleophilic character but is, instead, markedly electrophilic[9]. This reactivity of trivalent phosphorus of coordination number 2 is considerably enhanced by the nitrogen at position 4 [the π-electron density distribution indicated in *(12a)* is in agreement with CNDO/2 calculations[10] for the phosphorin system]. The compound *(12)* reacts with organometallic compounds (RLi and RMgX) and, unlike phosphabenzene, also with weak nucleophiles such as alcohols, phenols, thiols, and amines with addition of the nucleophile to phosphorus.



(13a), $R = OC_2H_5$, yield 78%; m.p. 117—120 °C.

Mass spectrum: $m/e = 295$, rel. intensity 11.4% (M); 249, 100% ($M - C_2H_5OH$) [= M(12)]; 250, 50% [M(12)+H]; 248, 89% [M(12)−H].

^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: $\tau = 2.2$—2.6, (10H, m); —OCH_2—: $\tau = 6.25$ (q), 6.44 (q) (2H), $^3J_{P-H} = 3.5$ Hz, $^3J_{H-H} = 3.5$ Hz; —CH_3: $\tau = 8.67$ (t), 8.71 (t) (3H), $^3J_{H-H} = 3.5$ Hz; vinyl-H: $\tau = 4.32$ (dd), $^2J_{P-H} = 4$ Hz, $J_{NH-H} = 1$ Hz; $\tau = 4.12$ (d), $^2J_{P-H} = 19$ Hz (2H); there are probably some equatorially and some axially attached ethoxy groups on the phosphorus.

(13b), $R = -OC_6H_5$, yield 64%; m.p. 197—199 °C.

Mass spectrum: M does not appear; $m/e = 266$, rel. intensity 2.1% ($M - C_6H_5$); 249, 100% ($M - C_6H_5OH$) [= M(12)]; 248, 60% [M(12)−H].

^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: $\tau = 3.32$—3.95 (15H, m); vinyl-H: $\tau = 5.6$ (2H, dd), $^2J_{P-H} = 4$ Hz, $J_{NH-H} = 1$ Hz.

(13c), $R = -SCH(CH_3)_2$, yield 59%; m.p. 263—265 °C (oxide).

^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: $\tau = 2.3$—2.78 (10H, m): vinyl-H: $\tau = 4.5$ (2H, dd), $^2J_{P-H} = 2.5$ Hz, $J_{NH-H} = 1$ Hz; S—CH: $\tau = 6.95$ (1 H, 2 septets), $^3J_{H-H} = 3$ Hz, $^3J_{P-H} = 1$ Hz; CH_3: $\tau = 8.68$ (6 H, d).

Reaction of *(12)* with organometallic compounds affords first the mesomeric anions *(14)*, whose hydrolysis gives the dihydroazaphosphorins *(13)* and whose alkylation gives the *N*-alkyl derivatives *(15)*.

tert-Butyl-MgCl affords the dihydro compound *(11)* in 72% yield.

In the reaction with phenyllithium the compound *(13d)* with $R = C_6H_5$ is formed in 58% yield as pale yellow needles, m.p. 145—146 °C.—Mass spectrum: $m/e = 327$, rel. intensity 100% (M); 328, 24% (M+H); 326, 6% (M−H); 250, 64% ($M - C_6H_5$); 219, 48% ($M - PC_6H_5$).—^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: $\tau = 1.8$—2.8 (15H, m); vinyl-H: $\tau = 4.68$ (2H, dd), $^2J_{P-H} = 7$ Hz, $^4J_{NH-H} = 1$ Hz.

After treatment of a solution of *(14)*, $R = C_6H_5$, with methyl iodide, the *N*-methyl derivative *(15)*, $R = C_6H_5$, can be isolated in 42% yield as colorless needles, m.p. 194—196 °C.—^{1}H-NMR spectrum ($CDCl_3$): phenyl-H: $\tau = 2.32$—2.72 (15H, m); vinyl-H: $\tau = 3.63$ (2H, s); N—CH_3: $\tau = 6.32$ (3H, s).

Received: August 4, 1972 [Z 699c IE]
German version: Angew. Chem. *84*, 1069 (1972)

[1] *G. Märkl*, Angew. Chem. *78*, 907 (1966); Angew. Chem. internat. Edit. *5*, 846 (1966). *G. Märkl*, *F. Lieb*, and *A. Merz*, Angew. Chem. *79*, 475, 947 (1967); Angew. Chem. internat. Edit. *6*, 458 (1967); *A. J. Ashe*, J. Amer. Chem. Soc. *93*, 3293 (1971).

[2] *R. F. Hudson*: Structure and Mechanism in Organo-Phosphorus Chemistry. Academic Press, New York 1965, pp. 20ff.

[3] *L. Kalb*, Liebigs Ann. Chem. *423*, 39 (1921).

[4] *H. Wieland* and *W. Rheinheimer*, Liebigs Ann. Chem. *423*, 1 (1921).

[5] *H. Veermer* and *F. Bickelhaupt*, Tetrahedron Lett. *1970*, 1323; 3255.

[6] *J. C. Williams*, *J. A. Kuczkowski*, *N. A. Portnoy*, *K. S. Yong*, *J. D. Wander*, and *A. M. Aguiar*, Tetrahedron Lett. *1971*, 4749.

[7] *G. Märkl* and *A. Merz*, Tetrahedron Lett. *1971*, 1215; *G. Märkl* and *D. E. Fischer*, *ibid.* *1970*, 645; *G. Märkl* and *K. H. Heier*, Angew. Chem. *84*, 1067 (1972); Angew. Chem. internat. Edit. *11*, 1017 (1972).

[8] *F. Lieb*, Dissertation, Universität Würzburg 1969.

[9] *G. Märkl*, *A. Merz*, and *F. Lieb*, Angew. Chem. *79*, 59 (1967); Angew. Chem. internat. Edit. *6*, 87 (1967). *G. Märkl* and *A. Merz*, Tetrahedron Lett. *1968*, 3611.

[10] *H. Oehling* and *A. Schweig*, Tetrahedron Lett. *1970*, 4941.

Preparation and Structure of the Fluoro Complex $Rb[Mo_2O_2F_9]$

By *Arndt Beuter* and *Wolfgang Sawodny*[*]

It has been concluded several times[1-3] from ^{19}F-NMR data that dimeric fluoro complexes of the formula $[M_2O_2F_9]^-$ should exist (M = Mo or W), but it has not previously been possible to isolate such compounds. In attempts to prepare the complex $[MoOF_5]^-$ we obtained by-products in varying amounts. One of these was obtained pure after treatment of RbF with $MoOF_4$ in liquid SO_2.

[*] Dipl.-Chem. A. Beuter and Prof. Dr. W. Sawodny
Abteilung für Anorganische Chemie der Universität
79 Ulm, Oberer Eselsberg (Germany)

Analytical results and vibrational spectra showed it to be $Rb[Mo_2O_2F_9]$.

It was found that the dimeric fluoro complex $[Mo_2O_2F_9]^-$ was formed as the main product by all the methods tried by us for preparation of $[MoOF_5]^-$ (treatment of moist CsF with MoF_6 in IF_5 or SO_2, reaction of $Cs_2[MoO_2F_4]$ with MoF_6 in SO_2, and reaction of K_2MoO_4 with anhydrous HF). On the other hand, the analogous tungsten complex $[W_2O_2F_9]^-$ could be detected as an impurity in $Cs[WOF_5]$ and $Cs[WF_6]$ by means of vibrational spectroscopy [ν_{WO} at 1032 (s) and 1047 (vw) cm^{-1}] but has not yet been isolated in a pure state[4].

Although the vibrational spectra of $Rb[Mo_2O_2F_9]$ cannot yet be fully assigned (Table 1), some conclusions about the structure of the $[Mo_2O_2F_9]^-$ ion can be drawn from them. The MoO stretching vibrations lying above 1000

Table 1. IR and Raman spectra of $Rb[Mo_2O_2F_9]$ [a].

IR [cm^{-1}]	Raman [cm^{-1}]	Assignment
1033 w	1033 m	ν_{MoO}sym.
1022 s		ν_{MoO}asym.
974, 953, 935 vw	984	See text
	930 vw	
689 sh	685 s	ν_{MoF}sym.
660 vs		ν_{MoF}asym.
635 w		ν_{MoF}
	576 w	ν_{MoF}
422 m		$\nu_{Mo-F-Mo}$asym.
	321 m	
310 w	310 w	bending vibrations
284 s		
270 m		

[a] The IR spectra were determined for a Nujol suspension on a grating spectrograph of Perkin-Elmer 325 type, and the Raman spectrum for the crystal powder in a glass capillary with the Coderg apparatus PH1 with excitation by the blue (4880 Å) and the green (5140 Å) line of an Ar/Kr mixture gas laser.

cm^{-1} (*i.e.* very high) show that the O atoms must be terminal, *i.e.* that there is no Mo—O—Mo bridge, and that there is not more than one oxygen atom on each Mo atom[5]. Besides the stretching frequencies of the terminal F atoms (579—689 cm^{-1}) an IR band appears at 422 cm^{-1} which, from its position, cannot be assigned to these stretching vibrations or to bending modes; it can be plausibly interpreted as an asymmetric Mo—F—Mo bridge vibration. The deformation vibrations (from 321 cm^{-1} downwards) are incomplete and cannot yet be assigned. In all the spectra, bands of various intensities between 900 and 1000 cm^{-1} are probably to be attributed to products of hydrolysis of this substance, which is very sensitive to moisture.

Assuming the coordination number 6 for the metal atom, we therefore consider the structure to be $OF_4Mo—F—MoF_4O$. The intensity ratio of 1:8 in the ^{19}F-NMR spectrum[1-3] makes it probable that the MoO bonds are in *trans*-position to the F bridge. Whether the bridge is bent or linear, and whether the equatorial F atoms of the two octahedra, linked at corners, are eclipsed or not, cannot by yet determined.

Experimental:

$MoOF_4$ (10 mmol) is stirred with RbF (3 mmol) in liquid SO_2 under N_2 for 2 h at −20 to −30 °C in a Pyrex glass apparatus. All the vessels and substances must have been well dried. After only a short time the very finely crystalline product separates. After the SO_2 and excess of $MoOF_4$ have been pumped off with gradual warming to 100 °C, the product $Rb[Mo_2O_2F_9]$ is obtained as a fine, pale bluish-grey powder. It is extremely sensitive to hydrolysis, which causes intense blue coloration. Presumably the pale blue color of our samples is due to slight hydrolysis, *i.e.* quite pure $Rb[Mo_2O_2F_9]$ should be white. In the reaction described, $Rb[Mo_2O_2F_9]$ is the sole product independently of the relative amounts of starting materials.

Received: August 8, 1971 [Z 701 IE]
German version: Angew. Chem. *84*, 1099 (1972)

[1] *Yu. A. Buslaev, Yu. V. Kokunov,* and *V. A. Bochkareva,* Dokl. Akad. Nauk SSSR *201*, 355 (1971).

[2] *J. I. Darragh, A. M. Noble,* and *D. M. A. Winfield,* J. Inorg. Nucl. Chem. *32*, 1745 (1970).

[3] *F. N. Tebbe* and *E. L. Muetterties,* Inorg. Chem. *7*, 172 (1968).

[4] *A. Beuter* and *W. Sawodny,* unpublished.

[5] *W. Sawodny* and *A. Beuter,* Z. Anorg. Allg. Chem. *381*, 1 (1971).

Total Synthesis of D-Aldgarose[1]

By *Hans Paulsen* and *Hartmut Redlich*[*]

Aldgamycin E, a neutral macrolide antibiotic from *Streptomyces lavendulae*, contains besides mycinose a further sugar component, called aldgarose[2, 3], which is a complex branched monosaccharide, the stereochemistry of whose sidechain has not previously been elucidated. We have now succeeded in introducing the desired sidechain[5] by *Seebach*'s procedure[4] of adding 1,3-dithiane anions to carbonyl compounds, and we have thus synthesized the four possible isomeric methyl β-D-aldgarosides. Comparing the physical and spectroscopic data with results from the natural product has made it possible to assign the configuration of the latter unambiguously.

The starting material for this synthesis was D-galactose pentaacetate *(1)*, which with HBr afforded the dibromo compound *(2)*, and this was at once converted into the methyl glycoside *(3)*, m.p. 93 °C, $[\alpha]_D^{20} = -5.3°$, in 72% yield. Hydrogenation of *(3)* gave *(4)*[6], from which methyl β-D-fucoside *(5)* was obtained by hydrolysis. Reaction of *(5)* with acetone dimethyl ketal yields the 3,4-acetal *(6)* selectively (a syrup, $[\alpha]_D^{20} = +24.5°$, yield quantitative), which was converted into the 2-benzyl ether *(7)* (a syrup, $[\alpha]_D^{20} = +39.8°$, yield quantitative). The acetal group of *(7)* was removed by acid, yielding *(8)* (a syrup, $[\alpha]_D^{20} = +10.0°$, yield quantitative), whose ditosylate *(9)* (m.p. 165 °C, $[\alpha]_D^{20} = +35.0°$) was then prepared in 75% yield. In a process developed by us[7] 1,2-*cis*-di-*O*-tosylpyranoses can be converted by hydrazine into deoxyketoses, the axial *O*-tosyl group being converted into a deoxy, and the equatorial *O*-tosyl group into a keto, group. This reaction can be effected with *(9)*, whereby the 3-ulose hydrazone *(10)* is formed and this is at once cleaved by salicylaldehyde into the free 3-ulose *(11)* (an oil, $[\alpha]_D^{20} = -64.0°$, yield 65%).

The 3-ulose *(11)* can be treated with 2-lithio-2-methyl-1,3-dithiane[4] in THF at −70 °C, whereupon the dithiane

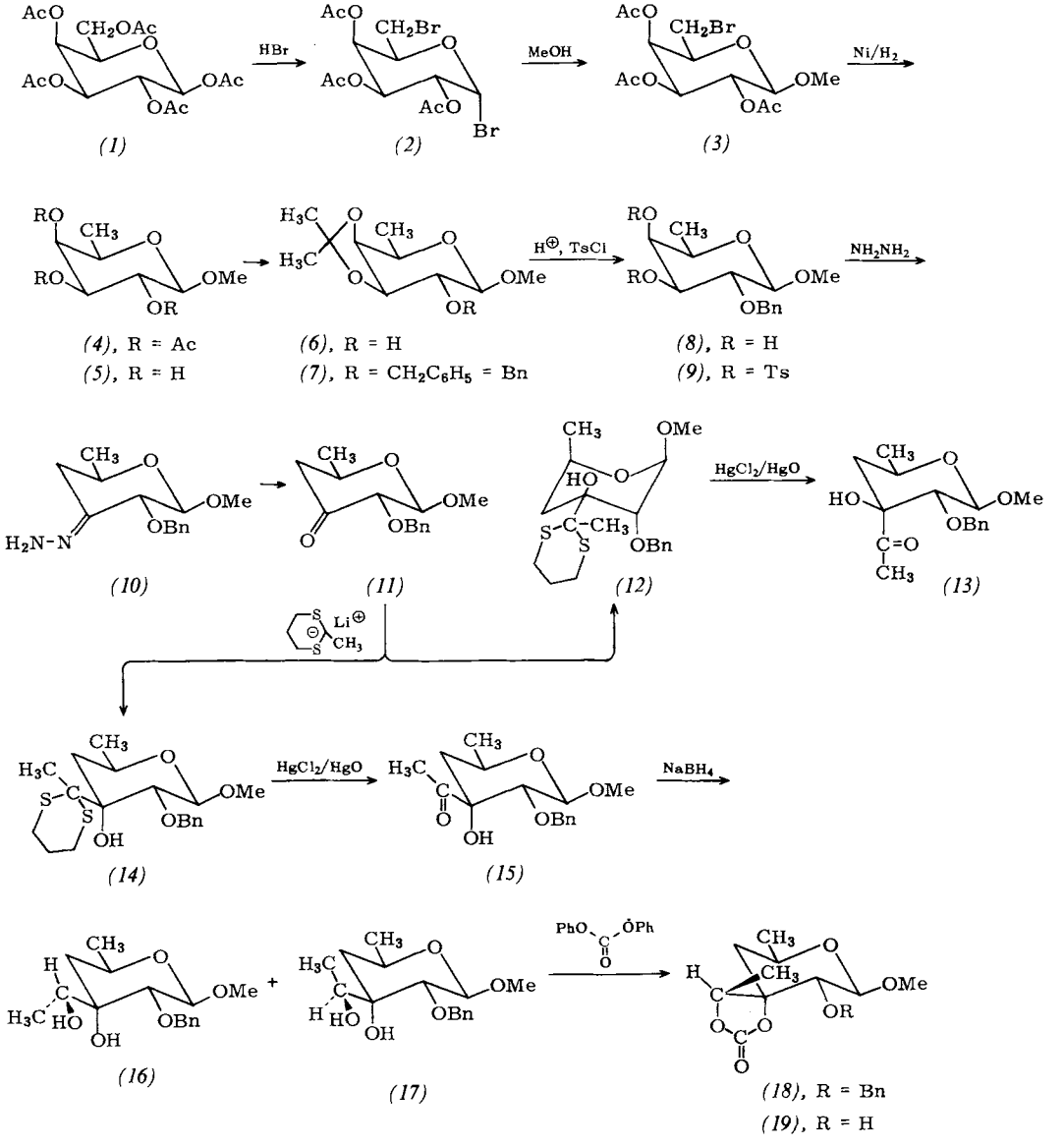
[*] Prof. Dr. H. Paulsen and Dipl.-Chem. H. Redlich
Institut für Organische Chemie und Biochemie der Universität
2 Hamburg 13, Papendamm 6 (Germany)

sugars *(14)* and *(12)* are obtained in a molar ratio of 3 : 2 (syrups, $[\alpha]_D^{20} = -7.4°$ and $+2.1°$, respectively, total yield 80%). The 2-methyl-1,3-dithiane sidechain behaves sterically as a *tert*-butyl group; therefore, *(14)* and *(12)* assume conformations in which the sidechain is equatorial, with the result that *(12)* assumes a reversed chair form. This finding is important because, with the chair form proved, the configuration at the branch point can be determined for both isomers by complete NMR analysis, and this would not be possible in any other simple way. Desulfuration of *(14)* by $HgCl_2/HgO$ affords ketone *(15)* (m.p. 107 °C, $[\alpha]_D^{20} = -0.8°$, yield 37%), and that of *(12)* affords the ketone *(13)* (m.p. 73 °C, $[\alpha]_D^{20} = -8.6°$, yield 21%). The side chain of *(13)* is not so sterically demanding, so that here the normal $^4C_1$ conformation with an axial acetyl group is once more assumed.

β-D-aldgarosides, of which the compound *(19)* (m.p. 178—180 °C, $[\alpha]_D^{20} = -43.5°$) proved identical in ^{1}H-NMR spectrum, melting point and optical rotation with the aldgaroside B described in the literature[2].

The configuration of the sidechain at C-7 is assigned from the following findings: In *(18)* and the carbonate from *(16)* a methyl group and a proton, respectively, are attached to C-7 of the sidechain in a 1,3-quasiaxial position relative to the *O*-benzyl group at C-2. In both cases the corresponding NMR signals are found to be shifted to lower field, whence the assignment can be made by the rules due to *Lemieux*[8] and *Zürcher*[9].

For the alcohol *(16)*, the *gauche* conformation shown in *(16)* should be favored, according to the views of *Lemieux*[10], and *ab initio* calculations by *Jeffrey* and *Pople*[11] and by



The ketones *(13)* and *(15)* each give two alcohols on reduction with $NaBH_4$; the alcohols *(16)* and *(17)* are formed from *(15)*. The two pairs of alcohols can be separated, and all four alcohols were converted into their respective 3,7-carbonates by diphenyl carbonate; in this way, *(17)* gave *(18)* (m.p. 181 °C, $[\alpha]_D^{20} = -14.9°$, yield 70%). Removal of the benzyl group by hydrogenolysis from each of the four carbonates afforded the four isomeric methyl

Wolfe et al.[12]. No preference can be recognized for either of the two possible *gauche* conformations of alcohol *(17)*. If, on these assumptions, one estimates the optical rotations, using the empirical standard values given by *Lemieux*[13] for all the asymmetric conformational elements, one finds that *(17)* should have a more negative optical rotation than *(16)*; the values found are *(17)*, $[M]_D^{20} = -109°$, and *(16)*, $[M]_D^{20} = -57.5°$. The two methods lead

to the same conclusion, namely that the configuration is (*S*) at C-7 of *(19)*.

Received: August 9, 1972 [Z 702 IE]
German version: Angew. Chem. *84*, 1100 (1972)

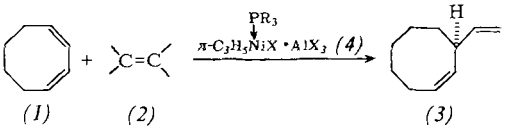
[1] Part 3 of Branched Sugars.—Part 2: *H. Paulsen, V. Sinnwell*, and *P. Stadler*, Chem. Ber. *105*, 1978 (1972).
[2] *G. A. Ellestad, M. P. Kunstmann, J. E. Lancaster, L. A. Mitscher*, and *G. Morton*, Tetrahedron *23*, 3893 (1967).
[3] *R. Schmid, H. Grisebach*, and *W. Karl*, Eur. J. Biochem. *14*, 243 (1970); *H. Grisebach* and *R. Schmid*, Angew. Chem. *84*, 192 (1972); Angew. Chem. internat. Edit. *11*, 159 (1972).
[4] *D. Seebach*, Synthesis *1969*, 17; Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969).
[5] *H. Paulsen, V. Sinnwell*, and *P. Stadler*, Angew. Chem. *84*, 112 (1972); Angew. Chem. internat. Edit. *11*, 149 (1972).
[6] The steps *(1)* to *(4)* were worked out by Prof. *C. Pedersen et al.*, Copenhagen. We thank them for sending us directions.
[7] *H. Paulsen* and *D. Stoye*, Chem. Ber. *102*, 834 (1969).
[8] *R. U. Lemieux* and *J. D. Stevens*, Can. J. Chem. *44*, 249 (1966).
[9] *R. F. Zürcher*, Progr. Nuclear Magnetic Resonance Spectrosc. *2*, 205 (1967).
[10] *R. U. Lemieux*, Pure Appl. Chem. *25*, 527 (1971).
[11] *G. A. Jeffrey, J. A. Pople*, and *L. Radom*, Carbohydrate Chem. in press.
[12] *S. Wolfe, A. Rauk, L. M. Tel*, and *J. G. Csizmadia*, J. Chem. Soc. *B 1971*, 136; *S. Wolfe*, Accounts Chem. Res. *5*, 102 (1972).
[13] *R. U. Lemieux* and *J. C. Martin*, Carbohydrate Res. *13*, 139 (1970).

A Catalyzed Asymmetric Synthesis

By *Borislav Bogdanović, Biserka Henc, Burkhard Meister, Horst Pauling*, and *Günther Wilke*[*]

Few asymmetric syntheses proceeding under catalytic conditions have been reported. High optical purity has been obtained only in hydrogenation using optically active catalysts in which the chiral centers are formed as a result of C—H bond formation[1].

During our studies[2] on the influence of phosphanes upon the oligomerization of olefins by π-allylnickel halide-Lewis acid systems we have developed catalysts which are able to convert 1,3-cyclooctadiene *(1)* and ethylene *(2)* into 3-vinylcyclooctene *(3)* having an optical purity of up to 70%.



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

The catalysts *(4)* were prepared, for example, in methylene chloride or chlorobenzene from π-allylnickel chloride, ethylaluminum sesquichloride and an optically active phosphane (molar ratio 1:2.5:1.2) in which the groups R on the phosphorus atom are chiral. Ethylene is led into a mixture of the catalyst solution and 1,3-cyclooctadiene.

The greatest optical induction was obtained with phosphanes containing very bulky, optically active groups R and by carrying out the catalysis at the lowest possible temperature. The high activity of the catalysts allows the reaction to be carried out even at temperatures around −75 °C, so that the maximum effect is obtained from the small differences in the free activation enthalpy for the reaction of the intermediate diastereoisomers formed from the catalyst and the substrate. The $\Delta\Delta H^{\neq}$ are about 1.1 kcal/mol to which the entropy and enthalpy terms contribute the following values at the temperatures stated: $T\Delta\Delta S^{\neq}$ 0 °C −0.82, −40 °C −0.70, −75 °C −0.59 kcal/mol; and $\Delta\Delta G^{\neq}$ 0 °C 0.28, −40 °C 0.40, −75 °C 0.51 kcal/mol. These values should be treated only as estimates of the orders of magnitude.

(+)-3-Methyl-1-pentene *(5)* [Ref. [3]: $[\alpha]_D^{22} = +36.95°$] with a maximum optical purity of 64% is a by-product formed by the trimerization of ethylene. Table 1 shows the relation of the optical yield to the nature of the phosphane (chlorobenzene and 0 °C being chosen as standard conditions for these comparisons).

Table 1. Relation of optical yield to the nature of the phosphane.

Phosphane	$[\alpha]_D^{22}$ [a]	3-Vinylcyclooctene *(3)* Sign of rotation	3-Vinylcyclooctene *(3)* Opt. purity (%)	3-Methyl-1-pentene *(5)* Sign of rotation	3-Methyl-1-pentene *(5)* Opt. purity (%)
(−)-Dimenthylisopropyl-	−158°	(−)	27	(+)	17
(−)-Dimenthylmethyl-	−199°	(−)	24	(+)	46
(−)-Tris(*trans*-myrtanyl)-[f]	− 12.6°	(−)	12	(±)	0
(−)-*trans*-Myrtanyl-*tert*-butylmethyl-	− 2.1° [b]	(−)	10	(±)	0
(+)-Dibornylmethyl-	+ 85.3°	(+)	9.5	(−)	12
Phenyl-*tert*-butylmethyl-	− [c]	(−)	8.0	(−)	12.5
(−)-Menthyldimethyl-	−119°	(+)	6	−	− [e]
(−)-Phenyl-*n*-propylmethyl- [4]	− [d]	(+)	5	−	− [e]
(−)-Menthyldiisopropyl-	−102°	(−)	3.5	(+)	14
(+)-Tris(2-methylbutyl)-	+110.4°	(−)	3.0	(+)	27
(−)-Tris(*cis*-myrtanyl)-	− 96.2°	(+)	0.5	(±)	0

[a] In benzene.
[b] Homogeneous.
[c] The adduct of racemic *tert*-butylmethylphenylphosphane to (+)-α-pinenylnickel bromide was recrystallized twice from ether and used as catalyst component.
[d] As benzylmethylphenyl-*n*-propylphosphonium bromide, $[\alpha]_D^{22} = -35.1°$ (Ref. [5]: $[\alpha]_D^{22} = +36.8°$).
[e] No C_6 olefin is formed in the catalyzed reaction.
[f] Myrtanyl = 10-pinanyl.

[*] Dr. B. Bogdanović, Dr. B. Henc, Dr. B. Meister [**], Dr. H. Pauling [***], and Prof. Dr. G. Wilke
Max-Planck-Institut für Kohlenforschung
433 Mülheim, Kaiser-Wilhelm-Platz 1 (Germany)
[**] Now Continental Gummi Werke AG., Hannover.
[***] Now Hoffmann La Roche, Basel (Switzerland).

The values obtained for the optical purities of *(3)* and *(5)* show that the catalysts are to some extent substrate-specific since the order of increasing optical purity found for *(3)* differs widely from that for *(5)*. When (−)-dimenthylmethylphosphane is used as catalyst the optical purity

of *(3)* increases with decreasing temperature: 0 °C 23.5%; −40 °C 41.5%; −75 °C 53% (in CH_2Cl_2).

The greatest optical purity for *(3)* (70%) is already obtained with (−)-dimenthylmethylphosphane at 0 °C with a Ni : P ratio of 1 : 3.8, so that in this case it is the effect of phosphane excess which is most important. It is possible that a second molecule of the inducing phosphane bonds to the Ni atom.

The absolute configuration and the rotation of optically pure 3-vinylcyclooctene were determined in three ways:

1. Degradation to (−)-3-methylnonene and correlation with the known (+)-(*S*)-3-methylnonane[6].

2. Conversion into 2- and 3-ethylcyclooctanol and gas-chromatographic analysis of the diastereoisomeric lactic esters[7].

3. A seven-stage synthesis with separation of the intermediate racemic 3-cyclooctenylacetic acid as its quinine salt.

(−)-(*S*)-3-Vinylcyclooctene with $[\alpha]_D^{22.8} = -162.3°$ was obtained by the third method. The optical yields determined by the three methods agreed within the experimental errors.

To the best of our knowledge, the codimerization of 1,3-cyclooctene and ethylene to give optically active 3-vinylcyclooctene as described here is the first case of an asymmetric synthesis, proceeding catalytically, in which the chiral centers are generated in high optical purity as a result of C—C bond formation. The phosphanes listed are new.

Received: August 14, 1972 [Z 705 IE]
German version: Angew. Chem. *84*, 1070 (1972)

[1] *S. Akabori, S. Aakurai, Y. Izumi,* and *Y. Fugii,* Nature *178*, 323 (1956); *W. S. Knowles* and *M. I. Sabacky,* Chem. Commun. *1969*, 1445; *L. Horner, H. Siegel,* and *H. Büthe,* Angew. Chem. *80*, 1034 (1968); Angew. Chem. internat. Edit. *7*, 942 (1968); *Y. Izumi,* Bull. Chem. Soc. Japan *21*, 241 (1969); *P. Abley* and *J. McQuillen,* Chem. Commun. *1969*, 477; *T. P. Dang* and *H. G. Kagan, ibid. 1971*, 481; *W. S. Knowles, M. I. Sabacky,* and *B. D. Vineyard, ibid. 1972*, 10.

[2] *G. Wilke et al.,* Angew. Chem. *78*, 157 (1966); Angew. Chem. internat. Edit. *5*, 151 (1966); *G. Wilke* and *B. Bogdanović,* Brennstoffchemie *49*, 323 (1968).

[3] *P. Pino, L. Lardicci,* and *L. Centoni,* J. Org. Chem. *24*, 1399 (1959).

[4] *D. Korpium, R. A. Lewis, J. Chickos,* and *K. Mislow,* J. Amer. Chem. Soc. *90*, 4842 (1968); *H. Fritsch, U. Hasserodt,* and *F. Korte,* Chem. Ber. *97*, 1988 (1964).

[5] *L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann,* and *P. Beck,* Tetrahedron Lett. *1961*, 161.

[6] *R. L. Leitsinger* and *J. G. Traynham,* J. Amer. Chem. Soc. *72*, 849 (1950).

[7] *E. Gil-Av, R. Charles-Sigler, G. Fischer,* and *D. Nwrok,* J. Gas-Chromatog. *4*, 51 (1966); *R. L. Stern, B. L. Karger, W. J. Keane,* and *H. C. Roth, ibid. 39*, 17 (1969).

Photolysis of 2,3-Diazido-2,3-dimethylbutane

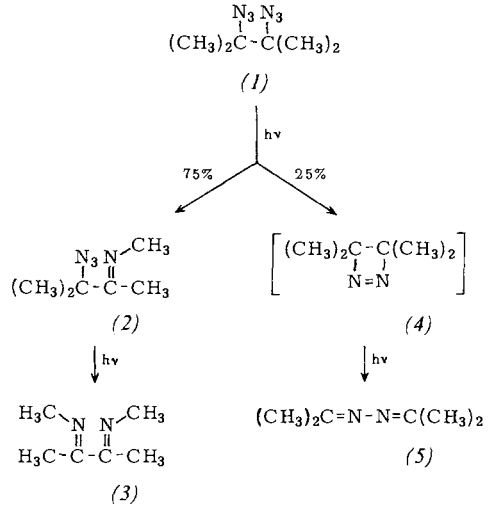
By *Paul Margaretha* and *Sonja Solar*[*]

There is no report in the literature about the photochemical behavior of vicinal diazides, though there are some about geminal diazides. We describe here the photolysis of the ditertiary[1] vicinal diazide *(1)*.

[*] Dr. P. Margaretha and Dr. S. Solar
Max-Planck-Institut für Kohlenforschung
Abteilung Strahlenchemie
433 Mülheim/Ruhr, Stiftstrasse 34—36 (Germany)

The main reaction takes the expected course: the Schiff bases *(2)* and *(3)* are formed in two successive steps by migration of methyl groups and elimination of nitrogen[2].

Remarkably, however, there is formation of acetone azine *(5)*, which can be understood by assuming elimination of nitrogen and simultaneous formation of a new N—N bond, whereby the 1,2-diazetine *(4)* is formed as an intermediate. In fact we were unable to detect *(4)* spectroscopically, but this may perhaps be ascribed to the instability of this compound under the experimental conditions.



Experimental:

Irradiations were carried out in pentane solutions at room temperature in a Pyrex glass apparatus with a HPK-125 W lamp (Philips).

Preparation of *(1)*: 2-Azido-1,1,3-trimethylpropyl nitrate[3] (0.1 mol; b.p. 47 °C/0.05 torr) and NaN_3 (0.2 mol) were heated in 90% ethanol (200 ml) for 10 min at 100 °C. Water (2 liters) was then added, the mixture was extracted with pentane, and the organic phase was dried and freed from solvent. Distillation (b.p. 26—27 °C/0.05 torr) and recrystallization from pentane at −40 °C afforded *(1)*, m.p. −10 °C, in 20% yield. NMR[4] ($CDCl_3$): $\delta = 1.33$ ppm; IR (CCl_4): 2085, 1265 cm^{-1}; UV (C_6H_{14}): $\lambda_{max} = 284$ nm, $\varepsilon = 43$.

(2) was isolated by gas chromatography after 2 hours' irradiation. NMR ($CDCl_3$): $\delta = 3.10$ (3), 1.82 (3), 1.37 (6) ppm; IR (CCl_4): 2090, 1665 cm^{-1}.

(3) and *(5)* were identified by means of NMR and IR spectra, and by gas-chromatographic comparison with authentic samples.

Received: August 21, 1972 [Z 708 IE]
German version: Angew. Chem. *84*, 1102 (1972)

[1] *P. Margaretha, S. Solar,* and *O. E. Polansky,* Angew. Chem. *83*, 410 (1971); Angew. Chem. internat. Edit. *10*, 412 (1971).

[2] *R. A. Abramovitch* and *E. P. Kyba,* J. Amer. Chem. Soc. *93*, 1537 (1971).

[3] *W. S. Trahanovsky* and *M. D. Robbins,* J. Amer. Chem. Soc. *93*, 5256 (1971).

[4] All NMR spectra measured against TMS as internal standard.

Protection of Adenosine 5′-Triphosphate toward Hydrolysis by the Formation of a Mixed-Ligand Metal Ion Complex[**]

By *David H. Buisson* and *Helmut Sigel*[*]

It is well known that metal ions of the 3d-series enhance the rate of hydrolysis of adenosine 5′-triphosphate (ATP) considerably[1, 2]. Cu^{2+}, in fact, was shown to be one of the most effective catalysts[1] and to form—within the mentioned series—the most stable binary complex with ATP[3]. We have now investigated the tendency for hydrolysis of ATP within a ternary complex.

Studies of mixed-ligand complexes revealed that those which contain an aromatic amine and a second ligand with O as donor atoms are especially stable[4, 5]. This is also true for 2,2′-bipyridyl(bpy)-Cu^{2+}-phosphate complexes[6]. Indeed, these ternary complexes are even more stable than the corresponding binary ones. Hence, equilibrium (a)

$$Cu(ATP)^{2-} + Cu(bpy)^{2+} \rightleftharpoons Cu(bpy)(ATP)^{2-} + Cu^{2+} \qquad (a)$$

is shifted towards the right. (Equilibrium constant:

$$\Delta \log K = \log K^{Cu(bpy)}_{Cu(bpy)(ATP)} - \log K^{Cu}_{Cu(ATP)} = 6.91 - 6.38 = 0.53^{[6]}).$$

This fact stimulated us to study the rate of the hydrolysis of ATP in the mixed-ligand complex, Cu(bpy) $(ATP)^{2-}$ [probable structure cf. *(1)*] and compare it with the corresponding rates for $Cu(ATP)^{2-}$ and free ATP. The results are shown in Figure 1, where the first order rate constant *(k)* is plotted against pH. Obviously, the hydrolysis of ATP in the ternary complex is insignificant compared with that of the binary complex. Moreover, even free ATP is somewhat more sensitive toward hydrolysis

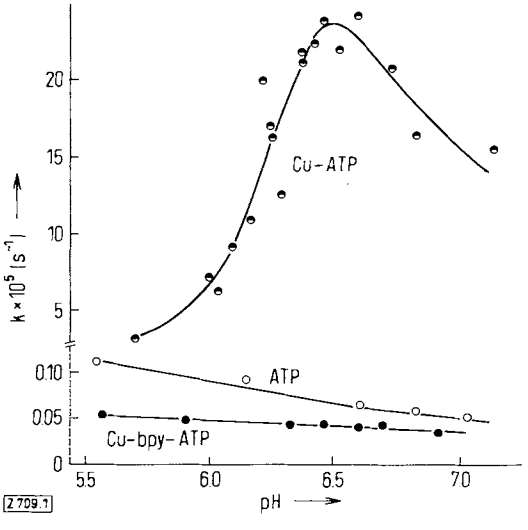
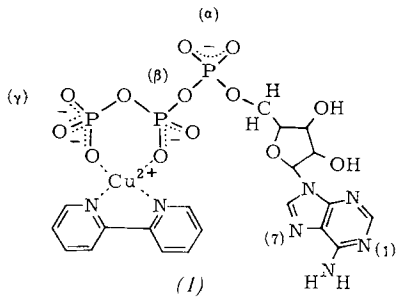


Fig. 1. Hydrolysis of ATP in dependence on pH, characterized as the first order rate constant. (The increasing concentration of phosphate was measured with molybdenum-reagent [8].) The reagent concentrations were each 10^{-3} M. In the pH range shown the binary complex, $Cu(ATP)^{2-}$, and the ternary complex, Cu(bpy) $(ATP)^{2-}$, are formed to more than 93% and 95%, respectively (computed with the constants given in Ref. [6]).

[*] Dr. D. H. Buisson and Doz. Dr. Helmut Sigel
Institut für Anorganische Chemie der Universität
CH—4056 Basel, Spitalstrasse 51 (Switzerland)

[**] The support of this work by the Swiss National Foundation, and a fellowship to D. H. B. from the University Grants Committee of New Zealand and from the Educational Department, Basel (Switzerland) is gratefully acknowledged.



(1)

than is ATP in the mixed-ligand complex. This demonstrates unequivocally that ATP is protected toward hydrolysis by the formation of the ternary complex, Cu(bpy)$(ATP)^{2-}$. This result is of interest with regard to biological systems, *e.g.* the transport of hydrolysis-sensitive phosphates.

The different behavior in the hydrolysis of these binary and ternary complexes can be rationalized as follows: As Cu^{2+} prefers a square-planar coordination sphere in aqueous solution, only two positions are left in $Cu(bpy)^{2+}$ for the coordination of ATP, namely by two of its phosphate groups. Hence, in the mixed-ligand complex, Cu(bpy) $(ATP)^{2-}$, the adenine moiety, *i.e.* N(7), is unable to participate in further complex formation[6] [cf. *(1)*]. In contrast it does so in the binary complex, $Cu(ATP)^{2-}$, by forming a macrochelate—which is obviously crucial for hydrolysis—with the β- and γ-phosphate groups and N(7)[1, 7].

In other cases $Cu(bpy)^{2+}$ is a better catalyst than Cu^{2+}_{aq}, *e.g.*, in the decarboxylation of acetonedicarboxylate[9] and the disproportionation of H_2O_2[10]. However, in these cases, the substrate coordinates identically in the binary and ternary complexes.

Received: August 11, 1972 [Z 709 IE]
German version: Angew. Chem. *84*, 1103 (1972)

[1] *P. W. Schneider* and *H. Brintzinger*, Helv. Chim. Acta *47*, 1717 (1964).
[2] *M. Tetas* and *J. M. Lowenstein*, Biochemistry *2*, 350 (1963).
[3] *R. Phillips*, Chem. Rev. *1966*, 501.
[4] *R. Griesser* and *H. Sigel*, Inorg. Chem. *9*, 1238 (1970); *10*, 2229 (1971).
[5] *H. Sigel* and *D. B. McCormick*, Accounts Chem. Res. *3*, 201 (1970).
[6] *H. Sigel*, *K. Becker*, and *D. B. McCormick*, Biochim. Biophys. Acta *148*, 655 (1967).
[7] *M. Cohn* and *T. R. Hughes, Jr.*, J. Biol. Chem. *237*, 176 (1962).
[8] *A. A. Hirata* and *D. Appleman*, Analyt. Chem. *31*, 2097 (1959).
[9] *R. W. Hay* and *K. N. Leong*, Chem. Commun. *1967*, 800; J. Chem. Soc. A *1971*, 3639.
[10] *H. Sigel*, *C. Flierl*, and *R. Griesser*, J. Amer. Chem. Soc. *91*, 1061 (1969); *H. Sigel* and *K. Wyss*, unpublished.

Structure and Properties of α,α-Diferrocenylmethylium Ion

By *S. Lupan*, *M. Kapon*, *Michael Cais*, and *Frank H. Herbstein*[*]

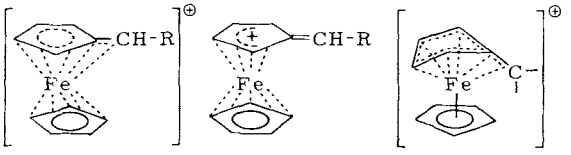
The origin of the unusual stabilization of carbenium ions adjacent to metallocenes has been a matter of vigorous debate for over a decade[1]. Three distinct models have been

[*] S. Lupan, M. Kapon, Prof. Dr. M. Cais, and Prof. Dr. F. H. Herbstein
Department of Chemistry, Israel Institute of Technology,
Haifa (Israel)

suggested[1] as appropriate for explaining the special stability of α-ferrocenylcarbenium ions:

(a) Interaction of the central metal atom with the π-electron system of the fulvene part with a concomitant shift of the metal towards the exocyclic carbon atom *(1)*[2, 3];

(b) Little or no interaction between the metal and the exocyclic carbon, stabilization being due to significant contribution of the resonance form *(2)*. The latter is said to



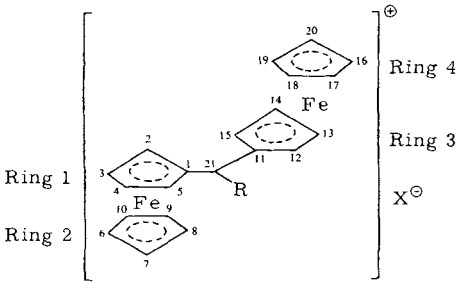
(1) *(2)* *(3)*

result from weakening of the bond between metal and carbon at the substituted position on the cyclopentadienyl ring[4];

(c) Distortion and bending of bonds in the substituted ring so as to bring the exocyclic carbon nearer the metal atom *(3)*[1].

Recently, iterative extended Hückel calculations[5] generated a structure supporting some of the features shown in *(3)*. Weakening of the bond ring-exocyclic carbon is said[5] to be caused by interaction of the filled non-bonding $3d_{z^2}$-orbital of iron with the empty π* orbital of the fulvene moiety, thus facilitating bending of the bond in question.

In view of our experience with the synthesis of α-ferrocenylcarbenium salts[1, 6] we have undertaken the preparation of a derivative suitable for X-ray structure analysis. Of the carbenium ions prepared for this purpose, *(4a)* —*(4j)*[7], the compound of choice was α,α-diferrocenylmethylium



(4)	R	X
(a)	H	BF_4
(b)	H	PF_6
(c)	H	$B(C_6H_5)_4$
(d)	D	BF_4
(e)	D	PF_6
(f)	D	$B(C_6H_5)_4$
(g)	CH_3	BF_4
(h)	CH_3	PF_6
(i)	CH_3	$B(C_6H_5)_4$
(j)	C_6H_5	BF_4

tetrafluoroborate *(4a)*. It could be recrystallized and recovered unchanged from a number of solvents, including even methanol, and was found to be stable on prolonged exposure to air.

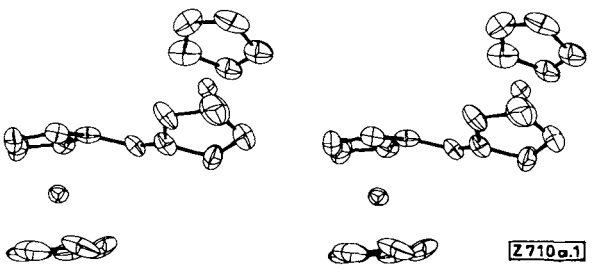


Fig. 1. Structure of α,α-diferrocenylmethylium ion (stereoscopic drawing prepared with *C. K. Johnson*'s ORTEP program).

An ORTEP diagram of the structure of α,α-diferrocenylmethylium ion is shown in Figure 1[8]. The principal results from the diffraction study are:

1. The carbenium ion is in the *transoid* conformation, and the angle ring center—Fe—ring center is 132.9°. The conformation of the carbenium ion is rather similar to that of diferrocenyl ketone[9]. However, the latter has an exact diad axis through the carbonyl group whereas the carbenium ion symmetry is C_1-1.

2. The rings in both ferrocenyl moieties are planar (maximum displacements 0.03 Å) and almost parallel (angles between the pairs of rings are 3.1° and 7.1° respectively). Mean distances between ring planes are 3.31 Å in both ferrocenyl moieties (3.32 Å in ferrocene); mean C—C distances in the rings are 1.41 and 1.43 Å (range 1.39 to 1.50), and 1.42 and 1.44 Å (range 1.34—1.52), while the mean Fe—C (ring) distances are 2.05 and 2.06 Å (range 2.02 to 2.15), also close to the values in ferrocene (2.03 to 2.06). The mean bond angle in the rings is 108° (range 102 to 115°). In one ferrocenyl moiety (rings 1/2) the twist away from the eclipsed conformation is 11.1°, while the second ferrocenyl moiety is fully eclipsed.

3. As previously predicted[1, 5], the exocyclic carbon atom has been found to deviate from the planes of the two cyclopentadienyl rings to which it is attached (19.9° toward the iron atom of ring 1/2, and 17.7° away from the iron atom of rings 3/4). The exocyclic carbon is displaced 0.5 Å below (*i.e.* towards Fe) the plane of ring 2 and 0.4 Å (in the same direction) below the plane of ring 3. As a result of the above features, the exocyclic carbon atom is closer to the Fe atom of rings 1/2 (2.71 Å) than to the other Fe atom (2.85 Å)[10]; nevertheless, the distances found are not indicative of strong *direct* interaction between the metal atoms and the methine carbon atom. The angle C(1)—C(21)—C(11) around the exocyclic carbon atom is 131(3)°, which is significantly larger than the value of 120° appropriate to symmetrical sp^2 hybridization. Increase of this angle reduces the steric hindrance between H-2 and H-5.

The special stability of α-ferrocenylcarbenium ions is, of course, also evinced in solution and hence it was of interest to study their NMR spectrum[3] over a range of temperatures. The ^{1}H-NMR spectrum of *(4a)* at 18 °C (CD_2Cl_2) consists of a sharp singlet at δ = 4.57 ppm (C_5H_5-ring protons), a triplet at δ = 5.00 ppm (H-2, H-5; H-12, H-15), and another triplet at δ = 5.61 ppm (H-3, H-4; H-13, H-14). The NMR spectrum of the deuterated derivative *(4d)* indicates that the methine proton absorption (H-21) is hidden under the triplet due to H-2 and H-5. The apparent pairwise magnetic equivalence of protons in the substituted rings of *(4)* (H-2, H-5 and H-3, H-4) is in sharp contrast to the experi-

mentally observable chemical shift non-equivalence of all four protons in the ferrocenylphenylmethylium ion[1b, 3, 12]. The NMR spectra in Figure 2 show that the rings in *(4a)*

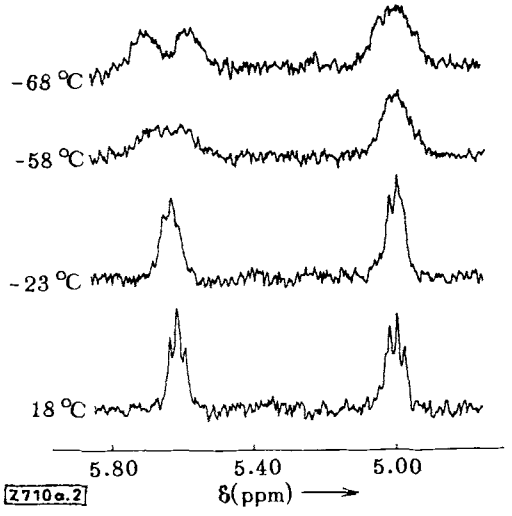


Fig. 2. Temperature dependence of ^{1}H-NMR spectrum of α,α-diferrocenylmethylium fluoroborate in the δ range of 4.8—5.8 ppm (recorded on a Bruker HFX-90 instrument with CH_3CN as internal standard).

can flip rapidly about the bond to the exocyclic carbon atom. Coalescence occurs at −66°C and rotation is apparently stopped at −70°C when protons H-3, H-4 (and H-13, H-14) show absorptions at δ = 5.55 and 5.68 ppm (Δν = 13 Hz). The absorption which corresponds to protons H-2, H-5 (and H-12, H-15) broadens on lowering the temperature but separation does not occur even at −100°C[13].

Similarly, the NMR spectrum of the phenyl derivative *(4j)*, which at 28°C shows absorptions at δ = 5.02 (H-2, H-5, H-12, H-15) and 5.85 ppm (H-3, H-4, H-13, H-14), coalesces at −30°C. At −45°C when rotation is apparently stopped, the spectrum exhibits absorptions for all four protons with H-2, H-5 (and H-12, H-15), absorptions appearing at δ = 4.44 and 5.53 ppm and those of H-3, H-4 (and H-13, H-14) at δ = 5.65 and 5.87 ppm[14]. In connection with the above results, it is noteworthy that measurements[16] of the Fe-$2p_{3/2}$ ionization energies by the ESCA method indicate that in *(4a)* the two Fe atoms appear to exhibit the same charge density.

The present results enable us to eliminate some of the structural models which have been proposed to account for the special stability of α-ferrocenylcarbenium ions. Unfortunately our results cannot in themselves provide an explanation for this special stability.

Received: August 16, 1972 [Z 710a IE]
German version: Angew. Chem. *84*, 1104 (1972)

[1] a) *M. Cais* in *E. D. Bergmann* and *B. Pullman:* Aromaticity, Pseudoaromaticity, Anti-aromaticity. Academic Press, New York 1971, p. 96; b) *M. Cais*, Organometal. Chem. Rev. *1*, 436 (1966).
[2] *E. A. Hill* and *J. H. Richards*, J. Amer. Chem. Soc. *81*, 3483 (1959); *83*, 3480, 4216 (1961).
[3] *M. Cais, J. J. Dannenberg, A. Eisenstadt, M. I. Levenberg*, and *J. H. Richards*, Tetrahedron Lett. *1966*, 1695.
[4] *J. C. Ware* and *T. G. Traylor*, Tetrahedron Lett. *1963*, 1295; J. Amer. Chem. Soc. *89*, 2304 (1967).
[5] *R. Gleiter* and *R. Seeger*, Helv. Chim. Acta *54*, 1217 (1971); Angew. Chem. *83*, 903 (1971); Angew. Chem. internat. Edit. *10*, 830 (1971).
[6] *M. Cais* and *A. Eisenstadt*, J. Org. Chem. *30*, 1148 (1965).
[7] The perchlorate analog of *(4a)* was first reported by *C. Jutz*, Tetrahedron Lett. *1959*, 1.
[8] Crystals of *(4a)* are monoclinic, $P2_1/a$, with $a = 15.96$ (2), $b = 12.75$ (1), $c = 9.36$ (2) Å, $\beta = 90°38$ (5)', and four formula weights per cell (here and elsewhere in this paper numbers in parentheses are the estimated standard deviations in the least significant digits). Intensities of 2720 reflections (layer lines *h0l* to *h8l*; 228 reflections had zero intensity) were measured on a Stoe semi-automatic Weissenberg diffractometer, using graphite-monochromatized Mo-Kα radiation. Appropriate geometrical and absorption corrections were applied; poor crystal quality prevented high accuracy in intensity measurements. The structure was solved by Patterson methods and refined by a combination of Fourier and least-squares methods. At the present stage of refinement $R = 0.12$; all non-hydrogen atoms were given anisotropic temperature factors, while two positions were found for the fluoroborate ion, with occupancies of $^2/_3$ and $^1/_3$ respectively. Hydrogen atoms were not found in the difference synthesis computed at this stage.
[9] *J. Trotter* and *A. C. Macdonald*, Acta Cryst. *21*, 359 (1966).
[10] Our results are very similar to those recently reported [11] for bis(tricarbonylcyclobutadienyliron) phenylcarbonium fluoroborate, which has a *transoid* conformation, with one Fe atom closer (2.85 Å) to the exocyclic carbon than the other (2.94 Å).
[11] *R. E. Davis, H. D. Simpson, N. Grice*, and *R. Pettit*, J. Amer. Chem. Soc. *93*, 6688 (1971).
[12] *M. Hisatome* and *K. Yamakawa*, Tetrahedron *27*, 2101 (1971).
[13] This effect might be due to one or both of the following factors: (a) accidental identity (or near-identity) of the chemical shifts of H-2, H-5 leading to $b_{1/2} > \Delta\nu$; (b) the superposition of the absorption band of the methine proton, H-21, on the absorptions due to H-2, H-5.
[14] Use of approximate equations to determine coalescence temperature rotation rates and the Eyring equation [15] produced the following values for the free enthalpy of activation: $\Delta G^{\neq}$ *(4a)* ≈ 11.1 kcal/mol; $\Delta G^{\neq}$ *(4j)* ≈ 12.7 kcal/mol. We wish to thank Dr. *H. Gilboa* for help in the measurement of low temperature spectra.
[15] For a review see *H. Kessler*, Angew. Chem. *82*, 237 (1970); Angew. Chem. internat. Edit. *9*, 219 (1970).
[16] *R. Gleiter, R. Seeger, H. Binder, E. Fluck*, and *M. Cais*, Angew. Chem. *84*, 1107 (1972); Angew. Chem. internat. Edit. *11*, 1028 (1972).

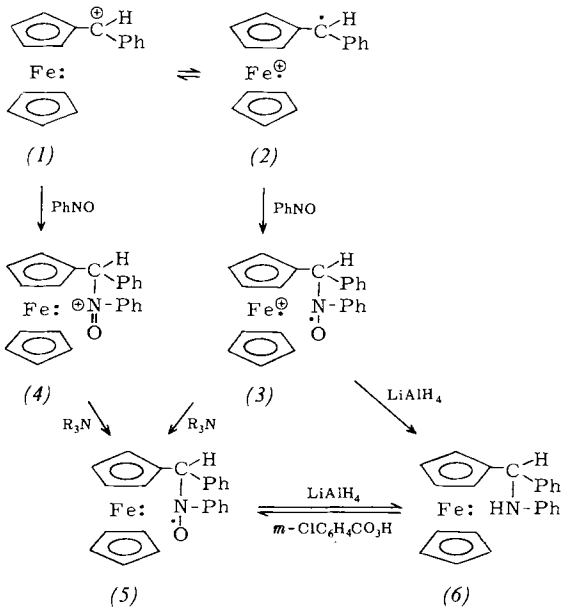
Reaction of Ferrocenylmethylium Ions with Nitrosobenzene

By *P. Ashkenazi* and *Michael Cais*[*]

The special behavior of ferrocenylmethylium ions[11] in various chemical reactions has led to the postulate that these ions are capable of reacting either as diamagnetic species *(1)* or as biradical cations *(2)*[2, 3]. We now report results of the reaction between ferrocenylphenylmethylium tetrafluoroborate and nitrosobenzene, which resemble results of spin-trapping experiments[4] and as such may lend support to the formulation *(1)* ⇌ *(2)*.

Addition of nitrosobenzene to a solution of ferrocenylphenylmethylium tetrafluoroborate in dichloromethane yielded a nitroxide radical which exhibited the typical triplet in the ESR spectrum (Fig. 1a). A simulated ESR spectrum (Figure 1b) gave a good fit with the following hyperfine splitting constants: $a_N = 10.90$ G; $a_H = 2.70$ G; $a_{H(o,p)} = 2.95$ G; $a_{Hm} = 1.00$ G[5]. The nitroxide is stable and decay of its spectrum was not noticeable during the ESR measurements. Ethyldiisopropylamine, which is known not to enter into nucleophilic reactions[3, 6] produces a color change (from violet to brown) as well as a highly enhanced ESR nitroxide signal when added to the carbenium ion/nitrosobenzene mixture. This effect may be due to the amine reducing the nitroxide cation *(3)* to the electrically neutral species *(5)* and thereby removing the line-broadening effect of the ferricenium species on the ESR signal of *(5)*. (We have observed that ferricenium

[*] P. Ashkenazi and Prof. Dr. M. Cais
Department of Chemistry, Israel Institute of Technology
Haifa (Israel)



tetrafluoroborate is quantitatively reduced to ferrocene by ethyldiisopropylamine.) Presumably the signal enhancement could also arise from an increase in the concentration of *(5)* as a result of the amine also reducing[7b]

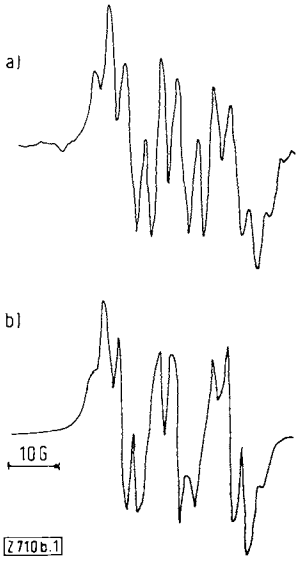


Fig. 1. (a) The ESR spectrum of nitroxide *(5)* and (b) the simulated spectrum with hyperfine splitting constants given in text. (Spectrum taken with Varian model V 4502-10 A instrument.)

the diamagnetic cation *(4)*[8]. In order to dispel suspicions that the nitroxides might not have any of the structures proposed but rather be due to some non-metal containing artifact of the system, the reaction mixture comprising the nitroxide(s) was treated with $LiAlH_4$ to yield the amine *(6)* which was shown to be identical with an authentic sample[9]. Furthermore, oxidation of the amine *(6)* with 3-chloroperoxybenzoic acid[11] gave rise to the same nitroxide *(5)* as demonstrated by an ESR spectrum identical to that obtained in our "spin-trapping" experiments.

Analogous experiments with a large variety of organometallic cations[12] gave similar results[13]. Hopefully, these may also help elucidate the stabilization mechanism operating in ferrocenylmethylium ions.

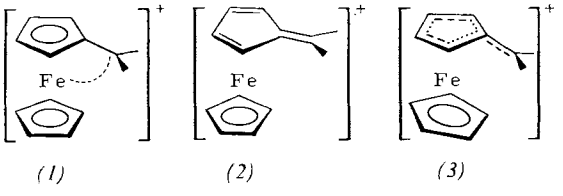
Received: August 16, 1972 [Z 710b IE]
German version: Angew. Chem. *84*, 1106 (1972)

[1] *M. Cais* in *E. D. Bergmann* and *B. Pullman*: Aromaticity, Pseudo-aromaticity, Anti-aromaticity. Academic Press, New York 1971, p. 96; *M. Cais*, Organometal. Chem. Rev. *1*, 436 (1966).
[2] *A. Eisenstadt* and *M. Cais*, Chem. Commun. *1972*, 217.
[3] *P. Ashkenazi, S. Lupan, A. Schwarz*, and *M. Cais*, Tetrahedron Lett. *1969*, 817.
[4] For a review of the spin-trapping technique see *E. G. Janzen*, Accounts Chem. Res. *4*, 31 (1971).
[5] *S. Terabe* and *R. Konaka*, J. Amer. Chem. Soc. *91*, 5655 (1969), report for the nitroxide Ph—N(CH<)—O· rather similar hyperfine splitting constants: $a_N = 10.75$ G; $a_{H(\beta)} = 2.42$ G; $a_{H(o,p)} = 2.75$ G; $a_{H(m)} = 0.97$ G.
[6] *S. Hünig* and *M. Kiessel*, Chem. Ber. *91*, 380 (1958).
[7] a) *J. H. Osiecki* and *E. F. Ullman*, J. Amer. Chem. Soc. *90*, 1078 (1968); b) *V. A. Golubev, E. G. Rozantsev*, and *M. B. Neiman*, Izv. Akad. Nauk SSSR, Ser. Khim. *1965*, 1927; c) *R. I. Zhdanov, V. A. Golubev*, and *E. G. Rozantsev, ibid. 1970*, 186.
[8] The cation *(4)*, may well be the major component in the reaction mixture, arising both from the initial nucleophilic attack on the carbenium ion and from the intramolecular electron transfer [*(3)* ⇌ *(4)*]. The ability of nitroxyls to donate electrons has been documented [7].
[9] Reaction of aniline with benzoylferrocene in the presence of $TiCl_4$ yielded the anil $C_5H_5FeC_5H_4C(C_6H_5)=NC_6H_5$ [10], which on reduction with $NaBH_4$ produced the required amine *(6)*.
[10] *W. A. White* and *H. Weingarten*, J. Org. Chem. *32*, 213 (1967); *H. Kono, M. Shiga, I. Motyoama*, and *K. Hatas*, Bull. Chem. Soc. Jap. *42*, 3267 (1969).
[11] *G. Chapelet Letourneaux, H. Lemaire*, and *A. Rassat*, Bull. Soc. Chim. France *1965*, 3283; *Y. Yost* and *H. R. Gutmann*, J. Chem. Soc. *C 1970*, 2497; *R. F. Bridger* and *E. T. Strom*, J. Org. Chem. *36*, 560 (1971).
[12] It may be convenient to refer to the equilibrium *(1)* ⇌ *(2)* or *(3)* ⇌ *(4)* as redox tautomerism [13] in order to emphasize the intramolecular oxidation-reduction aspect implied in this representation. We have reason to believe that such behavior which may be a consequence of spin-orbit coupling, is rather widely prevalent among organometallic cations.
[13] *M. Cais* and *P. Ashkenazi*, First IUPAC Conference on Physical Organic Chemistry, Crans sur Sierre (Switzerland), September 4—8, 1972.

Partial Charge on the Iron in the Diferrocenylmethylium Ion

By *Rolf Gleiter, Rolf Seeger, Herbert Binder, Ekkehard Fluck*, and *Michael Cais*[*]

The unusual thermodynamic stability[1] of ferrocenylmethylium ions has been explained either by metal participation *(1)*[1,2] or by conjugation of the 2p orbital of the methylene group with the π-system of the five-membered ring *(2)*[1,3]. A "bent" structure *(3)* was predicted by an iterative Extended-Hückel calculation[4]. Very recent X-ray



[*] Doz. Dr. R. Gleiter and R. Seeger
Physikalisch-Chemisches Institut der Universität
CH-4056 Basel (Switzerland)
Dr. H. Binder and Prof. Dr. E. Fluck
Institut für Anorganische Chemie der Universität
7 Stuttgart (Germany)
Prof. Dr. M. Cais
Department of Chemistry, Israel Institute of Technology
Haifa (Israel)

crystal structure investigations[5] have confirmed this. As a result of this calculation the Mulliken charge on the iron was only 0.2 charge units more positive than that in ferrocene in spite of the appreciable interaction between the metal and the fulvene moiety.

To learn more about the relative partial charge on the iron in a ferrocenylmethylium ion, we have measured the ionization energy of the Fe-$2p_{3/2}$ level[*] of ferrocene *(4)*, 1,1'-dibenzoylferrocene *(5)*, and diferrocenylmethylium tetrafluoroborate *(6)* as well as that of ferrocinium tetrafluoroborate *(7)*, by the ESCA method[6]. (The measurements were carried out with an A.E.I. ES-100 photoelectron spectrometer. The samples were irradiated with the Al-$K\alpha_{1,2}$ line (1486.6 eV). The relative positions of the bands refer to the C-1s line, for which an energy of 286.6 eV has been taken.)

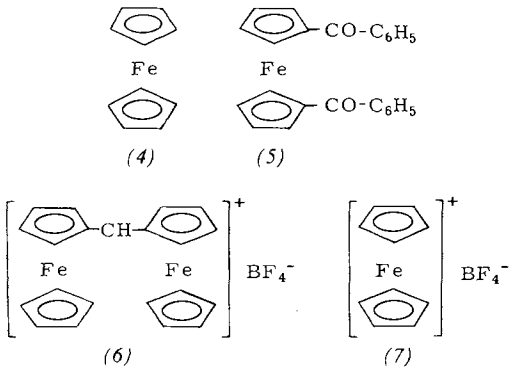


Table 1 shows the vertical ionization potentials found for the Fe-$2p_{3/2}$ bands. The ionization potentials of *(5)* and *(6)* are very similar, differing by only 0.5 eV from that for *(4)* but by about 1.3 eV from that for *(7)*. The results can be best explained as due to a similar partial charge on the iron in *(5)* and *(6)*, which differs markedly from the partial charge on the iron in *(7)*. A similar trend is shown by the isomeric shifts[12] listed in Table 2; these decrease from *(4)* to *(7)* and show similar values for *(4)*, *(5)*, and *(6)*.

Table 1 also lists the half-widths of the Fe-$2p_{3/2}$ signals. Calculations of the UHF type require that an exchange interaction between unpaired valence electrons (*e.g.* in Fe^{3+}) and inner electrons of the same spin should lead to line broadening or to splitting of the observed bands[7]. In some cases this was observed[8]. The same trend was found for the half-width of the Fe-$2p_{3/2}$ line as for the ionization potentials: similar values for *(4)*, *(5)*, and *(6)* that differ considerably from that for *(7)*. The relatively large half-width of the signal for *(6)* may be ascribed partly to the fact that the iron atoms in *(6)* are different[**]; a difference in the electron populations of *(6)* and *(4)*[9] could also be considered as explanation.

Table 1. Bond energies E_b and line widths for Fe-$2p_{3/2}$.

Compound	E_b (eV)	Line width (eV)
(4)	709.0	1.7
(5)	709.5	1.8
(6)	709.6	2.1
(7)	710.8	3.3

[*] The Fe-$2p_{3/2}$ level was chosen because its use led to the best signal-to-noise ratio and to the best resolution.

[**] Whereas the difference between the two iron atoms in *(6)* is too small to be detected by the ESCA method or by Mössbauer spectroscopy, two different iron atoms can be demonstrated by these methods in diferrocene picrate [8, 10].

The Mössbauer data[10, 11] given in Table 2 permit comparison of the half-widths of the Fe-$2p_{3/2}$ bands with the quadrupole splittings. The latter arise by interaction of the Fe nucleus in the excited state with an electric field gradient[12]. On the other hand, unpaired electrons, which are the cause of this electric field gradient, give rise to line broadening of the ionization bands[13]. There should thus be a relation between the two sets of values, and this was observed by *Cowan et al.*[8].

Table 2. Isomeric shifts and quadrupole splittings at 25 °C.

Compound	Isomeric shift [mm/s]	Quadrupole splitting [mm/s]
(4)	0.714 ± 0.005	2.396 ± 0.020
(5)	0.702 ± 0.005	2.185 ± 0.020
(6)	0.692 ± 0.005	2.100 ± 0.020
(7)	0.658 ± 0.010	0.609 ± 0.020

In Fig. 1 the quadrupole splitting is plotted against the half-width of the Fe-$2p_{3/2}$ bands. It is evident from the graph that the line width rises with increasing numbers of unpaired 3d electrons. The quadrupole splitting, however, is very small when, as in *(7)*, the 3d level is only half occupied, since in this case the electron shell around the Fe nucleus has almost spherical symmetry.

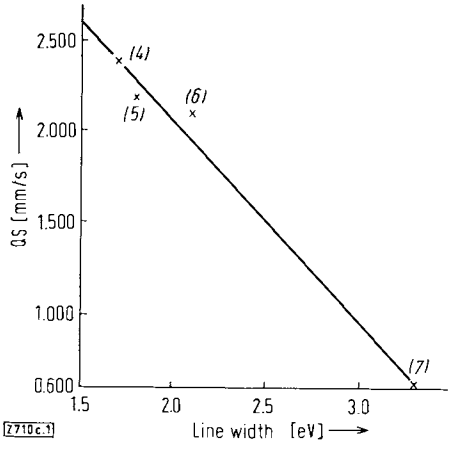


Fig. 1. Correlation between the measured quadrupole splitting (QS) and the line width of the Fe-$2p_{3/2}$ bands of ferrocene *(4)*, 1,1'-dibenzoylferrocene *(5)*, diferrocenylmethylium tetrafluoroborate *(6)*, and ferrocinium tetrafluoroborate *(7)*.

From our results it appears that the two iron atoms in *(6)* have approximately the same charge and that this does not differ appreciably from that in ferrocene. It is in accord with our results to assume a positive charge on the iron in all the compounds studied.

Received: August 22, 1972 [Z 710c IE]
German version: Angew. Chem. *84*, 1107 (1972)

[1] *M. Cais*, Rec. Chem. Progr. *27*, 177 (1966); Organometal. Chem. Rev. *1*, 435 (1966); *M. Rosenblum:* Chemistry of the Iron Group Metallocenes. Wiley, New York 1965, Part I, p. 129; Advan. Chem. Ser. *62*, 532 (1966).

[2] *E. A. Hill* and *J. H. Richards*, J. Amer. Chem. Soc. *83*, 3840 (1961).

[3] *T. G. Traylor* and *J. C. Ware*, J. Amer. Chem. Soc. *89*, 2304 (1967); *T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton*, and *R. S. Brown*, *ibid. 93*, 5715 (1971).

[4] *R. Gleiter* and *R. Seeger*, Helv. Chim. Acta *54*, 1217 (1971); Angew. Chem. *83*, 903 (1971); Angew. Chem. internat. Edit. *10*, 830 (1971).

[5] *S. Lupan, M. Kapon, M. Cais*, and *F. H. Herbstein*, Angew. Chem. *84*, 1104 (1972); Angew. Chem. internat. Edit. *11*, 1025 (1972).

[6] *C. Nordling*, Angew. Chem. *84*, 144 (1972); Angew. Chem. internat. Edit. *11*, 83 (1972).

[7] *J. H. Wood* and *G. W. Pratt*, Phys. Rev. *107*, 995 (1957); *T. E. Watson* and *A. J. Freeman*, *ibid. 120*, 1134 (1960); *P. S. Bagus* and *B. Kiu*, *ibid. 148*, 79 (1966).

[8] *D. O. Cowan, J. Park, M. Barber*, and *P. Swift*, Chem. Commun. *1971*, 1444.

[9] *A. Eisenstadt* and *M. Cais*, Chem. Commun. *1972*, 216.

[10] *D. O. Cowan, R. L. Collins*, and *F. Kaufman*, J. Phys. Chem. *75*, 2025 (1971).

[11] *E. Fluck* and *F. Hausser*, unpublished work.

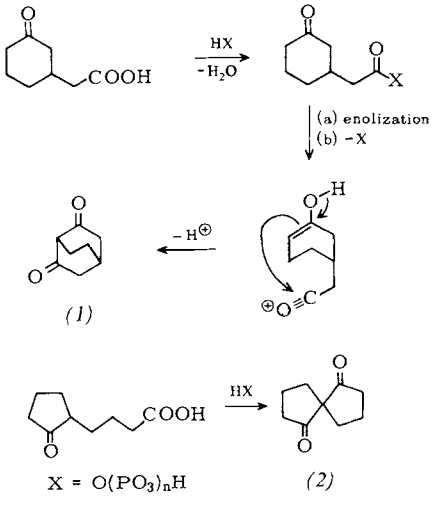
[12] Recent reviews: *E. Fluck*, Fortschr. Chem. Forsch. *5*, 395 (1966); *R. L. Mössbauer*, Angew. Chem. *83*, 524 (1971); Angew. Chem. internat. Edit. *10*, 462 (1971); *P. Gütlich*, Chemie in unserer Zeit *4*, 133 (1970); *6*, 131 (1972).

[13] *C. S. Fadley* and *D. A. Shirley*, Phys. Rev. Lett. *21*, 980 (1968); *J. Hedman, P. F. Heden, C. Nordling*, and *K. Siegbahn*, Phys. Lett. *29 A*, 178 (1969); *C. S. Fadley, D. A. Shirley, A. J. Freeman, P. S. Bagus*, and *J. V. Mallow*, Phys. Rev. Lett. *23*, 1397 (1969); *I. W. Drummond* and *H. Ilarker*, Nature *232*, 71 (1971).

Synthesis of Non-Enolizable β-Diketones by Acid-Catalyzed Intramolecular Claisen Condensation

By *Hans Gerlach* and *Werner Müller*[*]

According to the literature[1], synthesis of β-diketones by Claisen condensation appears to be possible only when the product can form an enol and can be stabilized as the enolate or boron fluoride complex. For example, bicyclo-[2.2.2]octane-2,6-dione cannot be obtained by base-catalyzed condensation of methyl 3-oxo-1-cyclohexaneacetate[2]; the diketone is obtained, and then in small yield, only when 3-oxo-1-cyclohexaneacetic acid is passed over manganese(II) oxide heated at 340 °C[2]. In diterpene syntheses important intermediates of analogous structure have been prepared by aldol condensation of keto aldehydes and subsequent oxidation[3].



[*] Dr. H. Gerlach and Dipl.-Chem. W. Müller
Laboratorium für organische Chemie der ETH
CH-8006 Zürich, Universitätsstrasse 6/8 (Switzerland)

We have found that 3-oxo-1-cyclohexaneacetic acid, dissolved in glacial acetic acid, is converted into bicyclo-[2.2.2]octane-2,6-dione *(1)* in 75% yield on reaction with polyphosphoric acid. Under the same conditions spiro-[4.4]nonane-1,6-dione *(2)* is obtained in 81% yield from 2-oxo-1-cyclopentanebutyric acid. Yields are smaller if acetic acid is omitted from the reaction mixture, and glacial acetic acid cannot be replaced by acetic anhydride.

The reaction can be considered to take the following course: the polyphosphoric acid and the oxo acid form a mixed anhydride which can decompose to give the acyl cation; at the same time, enol formation by protonation of the keto-carbonyl group is catalyzed; the resulting enol then reacts with the activated carboxyl group.

The cyclization of the oxo acid to the bicyclo[2.2.2]octane-2,6-dione is an acid-catalyzed intramolecular Claisen condensation, a type of reaction hardly ever used so far for the synthesis of non-enolizable β-diketones. The only example known to us is the cyclization of a gibberone precursor[4]. However, the latter reaction also occurs by heating to 180 °C on sublimation; this is so also for conversion of α-campholonic acid into 6-oxocamphor[5]. In contrast, the β-diketones *(1)* and *(2)* are not formed in detectable amount when the corresponding oxo carboxylic acids are heated.

Experimental:

Bicyclo[2.2.2]octane-2,6-dione *(1)*:

A solution of 3-oxo-1-cyclohexaneacetic acid[2] (10 g) in glacial acetic acid (180 g) is treated with polyphosphoric acid (100 g)[6] and heated at 100 °C for 7 h. For hydrolysis the mixture is poured on ice/water and extracted with benzene, and the benzene solution is washed with sodium hydrogen carbonate solution, dried and evaporated. Sublimation of the residue at 110 °C/0.05 torr and recrystallization from hexane/benzene (9:1) gives colorless crystals (6.6 g, 75%), m.p. 188—190 °C[7]; IR (CCl_4): 1720 and 1745 cm^{-1}; UV (cyclohexane): $\varepsilon_{max} = 75$ (330 nm), 100 (320 nm) and 100 (300 nm); 100 MHz ^{1}H-NMR (CCl_4): $\delta = 1.77$—2.00 (2 H), 2.00—2.25 (2 H), 2.33—2.40 (4 H), 2.62 (m, 1 H), 3.00 (t, $J = 2.5$, 1 H). Mass spectrum: M^+ at $m/e = 138$.

Spiro[4.4]nonane-1,6-dione *(2)*:

Analogously, heating 2-oxo-1-cyclopentanebutyric acid[8] (50.30 g), polyphosphoric acid (170 g) and glacial acetic acid (340 g) for 4 h at 100 °C, followed by hydrolysis, extraction with benzene and distillation of the crude product affords 37.35 g (81%) of the dione, b.p. 91—92 °C/9 torr, m.p. 38—40 °C; IR, ^{1}H-NMR and mass spectra agree with the spectra of a sample prepared by the method of Ref. [9].

Received: August 24, 1972 [Z 714 IE]
German version: Angew. Chem. *84*, 1110 (1972)

[1] *C. R. Hauser, F. W. Swamer*, and *J. T. Adams*, Organic Reactions *8*, 59 (1954).

[2] *P. D. Bartlett* and *G. F. Woods*, J. Amer. Chem. Soc. *62*, 2935 (1940).

[3] *K. Mori, Y. Nakahara*, and *M. Matsui*, Tetrahedron *28*, 3217 (1972), and early work.

[4] *Y. Kos* and *H. J. E. Loewenthal*, J. Chem. Soc. *1963*, 605.

[5] *G. Komppa* and *S. Beckmann*, Chem. Ber. *69*, 2783 (1936).

[6] 85% H_3PO_4 (100 ml) and P_4O_{10} (200 g) were heated until the mixture became homogeneous.

[7] M. p. according to Ref. [2]: 190—191 °C.

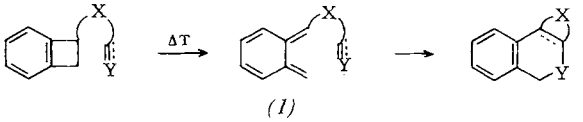
[8] *W. E. Bachmann* and *W. S. Struve*, J. Amer. Chem. Soc. *63*, 2589 (1941).

[9] *A. Horeau*, C. R. Hebd. Séances Sci. *228*, 2039 (1949); *D. J. Cram* and *H. Steinberg*, J. Amer. Chem. Soc. *76*, 2735 (1954).

Intramolecular Cycloadditions of C,O and C,N Multiple Bonds to *ortho*-Quinodimethanes[1]

By *Wolfgang Oppolzer*[*]

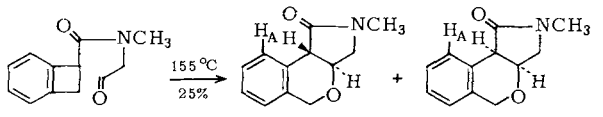
Recently the smooth intramolecular cycloadditions of even nonactivated olefins and acetylenes to *o*-quinodimethanes *(1a)*[2], have been described. This communication deals with the analogous reactions of weakly dienophilic carbonyl compounds, azomethines and nitriles *(1b)*[3].



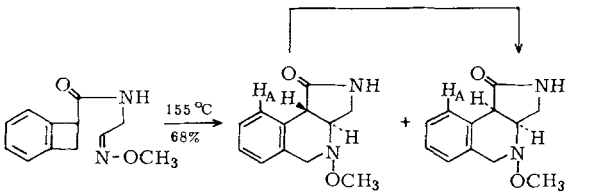
(1)

(a), Y = C
(b), Y = O, N

When a 1% solution of the aldehyde *(2)*[4] was heated in boiling bromobenzene under argon for 23 h a mixture of the stereoisomeric benzopyranopyrroles *(3)* (m. p. 134 to 135 °C; NMR: δ_{H_A} = 8.1 ppm) and *(4)* (m. p. 218—219 °C; NMR: δ_{H_A} = 7.64 ppm) resulted in 25% yield.



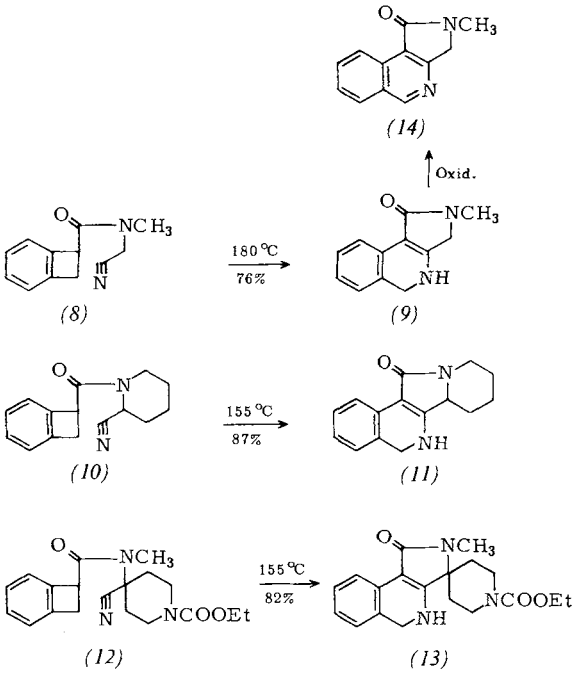
(2) *(3)* *(4)*



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

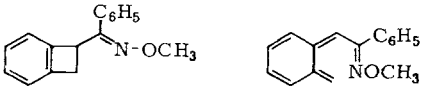
Similarly the oxime ether *(5)*[6] rearranged in boiling bromobenzene to the stereoisomers *(6)* (m. p. 124—126 °C; NMR: δ_{H_A} = 8.1 ppm) and *(7)* (m. p. 231—232 °C; NMR: δ_{H_A} = 7.65 ppm), in this case with a much better yield. After addition of a catalytic amount of *p*-toluenesulfonic acid, the *trans*-lactam *(6)* epimerized in boiling bromobenzene to the *cis*-lactam *(7)*. This sequence thus opens an efficient, stereo-controlled access to *cis*-pyrrolo[3,4-*c*]isoquinolines.

Surprisingly, even nitriles can add intramolecularly to *o*-quinodimethanes under similiar conditions. Thus the thermolysis of the nitriles[8] *(8)*, *(10)* and *(12)* gave a high yield of the dihydroquinolines *(9)*, *(11)* and *(13)*, which could be readily oxidized to the corresponding isoquinolines (*e. g. (9)* → *(14)*).



(14) *(8)* *(9)* *(10)* *(11)* *(12)* *(13)*

On thermolysis in boiling bromobenzene the oxime ether *(15)*[11] gave a low yield of 3-phenylisoquinoline[12]. This transformation obviously involves an electrocyclic reaction of the intermediate *o*-quinodimethane *(16)* similiar to the cyclizations recently described by *Schmid*[13] and *Kametani*[14].



(15) *(16)*

The new compounds described here were characterized by elemental analyses or high-resolution mass spectra as well as by IR, UV and NMR spectra ($CDCl_3$).

cis-2,3,3a,4,5,9b-Hexahydro-4-methoxy-1H-pyrrolo[3,4-c]-isoquinolin-1-one (7):

A solution of the oxime ether *(5)*[6] (99 g) in bromobenzene (2.5 liters) is refluxed for 20 h under argon atmosphere. The product *(7)* (57.2 g), which crystallizes from the cooled solution, is collected, washed with pentane and dried. The mother liquor (from which the isomer *(6)* can be isolated by chromatography) is refluxed for 14 h with *p*-toluenesulfonic acid (0.5 g) and evaporated. The residue is then purified by chromatography (silica gel) and crystallized (ether/pentane) to give a further 10.0 g of the product *(7)* (total yield 68%).

2,3,4,5-Tetrahydro-2-methyl-1H-pyrrolo[3,4-c]isoquinolin-1-one (9):

A solution of the nitrile *(8)*[8] (46 g) in toluene (460 ml) is transferred into a steel autoclave, flushed carefully with argon and then heated at 180 °C for 16 h. Evaporation of the reaction mixture and crystallization from dichloromethane affords the product *(9)* (35.2 g, 76%).

2,3-Dihydro-2-methyl-1H-pyrrolo[3,4-c]isoquinolin-1-one (14):

Oxygen is passed for 2 h through a solution of the compound *(9)* (12.5 g) in ethanol (500 ml) containing $FeCl_3$

[*] Dr. W. Oppolzer
Pharmazeutisch-Chemische Forschungslaboratorien, Sandoz AG
CH-4002 Basel (Switzerland)

(0.2 g) at 25 °C. The reaction mixture is evaporated and the residue crystallized from dichloromethane/ether: 8.9 g, 71 %; m. p. 178—180 °C.

Received: August 24, 1972 [Z 713 IE]
German version: Angew. Chem. *84*, 1108 (1972)

[1] Part of a lecture: 13th National Medicinal Chemistry Symposium, Iowa City (USA), June 1972.

[2] *W. Oppolzer*, J. Amer. Chem. Soc. *93*, 3833, 3834 (1971); *W. Oppolzer* and *K. Keller*, *ibid.* 3836; Angew. Chem. *84*, 712 (1972); Angew. Chem. internat. Edit. *11*, 728 (1972).

[3] Carbonyl compounds, azomethines and nitriles in general act as weak dienophiles, except for some derivatives that are activated by electron-withdrawing substituents: *J. Hamer*: 1,4-Cycloaddition Reactions, Academic Press, New York 1967, p. 97, 128, 205; *J.-M. Biehler*, *J. Perchais*, and *J.-P. Fleury*, Bull. Soc. Chim. Fr. *1971*, 2711; *M. F. Ansell* and *A. A. Charalambides*, J. C. S. Chem. Comm. *1972*, 739; *D. vor der Brück*, *R. Bühler*, and *H. Plieninger*, Tetrahedron *28*, 791 (1972).

[4] The oily aldehyde *(2)* was obtained by the following reaction sequence: a) acylation of (methylamino)acetaldehyde dimethylacetal by benzocyclobutene-1-carbonyl chloride [5] and 3 equiv. of pyridine in dichloromethane; b) cleavage of the acetal by 1 N $HClO_4$ in dioxane/water (1.5:1) for 6 h at 25 °C.

[5] *J. A. Skorcz* and *J. E. Robertson*, J. Med. Chem. *8*, 255 (1965).

[6] The oxime ether *(5)* (m. p. 92—94 °C) was prepared by reaction of the N-formylmethyl-benzocyclobutene-1-carboxamide (cf. Ref. [4]) with 1 equiv. methoxyamine-hydrochloride in pyridine in the presence of an excess of molecular sieves, 2 h, 25 °C.

[7] After heating a 2% solution of methyl benzocyclobutene-1-carboxylate in acetonitrile for 16 h at 200°, only dimethyl *trans*-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene-5,6-dicarboxylate (m. p. 154 to 156 °C) could be isolated. This shows how strongly the course of the reaction depends on the steric proximity of the nitrile group and the *o*-quinodimethane moiety.

[8] The nitriles *(8)* (m. p. 70—72 °C), *(10)* (mixture of diastereoisomers, m. p. 90—110 °C) and *(12)* (m. p. 138—140 °C) were obtained by treating benzocyclobutene-1-carbonyl chloride [5] with (methylamino)acetonitrile, 2-piperidenecarbonitrile [9], or ethyl 4-cyano-4-(methylamino)-1-piperidinecarboxylate [10] respectively, in the presence of 3 equiv. of pyridine in dichloromethane for 1 h at −15 °C.

[9] *C. A. Grob*, *H. P. Fischer*, *H. Link*, and *E. Renk*, Helv. Chim. Acta *46*, 1190 (1963).

[10] The ethyl 4-cyano-4-(methylamino)-1-piperidinecarboxylate (b. p. 125—139 °C/0.5 torr) is accessible by a Strecker synthesis: ethyl 4-oxo-1-piperidinecarboxylate (1 mol), NaCN (0.9 mol), methylamine hydrochloride (0.9 mol), methanol/water (1:1), 16 h, 25 °C.

[11] The oily oxime ether *(15)* was prepared from 1-benzoyl-benzocyclobutene [13]; cf. Ref. [6].

[12] *N. Vinot*, Bull. Soc. Chim. Fr. *1960*, 617.

[13] *R. Hug*, *H.-J. Hansen*, and *H. Schmid*, Helv. Chim. Acta *55*, 10 (1972).

[14] *T. Kametani*, *K. Ogasarawa*, and *T. Takahashi*, J. C. S. Chem. Comm. *1972*, 675.

The Influence of Haloalkanes on the ^{13}C-NMR spectra of *n*-Alkanes

By *Gerhard Bergmann* and *Joachim Dahm*[*]

In contrast to the extensive study of solvent effects in ^{1}H-NMR spectroscopy, little has hitherto been reported about such effects on ^{13}C-NMR spectra[1–6]. The observed effects have mostly been interpreted as due to hydrogen bonds[2,4] or the polar reaction field[3]. However, more recent results[5,6] with the apolar, isotropic tetramethylsilane indicate that other factors, perhaps van der Waals forces, also have a marked influence on the chemical shifts of ^{13}C signals.

We have measured the solvent-dependence of all the ^{13}C-NMR signals of a series of linear alkanes for infinite dilution in the halomethanes CH_2Cl_2, CCl_4, CH_2Br_2 and CH_3I. The changes of the chemical shifts $\Delta\sigma$ in halomethanes, referred to the shift at infinite dilution in cyclohexane, are listed in Table 1, from which the following facts can be recognized.

Table 1. ^{13}C solvent shifts $\Delta\sigma$ (ppm) [a].

Solvent	*n*-Alkane	Position of ^{13}C					
		1	2	3	4	5	6–8
CH_2Cl_2	C_5H_{12}	−0.46	−0.19	−0.11			
	C_8H_{18}	−0.46	−0.19	−0.12	−0.12		
	$C_{10}H_{22}$	−0.47	−0.19	−0.12	−0.16	−0.14	
	$C_{15}H_{32}$	−0.44	−0.19	−0.14	−0.13	−0.13	−0.13
CCl_4	C_5H_{12}	−0.87	−0.25	−0.18			
	C_8H_{18}	−0.85	−0.24	−0.18	−0.20		
	$C_{10}H_{22}$	−0.87	−0.24	−0.18	−0.20	−0.20	
	$C_{15}H_{32}$	−0.89	−0.25	−0.19	−0.21	−0.20	−0.20
CH_2Br_2	C_5H_{12}	−1.48	−0.63	−0.43			
	C_8H_{18}	−1.47	−0.63	−0.46	−0.47		
	$C_{10}H_{22}$	−1.46	−0.63	−0.44	−0.46	−0.46	
	$C_{15}H_{32}$	−1.45	−0.62	−0.46	−0.49	−0.48	−0.49
CH_3I	C_5H_{12}	−1.59	−0.80	−0.54			
	C_8H_{18}	−1.58	−0.80	−0.60	−0.64		
	$C_{10}H_{22}$	−1.59	−0.80	−0.58	−0.62	−0.63	
	$C_{15}H_{32}$	−1.60	−0.79	−0.60	−0.64	−0.62	−0.63

[a] Resonance frequencies ν for infinite dilution in haloalkanes minus ν for infinite dilution in cyclohexane and susceptibility correction; negative values towards lower field. Infinite dilution shifts were extrapolated from measurements at six different concentrations with a least squares parabola. Assignment of the signals by *Grant* and *Paul*'s method [8]; the assignment for C-5 to C-8 of *n*-pentadecane is uncertain; this has, however, no influence on the interpretation because of the almost equal solvent shifts of these signals.

1. With cyclohexane as reference solvent, all the haloalkanes studied shift the signals to lower field. A systematic relation exists between the shift of the ^{13}C signal and the position of the C atom: the methyl group is the most sensitive to solvent effects. Within any one alkane, $|\Delta\sigma|$ decreases rapidly with increase in the distance from the end of the chain and reaches, beginning with C-4, an approximately

[*] Prof. Dr. G. Bergmann and Dipl.-Chem. J. Dahm
Lehrstuhl für Analytische Chemie der Universität
463 Bochum-Querenburg, Buscheystr. NC 4/72 (Germany)

constant value for the methylene groups in the middle of the chain. The differences in sensitivity of the individual C atoms depends on the solvent.

2. The sensitivity to solvent influence does not decrease monotonically within one alkane but shows a feebly marked minimum at C-3.

3. The solvent shift of the signals of corresponding C atoms in different alkanes shows no recognizable relation to the length of the chain but only slight unsystematic variations (mean 0.03 ppm).

4. With the exception of CH_2Br_2a should have good linear correlation ($r^2 = 0.99$) exists between the $\Delta\sigma$ value of the methyl group of the alkanes and the McRae term[7] of the solvent $(n^2-1)/(2n^2+2)$. The correlation is poorer ($r^2 = 0.92$ and 0.93 respectively) for C-2 and C-3. Because of the slight polarity of alkanes the polar reaction field has no appreciable influence. Correspondingly there is no recognizable dependence on $(\varepsilon-1)/(2\varepsilon+n_0^2)$[3].

Received: March 8, 1972 [Z 706 IE]
Revised: August 15, 1972
German version: Angew. Chem. *84*, 1101 (1972)

[1] *H. Spiesecke* and *W. G. Schneider*, J. Chem. Phys. *35*, 722, 731 (1961).
[2] *G. E. Maciel et al.*, J. Amer. Chem. Soc. *85*, 3903 (1963); *86*, 3893 (1964); *88*, 220 (1966); J. Chem. Phys. *42*, 2752 (1965).
[3] *J. K. Becconsall* and *P. Hampson*, Mol. Phys. *10*, 21 (1965).
[4] *R. L. Lichter* and *J. D. Roberts*, J. Phys. Chem. *74*, 912 (1970).
[5] *M. Bacon, G. E. Maciel, W. K. Musker*, and *R. Scholl*, J. Amer. Chem. Soc. *93*, 2537 (1971).
[6] *D. Ziessow* and *M. Carroll*. Ber. Bunsenges. Phys. Chem. *76*, 61 (1972).
[7] *E. G. McRae*, J. Phys. Chem. *61*, 542 (1957).
[8] *D. M. Grant* and *E. G. Paul*, J. Amer. Chem. Soc. *86*, 2984 (1964).

CONFERENCE REPORTS

Properties of Molecules in Electric Fields

By *Armin Schweig*[*]

Molecules are composed primarily of electrically charged particles. Electric fields therefore play an important role in chemistry. Thus a polar dye molecule in solution gives rise to an electric dipole (reaction field) by orientation of the solvent molecules. Electronic absorption bands of the dye molecule can experience very powerful shifts and changes in intensity under the influence of the solvent- and temperature-dependent reaction field (solvatochromism and thermochromism).

A theory for calculating the solvatochromism of polar dyes which extends beyond the qualitative explanation due to *Förster* is developed. This theory poses the problem of calculating molecular dipole moments and polarizabilities in electronic ground and excited states. The solution of this problem afforded a method (*Kuhn* and *Schweig* 1964)[1] providing an exceptional stimulus to the calculation of quantities of second and higher order (polarizabilities[2], susceptibilities[3], shielding[3] and coupling[4] constants, hyperpolarizabilities[5]).

An extension of the theory has lead to the first theoretical treatments of quadrupole moments and quadrupole polarizabilities[6] of large molecules. Calculations of quadrupole moments including all valence electrons[7] show that the π-electron clouds obtained by this method do not extend far enough in a direction perpendicular to the molecular plane. A discussion of the quadrupole moments for molecules containing third-row elements suggests that an admixture of d orbitals becomes essential, in agreement with chemical intuition, whenever they can superimpose a bonding bridge on an antibonding orbital between two atoms[8]. The calculated quadrupole moments thus prove to be a new and highly sensitive probe for p-d bonding effects.

A study of intermolecular interaction on the basis of the calculated multipole moments and multipole polarizabilities furnished two noteworthy results[9]: in contrast to a view that previously found wide general acceptance, the interaction of π systems is not determined by dispersional interaction but by quadrupole-quadrupole interaction. An interaction of this kind suggests that the most favorable electrostatic arrangement of two π systems is achieved when the molecular plane of one system is twisted through 90° relative to the other one so that the π-electron cloud of one system is directed towards the nuclei of the other system. This finding offers a possible explanation of the mutual arrangement of molecules in hydrocarbon dimers and the arrangement of hydrocarbon molecules in the crystalline state.

Lecture at Köln, May 9, 1972 [VB 356 IE]
German version: Angew. Chem. *84*, 1074 (1972)

[*] Prof. Dr. A. Schweig
Fachbereich Physikalische Chemie der Universität
355 Marburg, Biegenstrasse 12 (Germany)

[1] *A. Schweig*, Dissertation, Marburg 1964; *A. Schweig, K. Dimroth*, and *H. Kuhn*, in: Optische Anregung organischer Systeme. Verlag Chemie, Weinheim 1966, p. 765; *A. Schweig*, Z. Naturforschung *22a*, 724 (1967); *A. Schweig*, Chem. Phys. Letters *1*, 163 (1967); *A. Schweig*, Chem. Phys. Letters *1*, 195 (1967); *A. Schweig*, Chem. Phys. Letters *4*, 266 (1969).
[2] *J. A. Pople*, J. Chem. Phys. *49*, 2960 (1968); *K. Seibold, H. Navangul*, and *H. Labhart*, Chem. Phys. Letters *3*, 275 (1969); *H. Navangul* and *H. Labhart*, Theoret. Chim. Acta *17*, 239 (1970); *N. S. Hush* and *M. L. Williams*, Chem. Phys. Letters *5*, 507 (1970); *J. J. C. Teixeira-Dias* and *J. N. Murrel*, Mol. Phys. *19*, 329 (1970); *C. A. G. O. Varma* and *L. J. Oosterhoff*, Chem. Phys. Letters *8*, 1 (1971).
[3] *J. A. Pople*, J. Chem. Phys. *53*, 613 (1970).
[4] *J. A. Pople*, Chem. Phys. Letters *1*, 461 (1967); *G. E. Maciel*, J. Amer. Chem. Soc. *92*, 5829 (1970); *H. Nakatsuji, K. Hirao, H. Kato*, and *T. Yonezawa*, Chem. Phys. Letters *6*, 541 (1970).
[5] *N. S. Hush* and *M. L. Williams*, Theoret. Chim. Acta *25*, 346 (1972).
[6] *A. Schweig*, Mol. Phys. *14*, 533 (1968).
[7] *H. Meyer* and *A. Schweig*, Chem. Phys. Letters *9*, 451 (1971).
[8] *H. L. Hase* and *A. Schweig*, Chem. Phys. Letters *12*, 238 (1971).
[9] *A. Schweig*, Int. J. Quant. Chem. *3*, 823 (1969).

Short-lived Molecules as Ligands in Coordination Compounds

By *Günter Schmid*[*]

Short-lived molecules that cannot be isolated under normal conditions often appear as ligands in coordination compounds. Carbene, cyclobutadiene and thiocarbonyl complexes may be cited as examples, in which the unstable molecules CR^1R^2, C_4H_4 and CS are stabilized by coordination to the metal atoms.

Our attempts to stabilize the lower oxidation states of main group elements in this way have led to compounds of boron, aluminum and silicon. Borylenes of the type BNR_2 exist as ligands in carbonyliron derivatives $(CO)_4FeBNR_2$ ($R=CH_3$ or C_2H_5) that are derived from pentacarbonyliron, a CO group being replaced by BNR_2. Aluminum(I) in the form of the unstable $AlN(CH_3)_2$ replaces a carbonyl group of $(CO)_4FeBr_2$ and thus forms the dimeric $\{(CO)_3[(CH_3)_2NAl]FeBr_2\}_2$ that is bridged by the amino groups. Finally silylenes SiX_2 (X = Cl, Br or I) are fixed in platinum complexes of composition $[(C_6H_5)_3P]_2Pt(SiX_2)_2$ (X = Cl or Br) or $[(CO)_5WSiI_2]_2$ where SiI_2 occurs in place of a CO group in hexacarbonyltungsten. The dimeric character of the compound is probably due to Si—I→Si bridges which lead to better coordinative saturation of the silicon atom, whereby the formal oxidation state 2 is retained. Similar bond relations appear to exist in the dimeric aluminum(I) compound $\{(CO)_3[(CH_3)_2NAl]FeBr_2\}_2$, where the dimethylamino groups act as bridging ligands between the aluminum atoms without changing the univalent character of the Al atoms.

The Al—N bonds readily become involved in insertion reactions, as reactions with CO_2 and CO show.

The bond relations in the B^I, Al^I and Si^{II} complexes are marked by the efforts of the main-group elements to achieve electronic saturation. This can occur by backbonding from the metal atoms but the extent of this backbonding is not known. On the other hand, the ligands NR_2, Cl, Br and I can also reduce the electron deficiency of the elements boron, aluminum and silicon by π-bond contributions. In the dimeric compounds $\{(CO)_3[(CH_3)_2NAl]FeBr_2\}_2$ and $[(CO)_5WSiI_2]_2$ the increase in the coordination number of aluminum and silicon is clearly more important than intramolecular saturation by π-bond contributions.

[*] Prof. Dr. G. Schmid
Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

Lecture at München, June 15, 1972 [VB 359 IE]
German version: Angew. Chem. *84*, 1111 (1972)

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The vibrational spectroscopy of polymers is the theme of a review by *F. J. Boeris* and *J. L. Koenig*. IR spectroscopy is of use not only for the identification of polymers but also for the determination of crystallinity, conformation, terminal groups, branching, cross-linking, hydrogen bonding, and folding in polymers. In the case of copolymers it can also be used for the determination of composition and distribution of monomers. Owing to the progress made in spectroscopical methods both Raman spectroscopy and the investigation of the inelastic scattering of neutrons play an important role in polymer research. In this review the authors first deal with the theory of vibration spectroscopy and then describe its application to eight types of polymers. [Vibrational Spectroscopy of Polymers. Rev. Macromol. Chem. *8*, 209—249 (1972); 113 References]

[Rd 529 IE—G]

Hydride complexes, in which hydrogen is bonded to a transition metal and other stabilizing ligands are present as separate molecules or ionic species, are reviewed by *H. D. Kaez* and *R. B. Saillant*. The syntheses of transition metal hydrides can be divided into five groups: direct hydrogenation (1); reduction of metal halide complexes (2); H transfer from the solvent or from a group coordinated to the metal (3); hydrolysis of metal complex anions in water or acid (4); and protonation of metal complexes (5).

$$FeI_2 + Co + H_2 + PF_3 \rightarrow HCo(PF_3)_3 \quad (1)$$

$$HIrCl_2(AsEt_2Ph)_3 + LiAlH_4 \rightarrow mer\text{-}H_3Ir(AsEt_2Ph)_3 \quad (2)$$

$$OsCl_3L_3 + N_2H_4 \cdot H_2O + C_2H_5OH \rightarrow HOsCl_2L_3 \quad (3)$$
$$L = Pn\text{-}Bu_2Ph$$

$$Ir_4(CO)_{12} \xrightarrow{H^{\ominus}} HIr_4(CO)_{11}^{\ominus} \xrightarrow{H^{\oplus}} H_2Ir_4(CO)_{11} \quad (4)$$

$$HIr(CO)L_3 + HCl \rightarrow [H_2IrCOL_2]^{\oplus}Cl^{\ominus} \quad (5)$$
$$L = PPh_3$$

The authors discuss the properties and reactions of transition metal hydrides, *e.g.* reactions with halogens, mercury (II) halides, and halohydrocarbons, addition to unsaturated compounds, as well as participation in olefin isomerizations, hydrogenation, and hydroformylation. [Hydride Complexes of the Transition Metals. Chem. Rev. *72*, 231-281 (1972); 395 references]

[Rd 536 IE—M]

Poly(tertiary phosphanes) and their metal complexes are summarized by *R. B. King*. Tertiary phosphanes play an important role as ligands in coordination chemistry. A new method of synthesis consists in the addition of a P-H bond to the double bond of a vinylphosphane in the presence of a basic catalyst such as phenyl-Li:

$$C_6H_5PH_2 + 2(C_6H_5)_2P{-}CH{=}CH_2 \rightarrow C_6H_5P[CH_2{-}CH_2{-}P(C_6H_5)_2]_2$$
$$2(C_6H_5)_2PH + C_6H_5P(CH{=}CH_2)_2 \rightarrow \underset{(1)}{}$$
$$PH_3 + 3(C_6H_5)_2P{-}CH{=}CH_2 \rightarrow P[CH_2{-}CH_2{-}P(C_6H_5)_2]_3$$

Mixed arsane-phosphane compounds can also be prepared by this technique. Moreover, it also proves possible to synthesize P^{III} and As^{III} derivatives by addition of P-H and As-H bonds, *e.g.* to vinyl isocyanide. The reaction yields azaphospholines or the analogous arsenic compounds. The new compounds of type *(1)* react with transition metals to give numerous new complexes in which they act as mono-, bi-, and/or tridentate ligands. The coordination chemistry of poly(tertiary phosphanes) opens up new possibilities in fields of practical importance (nitrogen fixation, fuel cell technology, homogeneous hydrogenation, catalysts for new processes). [Some Recent Studies on Poly(tertiary phosphines) and Their Metal Complexes. Accounts Chem. Res. *5*, 177—185 (1972); 32 references]

[Rd 537 IE—M]

The reduction of organic compounds by alkoxyhydridoaluminates *(1)* forms the subject of a review by *J. Málek* and *M. Černý*. Introduction of alkoxy groups into $LiAlH_4$, $NaAlH_4$, and AlH_3 alters the bulk and thus modifies the reducing properties of the hydrides. A survey of methods available for production of *(1)* is followed by a discussion of their reactions, particularly the selective reduction of functional groups in the presence of other reducible groups,

$$R{-}COOC_6H_5 + \underset{(1a)}{LiAlH(OtBu)_3} \xrightarrow[0\,^\circ C]{THF} R{-}CHO + LiAl(OC_6H_5)(OtBu)_3$$
$$R{-}COCl + (1a) \xrightarrow[-70 \text{ to } -80\,^\circ C]{THF} R{-}CHO + LiCl + Al(OtBu)_3$$

e.g. the partial reduction of esters, carbonyl halides, amides, and nitriles to aldehydes, especial interest pertaining to the partial reduction of aromatic and aliphatic nitriles with $LiAlH(OC_2H_5)_3$. The compound $LiAlH(OCH_3)_3$ reduces bicyclic alcohols such as camphor, norcamphor, isopinocamphor, and fenchone to the thermodynamically less stable of the two possible alcohols in a high degree of optical purity. Hydrogenolyses with *(1)* are compared with those of the simple hydridoaluminates. The paper contains preparative examples. [Reduction of Organic Compounds by Alkoxyaluminohydrides. Synthesis *1972*, 217—234; 177 references]

[Rd 538 IE—M]

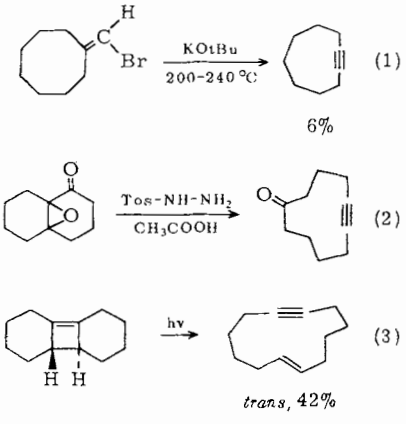
The chemistry of vitamin B_{12} enzymes is reviewed by *J. M. Wood* and *D. G. Brown*. Methyl- and hydrogen-transferring enzymes are amply treated. Magnetic resonance methods are recommended as promising methods for the study of these enzymes: ESR for Co(II) corrinoids and for "spin-labeled" derivatives, NMR (^1H, ^{13}C, ^{19}F) for the evaluation of electronic effects of the ligands coordinated with the Co atom and for conformational studies, *e.g.* of the dimethylbenzimidazole group. [The Chemistry of Vitamin B_{12}-Enzymes. Structure and Bonding *11*, 47—105 (1972); 146 references]

[Rd 542 IE—H]

Possible interactions of transition metal complexes with biological macromolecules are depicted by *A. J. Thomson*, *R. J. P. Williams*, and *S. Reslova*. The anti-tumor activity of *cis*-$Pt(NH_3)_2Cl_2$ and some related compounds is the starting point of the article. Two-thirds of the paper are concerned with the chemistry relevant to this subject (thermodynamic and kinetic stability, oxidation states, spectroscopic properties, photochemical behavior, while the rest considers the interaction of metal complexes with amino acids, proteins, and nucleotides. The review concludes with a discussion of the possible modes of biological action of complexes. [The Chemistry of Complexes Related to *cis*-$Pt(NH_3)_2Cl_2$. An Anti-Tumour Drug. Structure and Bonding *11*, 1—46 (1972); 90 references]

[Rd 541 IE—H]

The synthesis of stable, isolable cycloalkynes having 7- to 12-membered rings including carbocycles having additional unsaturated groups or aromatic rings and cycloalkynes with heteroatoms in the ring, is reviewed by *H. Meier*. In the case of cyclic acetylenes one has to expect valence isomerizations (transannular π-electron interactions), isomerization to allenes and other dimers, particularly when syntheses are carried out in the presence of strong bases. The most important synthetic routes are the elimination reactions of types (1) to (3). Dehalogenations and dehydrohalogenations of 8-, 9-, and 10-membered rings generally give poor yields. The photolysis of bistosylhydrazones



and the thermolysis of polymethylenecyclopropenones represent fairly new methods. [Synthesewege zu Cycloalkinen mittlerer Ringgrösse. Synthesis *1972*, 235—253; 124 references]

[Rd 539 IE—M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Difluoromethyl-1,2,2,3,3-pentafluoropropyl ether *(2)*, a process for its preparation, and anesthetics containing *(2)* are claimed. The compound *(2)* can be obtained by reaction of tetrafluoropropanol with chlorodifluoromethane in the presence of strong alkali to form the difluoromethyl ether *(1)*, followed by chlorination and halogen exchange.

The compound exhibits good anesthetic effects, whereas related isomers are known only as (lethal) convulsants.

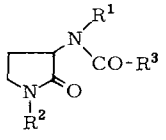
$$CHF_2-CF_2-CH_2OH \xrightarrow{CHF_2Cl} CHF_2-CF_2-CH_2-O-CHF_2$$
(1)

$$\xrightarrow[2.\ BrF_3]{1.\ Cl_2} CHF_2-CF_2-CHF-O-CHF_2$$
(2)

[DOS 2139398; Baxter Laboratories, Inc., Morton Grove]

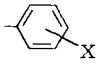
[PR 10 IE—N]

New *N*-acylaminopyrrolidinone derivatives *(1)* can be used as central muscle relaxants, and also have an anti-inflammatory and analgesic action. The compounds can be prepared by known methods by reaction of the optically active or racemic aminopyrrolidinones with carboxyl

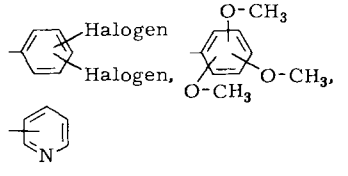


(1)

R^1 = H, CH_3

R^2 = 

X = H, Halogen, $O-CH_3$, CF_3, NO_2

R^3 = 

compounds or their functional derivatives. [DOS 2140694; Tanabe Seiyaku Co., Ltd., Osaka]

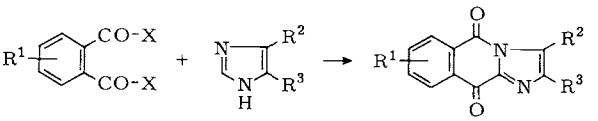
[PR 17 IE—N]

Easily extrudable plastic mixtures based on polyvinyl chloride suitable for the production of transparent bottles and having a Fikentscher *K* number of 58 to 67, measured in dichloroethane, are obtained by polymerization of vinyl chloride under a partial pressure that is always below the saturation vapor pressure of the monomer at the polymerization temperature, in the presence of polyethylene having 0.2 to 4 double bonds and/or 5—30 methyl groups per 1000 C atoms and a melt index of 0.3 to 40, followed by mixing of 0.1 to 5 parts by weight of this product, which consists of graft polymers of vinyl chloride with polyethylene and unchanged polyethylene, with 100 parts by weight of polyvinyl chloride. The total quantity of polyethylene in the mixture is at most 2.5 wt.%, based on polyvinyl chloride.

0.5 to 20 wt.% of reinforcing agent, *e.g.* graft polymers of polybutadiene or butadiene-styrene copolymers with methyl methacrylate and styrene or methyl methacrylate and acrylonitrile or methyl methacrylate, styrene, and acrylonitrile or methyl methacrylate, styrene, and ethyl methacrylate, may be added to improve the impact strength. Good results are also obtained if instead of polyethylene and polyvinyl chloride, the corresponding copolymers of ethylene and 0.4 to 6 mole % of other α-olefins or of more than 80 wt.% of vinyl chloride are used. [DOS 2138875; Solvay & Cie., Brussels]

[PR 29 IE—C]

Imidazoisoquinolinediones *(3)* can be obtained in a smooth reaction and in good yields by reaction of halides of phthalic acid *(1)* with imidazoles *(2)* in the presence of a polar solvent and a base. The dielectric constant of the solvent should be at least 4.8, and the parity constant of the base should be at most 8.7. The diones *(3)*, some of which are



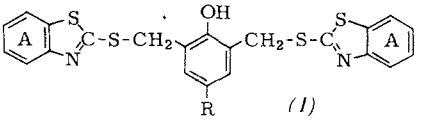
(1) *(2)* *(3)*

R^1 = H, NO_2, alkyl, halogen, alkoxy, (substituted) aryl;
$R^2 = R^3$ = H, alkyl, aryl, halogen;
$R^2 + R^3$ = (substituted) benzene ring (including the C atoms of the imidazole ring)
X = halogen

known, exhibit herbicidal properties and can be used both as total herbicides and as selective weedkillers. [DOS 2043649; Farbenfabriken Bayer AG, Leverkusen]

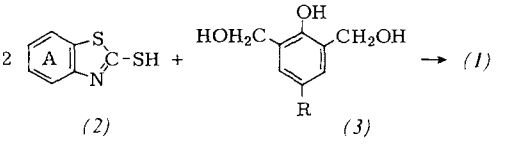
[PR 32 IE—N]

Phenols substituted with benzothiazylthioalkyl groups *(1)* are used as stabilizers for natural and synthetic rubber.



(1)

R denotes alkyl, cycloalkyl, alkylcycloalkyl, or aralkyl; the ring A may be substituted with alkyl, alkylamino, or alkoxy and chlorine. The compounds are obtained from *(2)* and *(3)* at 60 to 120°C (molar ratio roughly 2:1).



(2) *(3)*

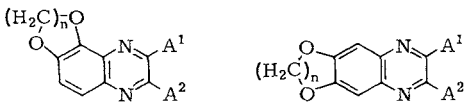
(1) has good antiozonant and antioxidant properties, and is non-staining. [DOS 1694446, Imperial Chemical Industries, Ltd., London]

[PR 35 IE—E]

Foamed thermoplastic resins are obtained by extrusion of a thermoplastic resin that contains a volatile blowing agent and orthoboric acid as a nucleating agent, the extrusion conditions being such that the orthoboric acid decomposes with formation of nucleation sites for the cell formation. Orthoboric acid may also be used in combination with known nucleating agents, which have undesirable side effects when used alone. Aliphatic hydrocarbons, lower alkyl halides, acetone, and inorganic gases may be used as blowing agents. The foamed resins have a fine, uniform cell size. [DOS 1694649; Monsanto Chemicals Ltd., London]

[PR 41 IE—E]

The quinoxalines *(1)* can be used as hydrogen carriers in photographic processes, particularly as bleaching catalysts in the silver bleaching process for the production of color photographs.



(1a) n = 1, 2 *(1b)*

A^1, A^2 = alkyl (C_1-C_5), at most bicyclic (substituted) aryl, five- or six-membered heterocycle containing N, O, or S.

The ring containing O is linked to the quinoxaline grouping in the 5,6 *(1a)* or the 6,7 position *(1b)*. The new bleaching catalysts *(1)* give uniform bleaching of all three dye layers of a multilayer material. Catalysts known in the past have very different effects on azo dyes having different constitutions. The compounds *(1)* have favorable redox potentials and good solubility and activity properties, and they give good gradation. Bleach coupling between the individual layers containing the dyes is also largely suppressed. [DOS 2144298; CIBA-Geigy AG, Basel]

[PR 46 IE—B]

BOOK REVIEWS

Adsorption of Organic Compounds on Electrodes. By *B. B. Damaskin, O. A. Petrii,* and *V. V. Batrakov.* Plenum Press, New York—London 1972. 1st Edit., xvi, 499 pp., numerous figures, bound $ 40.50.

The present book is an English translation of a 1968 Russian edition revised by the authors for this purpose. It presents a hitherto lacking, comprehensive description of the entire field of the adsorption of organic substances on liquid and solid metals, written by members of the Flumkin school, whose mark it clearly bears. The first part describes the methods for the investigation of adsorption on liquid metals, mainly mercury, and the numerous results that have been obtained by these methods, including the hypotheses and theories derived from them. Chapter 3 in particular provides an insight into the controversy about the choice of the electrode potential or the electrode charge as the more appropriate independent variable, a decision being made here in favor of the electrode potential.

The second part deals with the methods and results for solid metals; a distinction is drawn between metals with high and with low hydrogen overvoltages. The metals of the iron group and those of the platinum group are treated separately. All problems in which the adsorption of organic substances plays a part, including those of practical importance, are discussed: additives in the deposition of metals, inhibitors in corrosion, fuel cells. To allow a better understanding of the processes involved in the adsorption, the kinetics of the actual electrode process are considered to some extent.

The book is worth reading for theoretical and practical workers in the fields of electrochemistry and physical chemistry, and because of the unusually large number of references it is a mine of information. An effort is made to show to whom or to which research group the priority belongs for given results or lines of investigation.

This abundance of references may actually be confusing to the beginner, since a number of conclusions are clearly understandable only when one knows the cited works in some detail. This is true in particular where *e.g.* in the case of alternating current measuring bridges (p. 16), Russian textbooks and handbooks are cited, whereas references to more easily accessible literature would have been preferable in the translation.

The numerous tables are very useful, particularly those giving values for the point of zero charge of the metals, which are otherwise widely scattered in the literature.

Horst Binder [NB 67 IE]

Anstrichstoffe und ähnliche Beschichtungsstoffe, Pigmente (Paints and Similar Coating Materials, Pigments). Issued by the Deutscher Normenausschuss. Beuth-Vertrieb GmbH, Berlin-Köln-Frankfurt 1971. 1st ed., 392 pp., numerous figures, stitched DM 54.—.

The publication of this pocket book is very welcome to the practical worker. Whereas it was formerly necessary to acquire individual standards in his field of interest, which were difficult to keep together, he now has available a neat collection of the relevant standards.

The collection has been carefully prepared, and a quick examination gives some idea of the numerous matters in the field of paints and pigments for which standardization has been necessary. A glance at the appended list of standards and draft standards that have not been reproduced shows how many more matters in daily work are covered only by draft standards, so that even now it is necessary to express the wish for a new edition as soon as a sufficiently large number of the drafts dealt with by the committees have become preliminary standards or standards.

Some readers will no doubt regret that complete standards for certain fringe areas have not been reproduced, but the inclusion of these standards would probably have made the book too large, to the inconvenience of other users.

The existence of a standard does not mean the end of the matter, as is shown *e.g.* in the field of definitions by an article that appeared in the journal "Farbe + Lack" in February 1972, in which the definition of a pigment as laid down in a standard was critically examined and found to be in need of modification.

The present book is arranged in numerical order, and contains an index arranged according to field as well as an alphabetic subject index.

It contains the standards on terminology and abbreviations, binders, solvents, driers, softeners, pigments and fillers, paints and similar coating materials, and color. The very wide field of pigments and fillers is broken down into general test methods, white pigments, colored pigments, luminous pigments, carbon blacks, and fillers.

The aquisition (and the frequent use) of this pocket book can be strongly recommended to all practical workers.

Heinz Rechmann [NB 78 IE]

Atomic and Molecular Radiation Physics. By *L. Christophorou*. John Wiley & Sons Ltd., New York—London 1971. 1st ed., x, 672 pp., numerous figures and tables, bound £ 10.50.

The book deals with the processes in the eV to keV range that occur on interaction of electrons, ions, and photons with individual atoms and molecules. Processes in liquids and solids are merely touched upon. It should be stressed that triatomic and polyatomic molecules are included in the discussion. The physical principles are presented clearly before the description of the experimental methods and the results obtained by these methods. Practically all the results mentioned are supported by references; this enhances the value of the book, since original papers up to and including 1969 are covered.

The book is divided into nine chapters. The first two deal with the deceleration and the resulting total ionization during the passage of ionizing radiation through matter. The next six chapters form the main part of the book, and deal with the processes that are brought about in or on atoms and molecules by photons, electrons, and ions: photophysical processes; elastic scattering of slow electrons; inelastic scattering of electrons; negative ions; electron detachment from negative ions and electron affinities of atoms and molecules; interactions between heavy neutral and charged particles. In the concluding chapter on biophotophysics and bioelectronics, reference is made to the importance of the physical understanding of molecular processes to biological problems, with the development of cancer as an example. The appendix contains ionization potentials of atoms, molecules, and radicals, some physical constants and conversion factors, and the periodic table and the table of radioactive isotopes. An author index and subject index are included. The book can be recommended to anyone who wishes a general picture of the present position of knowledge on the interactions of photons, electrons, and ions with free atoms and molecules in the low-energy range.

Hans Steidl [NB 82 IE]

***In Vitro* Methods in Cell-Mediated Immunity.** Ed. by *B. R. Bloom* and *P. R. Glade*. Academic Press, New York—London 1971, 1st edit., xxiv, 578 pp., numerous figs, bound, $ 14.00.

At a conference held in April 1969 at Brook Lodge on "Mediators of Cellular Immunology" it became apparent how greatly the clarification of the mechanisms of cellular immunity depended upon suitable *in-vitro* methods. These in their turn became the subject of a symposium held at the New York University, Bellevue Medical Center, New York, on May 28-29, 1970. The present book is an edited version of the discussions at this meeting, supplemented by an extensive section on the methods used.

The topics discussed are the characterization of the currently known supposed mediators of cellular immunity by simple chemical and physical parameters and their differentiation from one another (some short summary tables on this are given at the end of the book), the appropriate *in-vitro* systems, which are described by several of the participants and subsequently freely discussed and criticized, the correlation with *in-vivo* phenomena, and starting points for the development of new experimental systems.

The second part of the book consists of a clearly arranged description of 37 experimental *in-vitro* systems, by means of which the following phenomena may be studied: cell migration (particularly macrophage migration and related effects on macrophages), cytotoxicity of lymphocytes, lymphocyte transformation, inhibition of cell growth, chemotaxis, production of skin-reactive factor and of interferon, transference of delayed type of skin reactivity by transfer factor, and intracellular virus multiplication. A guide to the cultivation of human lymphocytes in long-term cultures is also given.

One great advantage of this book is that the methods represented are not merely described but are also discussed in an extremely lively fashion. It is true that this makes it difficult to obtain a good allover view, but this disadvantage is far outweighed by the wealth of suggestions and critical objections arising from the discussions. The extensive practical section which derives from the contributions of well-known scientists, in many cases the originators of the systems in question, is impressive in the clarity of its arrangement and in the precision and detail of its descriptions.

The book is highly recommended to all immunologists and immunological chemists active in this field.

Günter Sommer [NB 79 IE]

Organisch-chemisches Praktikum (Practical Organic Chemistry). By *G. Kempter*. Vieweg Verlag, Braunschweig 1971. 1st edit. 203 pp., 85 figs., bound, DM 9.80.

This is a brief practical manual produced by the author and a group of associates for students who are taking chemistry as a subsidiary subject. An introduction to instrument technology is followed by expositions on safety and fire precautions and on general methods (melting point, sublimation, distillation, rectification, and chromatographic methods). The organic experiments which follow are arranged by type of reaction. Each set of operating instructions is preceded by a brief theoretical introduction. Access to the literature is simplified for the student by a short introductory chapter. The book ends with sections on qualitative analysis and on ultraviolet and infrared spectroscopy. Each chapter is accompanied by test questions and practical exercises.

An attractive feature of the book is its compact and precise presentation, together with the clarity of the figures and formulas. The experiments to be carried out are simple, in accordance with the level of experience of the intended readership. In the reviewer's opinion the theoretical introductions are too short, for in many cases they do no more than show the student the concept he will need to study more thoroughly in a textbook. In addition, the brevity of the entries sometimes leads to the risk of making false statements due to excessive simplification (*e.g.* p. 74, nucleophilic substitution by $^{\ominus}NO_2$; p. 97, 1st section on poly-

merization, *etc.*). In general, one misses references to further literature; even in a book for beginners they should not really be left out. It is also a pity that the chapters on analytical methods and spectroscopy are separated from the preparations. If these chapters could have been integrated into the preparative sections the student would have had a much greater motivation for learning these techniques, *i.e.* he would learn the method in relation to its use on "his own preparation".

One minor point: it is to be hoped that the extremely good section on safety and fire precautions (p. 70) will not be spoilt in the next edition by the comment "All pranks, larks, and squabbles at the laboratory bench are absolutely forbidden."

For students whose main subject is something other than chemistry (teachers, physicists, pharmaceutical chemists), this brief practical manual can be recommended, if used in conjunction with a good textbook. For chemistry students the level is too low, even for the early organic practicals. Medical students will probably find the lack of medical applications a drawback.

Jürgen Sauer [NB 81 IE]

Organotin Compounds Vol. 1. By *A. K. Sawyer*. Marcel Dekker Inc., New York 1971, 1st ed., xiv, 252 pp., numerous tables, bound, $ 30.00.

The chemistry of organotin compounds, which has been advancing in leaps and bounds, is to be covered in three volumes, comprising fourteen survey articles by leading authors. Ten articles will deal with the main groups of compounds, arranged in the classical way as Sn—X compounds where X is *e.g.* hydrogen, halogen, oxygen, sulfur, or nitrogen. The other four chapters will be about technical applications, biological effects, tin-containing polymers, and analysis. However, the reviewer would have preferred to find in a reasonably comprehensive treatise a more detailed account in the form of some general chapters about theory, thermochemistry, bond lengths, and bond energies, structural chemistry, reaction mechanisms, and comparison with other organometallic compounds. It is to be hoped, however, that the separate chapters will contain some data on these aspects as well.

Volume 1 contains three survey articles, with literature up to the middle of 1968. The way the material is treated reflects the approach of the author in each case. The first article, by *E. J. Kupchik*, on 72 pages and with 316 references, is about organotin hydrides, and it discusses the results of relevant work in a rigid pattern. Mechanisms are mentioned only occasionally, as are also the ways of using these compounds, which can be deduced from the mechanisms. The author often refrains from criticism and reports some partly or fully invalid results without comments (*e.g.* Eq (7) or at the top of p. 35, with conflicting results in the middle of the same page). Comments and an explanation of the causes (*e.g.* competition between two mechanisms) would have been desirable in places.

The second article, in which *G. P. Van der Kelen, E. V. Van den Berghe*, and *L. Verdonck* discuss organotin halides (excluding organotin pseudohalides) on 70 pages, with 567 references, is a thorough account of the essentials with special emphasis on structure and spectroscopy, which are the authors' fields.

The third article is about organotin compounds, containing the Sn—O bond (Part I—alkoxides, oxides, and related compounds; 99 pages, with 347 references). It is written by *A. J. Bloodworth* and *A. G. Davies*, who are leading authors in this field and who have given a complete and critical account, including some unpublished results. The tables for compounds giving the recommended methods of preparation, are very extensive. The correlations are explained clearly, and the mechanisms and their useful applications are not omitted either. It is altogether an excellent and useful article.

This work is not a textbook but a collection of competent review articles, such as appear elsewhere as well (*e.g.* Advances in Organometallic Chemistry and Organometallic Chemistry Reviews). This is why the book will be found useful by those working in this field. Volume 2 has been published recently. It is hoped that volume 3 will be available soon because it will carry the cumulative index.

W. P. Neumann [NB 85 IE]

The Nitrile Oxides. Organische Chemie in Einzeldarstellungen, Vol. 13, By *Ch. Grundmann* and *P. Grünanger*. Springer Verlag, Berlin-Heidelberg-New York 1971. 1st ed., ix, 242 pp., numerous figures and tables, bound DM 98.—.

Until about 20 years ago the nitrile oxides were a little-known and only sporadically investigated class of compounds. They have recently become the subject of growing interest. Some recently published reviews made no effort to present a complete survey, and the publication of a comprehensive monograph thus seemed justified.

The authors have divided the book into nine chapters. The introduction contains, *inter alia*, a historical outline most of which is devoted to the 200 year odyssey of the structure of fulminic acid. The physical properties and the methods for the preparation of nitrile oxides and their rearrangement into isocyanates, their reduction to nitriles, and their polymerization reactions are then discussed. The fifth and longest section describes the numerous 1,3-dipolar cycloadditions. The representative examples are well chosen, and are explained only in so far as is necessary for understanding. A complete list of all cycloadducts in the form of tables is presented in the ninth chapter. In the sixth section, reactions leading to open-chain products are discussed under 1,3-additions. Finally, two short chapters deal with further reactions and with physiological properties and practical uses of nitrile oxides.

The widely scattered and in part poorly accessible literature has been carefully collected and arranged; a strikingly large proportion of the publications appeared during the past ten years. The shortness of the book facilitates reading. It is well worth the price both to those interested in synthesis and to those whose interest is mechanistic. The authors' personal involvement can be seen in occasional critical comments.

This is a successful attempt to present the latest position in the chemistry of nitrile oxides, and fills a gap in the chemical literature.

Manfred Christl [NB 76 IE]

Zement, Herstellung und Eigenschaften (Manufacture and Properties of Cement) by *F. Keil*. Springer-Verlag, Berlin-Heidelberg—New York, 1971. 1st ed., viii, 439 pp., 96 figs., bound, DM 88.—.

Most books on cement deal with the physical chemistry of the manufacture and hardening of cement either in a simple and readily understandable manner for technologists or comprehensively for scientists. *Keil's* aim seems to have been to do both. Though he says in the Preface that he has omitted many details, the table of contents and about 900 references indicate that he has succeeded in giving the fullest possible account of present-day knowledge of cement.

The first of the five chapters deals with the various types of cement and their uses, besides explaining how to make mortar and concrete. The second chapter, which is about the chemistry of cement clinker, gives a concise description of the reactions during the burning of cement clinker, the properties of the clinker phases and the hydraulic additives, as well as the products of the hydration of cement and the processes involved in hardening. This is followed by an account of the methods of investigation. The next two chapters discuss the physical characteristics (structures, strength, volume changes of hardened cement paste and concrete, and the influence of temperature on setting) and natural and technological effects (weathering and its significance for the formation of the raw materials and in connection with the chemical attack of concrete; corrosion and its prevention in steel reinforcing elements). The last chapter describes the technology of cement manufacture with particular emphasis on kiln processes and the topical question of emission and immission.

In just under 400 pages the author gives a complete picture of the physical chemistry and the technology of cement and the main properties of mortar and concrete. This book therefore enables students and technologists who prefer a clear and concise account to acquire an up-to-date knowledge of cement. The scientist will find this book interesting mostly because it is based on the literature and so it gives an excellent brief and objective account of all the main results, including the most recent ones. It will be an indispensable reference work for all those who are involved in the research and development of cement.

F. W. Locher [NB 84 IE]

Physical Chemistry—An Advanced Treatise. Vol. I. By *H. Eyring, D. Henderson*, and *W. Jost*. Academic Press, New York—London, 1971. 1st ed., xxii, 659 pp., bound, £ 13.—.

This volume, which is the first of a work that is expected to run to 11 volumes and of which a series of single volumes have appeared during the past few years[1], deals with the thermodynamic principles in twelve sections written by nine authors. This division into sections guarantees that each section provides a good foundation and at the same time takes the latest research results into account in its approach.

A wide range of applications, such as interfacial thermodynamics, treatment of several simultaneous equilibria, thermodynamics of extreme pressures and temperatures, irreversible thermodynamics, and thermodynamics in external fields are therefore discussed. A fundamental section deals with the Second Law from the Caratheodory standpoint; however, other fundamental questions such as the problem of the unattainability of absolute zero and the formalism of negative temperatures are also discussed.

In view of this diversity, it is not surprising that some matters that are important to the applications receive rather too little attention. These include the thermodynamic phenomena in gravitational fields, which play a role in meteorology and even in the theory of the constitution of the stars. Certain areas of thermodynamics, on the other hand, are dealt with more than once by different authors. It is often too much to expect the editor to eliminate overlapping of this nature; moreover, a section becomes too difficult to read if it is necessary to refer too often to other sections.

The presentation naturally differs from section to section, but it is always sufficiently clear to enable the reader to follow the course of developments without too much difficulty. The main advantage of the presentation lies in the fact that the reader is brought abreast with present-day research, and an extensive bibliography makes it easy to find further information where the book lacks space for detailed discussions. The work can therefore be wholeheartedly recommended to all those who are interested in gaining a more thorough knowledge of thermodynamics, particularly for their own research work.

[1] Cf. Angew. Chem. internat. Edit. *10*, 587 (1971).

Klaus Schäfer [NB 75 IE]

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1973. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 40 36/40 37, Telex 46 55 16 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson*.

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N.Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P.O. Box 129/149 Germany, Telephone Weinheim (0 62 01) 40 31, Telex 46 55 16 vchwh d.

ANGEWANDTE CHEMIE

Volume 11 · Number 12
December 1972
Pages 1041–1110

International Edition in English

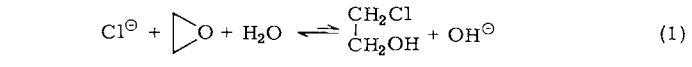
Basic Behavior of Epoxides in the Presence of Halide Ions[1]

By J. Buddrus[*]

Epoxides behave as bases in the presence of catalytic quantities of halide ions. They convert halogenated hydrocarbons into olefins, suitable phosphonium salts into ylides, and haloforms into dihalocarbenes. Kinetic studies with the aid of IR and NMR spectroscopy show that the species that functions as the proton acceptor is neither the epoxide ion nor the halide ion, but the 2-haloethoxide ion.

1. Introduction[2a–2c]

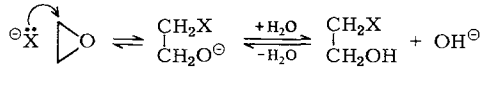
Brønsted et al. observed in 1929 that an aqueous solution of KCl has an alkaline reaction after the addition of an epoxide[2d]. The weakly basic chloride ion enters into a covalent bond and liberates the equivalent quantity of the stronger base OH^-. Eq. (1) is an equilibrium reaction[3a, 3b]. The reverse reaction is the well-known epoxide formation from 2-haloalcohols and hydroxide ions.



(1)

The equilibrium is displaced well to the side of the epoxide. Thus the equilibrium constant for ethylene oxide and sodium chloride at 20 °C is 3.2×10^{-4}, *i. e.* an equimolar solution of ethylene oxide and NaCl contains the components of the left-hand and of the right-hand sides of eq. (1) in contents of 98% and 2% respectively[**].

The forward reaction and the reverse reaction both proceed *via* the same intermediate (principle of microscopic reversibility[3b]). The intermediate (2-haloethoxide) can be intercepted by electrophilic compounds such as acrylonitrile[4], and can also be observed by measurement of conductivity and heat of mixing[5]. Among the halide ions, the iodide ion reacts fastest[2d], in agreement with the increase in nucleophilic character in the order $Cl^- < Br^- < I^-$ in protonic solvents[6].

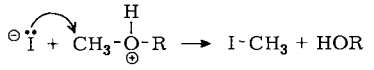


The fact that epoxides undergo ring cleavage so readily is evidently connected with their ring strain, since halide ions do not cleave cyclic ethers with larger rings or open-chain ethers. Additional protonation or other complex formation on the oxygen is necessary to weaken the C—O bond to

[*] Priv.-Doz. Dr. J. Buddrus
Fachbereich Synthetische und Analytische Chemie
Technische Universität, Berlin (Germany) and
Institut für Spektrochemie und angewandte Spektroskopie
46 Dortmund, Bunsen-Kirchhoff-Strasse 11 (Germany)
(present address)

[**] *Brønsted*'s observation can be easily demonstrated in a small-scale experiment. 1 g of KI is dissolved in 10 ml of water, and a few drops of phenolphthalein solution are added. 1 ml of ethylene oxide [alternatives: propylene oxide; epichlorohydrin (chloromethyloxirane)] is also dissolved (or suspended) in 10 ml of water, and phenolphthalein is added to the solution. The two colorless solutions are combined. After a few seconds, the solution is turned deep red by the hydroxide ions produced.

such a degree that it can be broken by the attack of a halide ion[7,8] ["ether cleavage", eq. (2)].

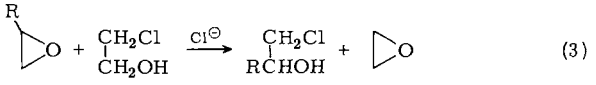


(2)

2. Rediscovery of the Basic Behavior

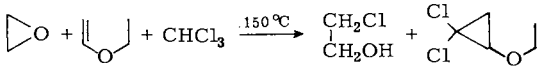
The uptake of a proton in accordance with eq. (1) should not be confined to water, but should also extend to other compounds containing mobile hydrogen (alcohols, C—H acid compounds).

However, only isolated experiments have been carried out in this direction. Thus the dehydrohalogenation of β-haloalcohols by epoxides in the presence of halide ions has been described [eq. (3)][9].



(3)

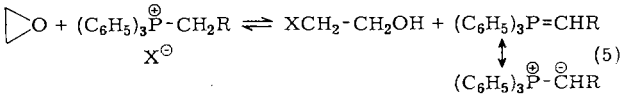
The basic behavior of the halide ion/epoxide system was rediscovered by accident. Attempts made by the author to add the three-membered ring of the epoxide to a double bond to obtain tetrahydrofuran derivatives were unsuccessful[10]. The reaction (4) took place instead in the "solvent" chloroform[11,12]. In this reaction, ethylene oxide eliminates



(4)

hydrogen chloride from chloroform and is converted into 2-chloroethanol. Quaternary ammonium halide, whose activating effect on epoxides has been described[13], was used as the catalyst.

In another experiment, a quaternary phosphonium halide was tried as the catalyst. Ethylene oxide was again found to be a base, but this time toward the "catalyst" [eq. (5)][14].

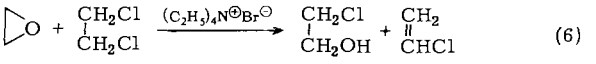


(5)

We shall first discuss the 1,2-elimination of hydrogen halide from haloalkanes, a reaction that we have also investigated kinetically. The deprotonation of phosphonium salts and the 1,1-elimination will then be discussed mainly from the preparative standpoint.

3. 1,2-Elimination from Haloalkanes[15-17]

Epoxides eliminate hydrogen halide from reactive haloalkanes, *e.g.* in accordance with eq. (6). The reaction proceeds only in the presence of catalytic quantities of a halide such as tetraethylammonium halide. The lower the



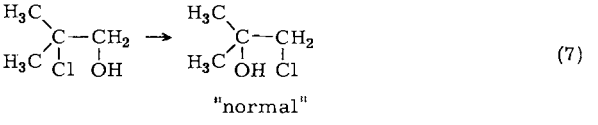
(6)

C—H acidity of the haloalkane, the higher is the reaction temperature (Table 1). Simple haloalkanes such as isopropyl bromide, *n*-butyl bromide, and cyclohexyl chloride do not react.

Table 1. Conversion of some haloalkanes into olefins by ethylene oxide in the presence of $(C_2H_5)_4N^{\oplus}Br^{\ominus}$.

Haloalkane	*T* [°C]	Olefin	Yield [%]
$CHCl_2$—$CHCl_2$	80	$CHCl{=}CCl_2$	92
CH_2Br—CH_2Br	150	$CH_2{=}CHBr$	63
CH_2Cl—CH_2Cl	150	$CH_2{=}CHCl$	61
$(CH_3)_3CCl$	150	$(CH_3)_2C{=}CH_2$	54
trans-1,2-Dibromocyclohexane	150	1-Bromocyclohexene	21

Alkyl-substituted epoxides give two isomeric alcohols in reaction (6), the isomer with terminal halogen ("normal isomer") predominating. However, the ratio of the normal isomer to the other isomer provides no information about the course of the dehydrohalogenation, for two reasons. Firstly, ring cleavages of epoxides both in acidic and in alkaline solution lead mainly to the normal isomer[18-24]. Secondly, at least at 150 °C, the ratio is controlled thermodynamically and not kinetically, as is shown by the following isomerization effected by isobutylene oxide and chloride ions at 150 °C [reaction (7)][15,9,25].



(7)

The base in the epoxide/halide ion system could be:

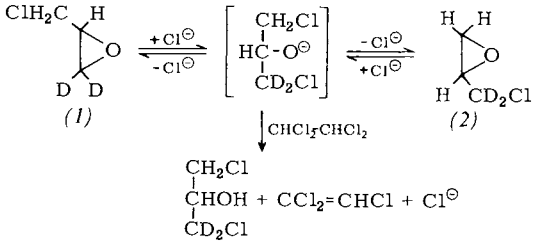
a) the halide ion (with subsequent transfer of hydrogen halide to the epoxide ring). *Winstein, Parker et al.*[26] showed that tetrabutylammonium chloride in acetone converts tosylates and (more slowly) haloalkanes into alkenes

b) the epoxide ring (with subsequent ring cleavage of the protonated epoxide by halide ions). *Searles* and *Tamres* detected hydrogen bonds between epoxides and alcohols[27]

c) the 2-haloethoxide ion. As was pointed out earlier, this intermediate has been detected indirectly in water. Hydrogen bonds presumably contribute appreciably to the formation and stability of the ion, since cleavage of the epoxide ring occurs only very slowly, if at all, in aprotic solvents. Thus ethylene oxide reacts with diethylamine in methanol to give *N*,*N*-diethylaminoethanol; in the absence of methanol, no reaction occurs[2c]. Styrene oxide and

benzylamine react 100 times as rapidly in methanol as in acetonitrile[19].

Investigations were first carried out to establish whether halides could cleave the epoxide ring in *aprotic* media. If tetrabutylammonium chloride is allowed to react with deuterated epichlorohydrin *(1)*, a 1:1 equilibrium *(1)*⇌*(2)* is slowly established, as is shown by ^{1}H-NMR spectroscopic investigation.



As is to be expected, the isomerization is first order with respect to the epoxide and with respect to the chloride. The rate constant k_i at 43.5 °C is 4.6×10^{-3} l.mol^{-1}.min^{-1}.

If 1,1,2,2-tetrachloroethane is now added to this solution, the isomerization is suppressed (as long as tetrachloroethane is still present), and dehydrohalogenation to form trichloroethylene occurs instead. IR spectroscopic investigation of the ethylene formation shows the same order with respect to the epoxide and to the salt. Tetrachloroethane is not involved in the rate-determining step, and its deuterated form exhibits no appreciable kinetic isotope effect: $k_H/k_D = 1.2$. The rate constant k_d at 43.5 °C, however, is 10.65×10^{-3} l.mol^{-1}.min^{-1}; it is roughly *double* k_i. This doubling can be readily explained by the occurrence of the alkoxide as an intermediate. Each successful nucleophilic attack by the chloride on *(1)* leads to alkoxide formation, and hence to (fast) dehydrohalogenation, but only every *second* intermediate molecule is converted into *(2)* (1:1 equilibrium).

If, on the other hand, a relatively inert haloalkane such as 1,2-dichloroethane is added, a different kinetic picture is found, though the mechanism does not change. The dehydrohalogenation is now by far the slowest step. In addition to the epoxide and the salt, 1,2-dichloroethane also appears with an order of one in the rate equation for the vinyl chloride formation. Therefore an appreciable kinetic isotope effect is observed: $k_H/k_D = 40$ at 43.5 °C. Furthermore, a kinetic analysis reveals that out of 50 alkoxide ions $(CH_2Cl)_2CHO^-$ formed, 49 revert to epichlorohydrin and chloride "without having done anything", while only one undergoes further reaction with 1,2-dichloroethane (c = 1 mol/l)[15]. The isomerization (with the rate constant k_i) is fast in comparison with this process, and is practically complete before appreciable quantities of vinyl chloride have been formed.

These experiments show that the epoxide ring is opened by chloride ions even in aprotic media, and that the *alkoxide* formed is the actual base.

Electron-attracting residues on the epoxide ring accelerate the ring cleavage:

$$C_2H_5 < CH_3 < H < CH_2Cl < CCl_3 < CF_3$$

This increase is in agreement with a nucleophilic ring cleavage of the epoxide. ρ^*, the reaction constant of the Taft equation, is +0.86. The influence of substituents is thus small. No differences were observed in the reactivity of free chloride and of ion-pair chloride in the solvent (and reactant) epichlorohydrin (dielectric constant 22) and at salt concentrations of 0.01 to 0.15 mol/l, presumably because the chloride ion is surrounded by the reactant epichlorohydrin in both cases.

4. Deprotonation of Phosphonium Salts[14]

As was mentioned earlier, epoxides deprotonate phosphonium salts [eq. (5)]. This was surprising, since strong bases[28] such as alkoxides or organometallic compounds had previously been used in most cases for deprotonation. The preparative possibilities of the deprotonation and of the Wittig reaction will be discussed first, and this will be followed by studies on the mechanism of the deprotonation.

Epoxides react with alkyltriphenylphosphonium halides[29] having a CH group α to the phosphorus to form phosphonium ylides and 2-haloalcohols [eq. (5)]. The halide required is itself the reactant in this case. Phosphonium *tetrafluoroborates* accordingly do not react, since the BF_4^- ion cannot form a covalent bond with the epoxide. This dependence on the anion is unknown for conventional bases.

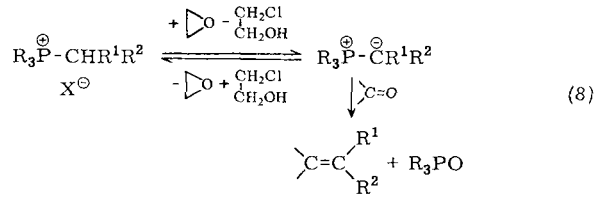
The reaction in accordance with eq. (5) is reversible[30]. Thus $(C_6H_5)_3P^+—CH_2—C_6H_5\ Cl^-$ reacts with ethylene oxide to a smaller extent to form the ylide (recognizable by the red color) and 2-chloroethanol, while the ylide and 2-chloroethanol react instantaneously to give the salt and ethylene oxide. The position of the equilibrium, as expected, depends on the C—H acidity of the phosphonium ion. C—H-acidic cations of the type *(3)* (pK_a 4—11[31a]) are almost completely converted into chloroform by excess epoxide at room temperature, those of the type *(4)* ($pK_a > 11$[31b]) are only partly deprotonated, and those of the type *(5)* are no longer deprotonated at room temperature, but only at higher temperatures.

$(C_6H_5)_3\overset{\oplus}{P}—CH_2—COR$ *(3)* $(C_6H_5)_3\overset{\oplus}{P}—CH_2—Aryl$ *(4)* $(C_6H_5)_3\overset{\oplus}{P}—Alkyl$ *(5)*

Irreversible reactions may be superimposed on the equilibrium. Thus ylides react with excess epoxide to form cyclopropane compounds, among other things[32-36]. However, these (side) reactions proceed slowly and at relatively high temperatures. Only in exceptional cases do they interfere with the faster reaction between the ylide present in equilibrium and carbonyl compounds.

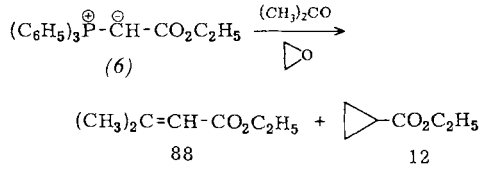
4.1. Reaction of the Ylides with Carbonyl Compounds

The ylides present in equilibrium in accordance with eq. (5) can be intercepted with carbonyl compounds. The irreversible reaction sequence (8) then occurs instead of the equilibrium (5). Excess epoxide does not interfere.



(8)

There is one exception: ethylene oxide successfully competes with inert ketones such as acetone for the ylide only in the case of the weakly nucleophilic ylide *(6)*.



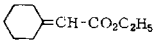
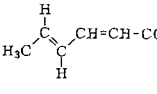
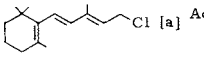
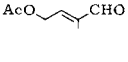
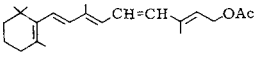
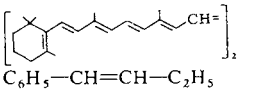
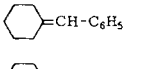
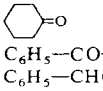
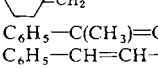
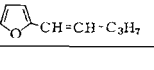
The Wittig olefination of carbonyl compounds proceeds surprisingly easily in this way (Table 2). The phosphonium salt (examples 6—8, 10, 13—15) or its precursors, *i. e.* triphenylphosphane and halogen compound (examples 1—5, 9, 11, 12) are dissolved in an aprotic solvent, excess epoxide (usually ethylene oxide) and carbonyl compound are added, and the mixture is heated if necessary (sealed tube or autoclave). The reaction temperature depends mainly on the acidity of the phosphonium salt, and also on the reactivity of the ylide formed *in situ* toward the carbonyl compound. Salts having cations of the type *(3)* are deprotonated by ethylene oxide even at room temperature (examples 1—6), and those with cations of the type *(4)* are deprotonated between room temperature and 90 °C (examples 7—10). Ethylene oxide surprisingly also removes the proton from the salts having low C—H acidities [cations of the type *(5)*], but only at 150 °C (examples 11—15). Resonance-stabilized ylides, as expected, give mainly *trans*-olefins; unstabilized ylides give mixtures of *cis* and *trans* olefins, in which the *cis* isomer usually predominates somewhat (examples 9, 13, 15).

The advantage of ethylene oxide over the bases normally used in the Wittig reaction, such as alkoxide and organolithium compounds, is that the reaction is easier to carry out[37] (no separate preparation of ylide). α,β-Unsaturated esters can be prepared particularly easily. Moreover, the reaction medium is not basic; the typical side reactions brought about by bases are thus avoided. Whereas furfural reacts with butylidenetriphenylphosphorane to give mainly disproportionation products of the aldehyde[38,39], the reaction with ethylene oxide and triphenylbutylphosphonium bromide leads to the desired olefin, 2-(1-pentenyl)-furan (example 15). One disadvantage is that weakly C—H-acidic salts with cations of the type *(5)* are deprotonated to the ylides only at 150 °C. The equilibrium concentration of the ylides is very low here; aldehydes are still olefinated surprisingly well (examples 13—15), whereas the olefination of ketones is poorer (examples 11, 12).

4.2. Kinetic Investigation of the Deprotonation of Phosphonium Salts with Epoxides[40]

The C—H-acidic salts with cations of the type *(3)* react rapidly (half lives under the conditions chosen here between one minute and a few hours) and practically com-

Table 2. Examples of the reaction
$(C_6H_5)_3P$ + halogen compound + ethylene oxide + carbonyl compound → $(C_6H_5)_3P{=}O$ + olefin + Hal-CH_2—CH_2—OH

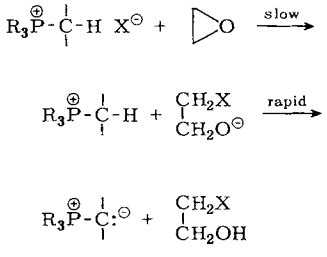
Example	Halogen compound	Carbonyl compound	Conditions	Olefin	Yield [%]	*cis*: *trans*
1	CH_2Br—CO—CH_3	*p*-O_2N—C_6H_4—CHO	RT, 24 h	*p*-O_2N—C_6H_4—CH=CH—CO—CH_3	52	0:100
2	CH_2Br—$CO_2C_2H_5$	CH_3—CHO	RT, 24 h	CH_3—CH=CH—$CO_2C_2H_5$	82	11: 89
3	CH_2Br—$CO_2C_2H_5$		100 °C, 20 h		68	—
4	CH_2Br—$CO_2C_2H_5$	*trans*-CH_3—CH=CH—CHO	RT, 24 h		85	16: 84
5	CH_2Br—$CO_2C_2H_5$	C_6H_5—CHO	RT, 24 h	C_6H_5—CH=CH—$CO_2C_2H_5$	91	7: 93
6	CH_3CHBr—CO_2CH_3 [a]	CH_3—CHO	RT, 24 h	CH_3—CH=C(CH_3)—CO_2CH_3	74	5: 95
7			RT, 16 h then 60 °C 4 h		79	
8	Axerophthyl chloride	Vitamin A aldehyde	RT, 16 h then 75 °C, 5 h		80	
9	C_6H_5—CH_2Br	C_2H_5—CHO	RT, 48 h	C_6H_5—CH=CH—C_2H_5	90	44: 56
10	C_6H_5—CH_2Cl [a]		90 °C, 8 h		69	—
11	CH_3Br		150 °C, 8 h		18	—
12	CH_3Br	C_6H_5—CO—CH_3	150 °C, 8 h	C_6H_5—C(CH_3)=CH_2	36	—
13	CH_3—CH_2—CH_2Br [a]	C_6H_5—CHO	150 °C, 8 h	C_6H_5—CH=CH—C_2H_5	74	60: 40
14	$(CH_3)_2CHBr$ [a]	C_6H_5—CHO	150 °C, 8 h	C_6H_5—CH=C(CH_3)$_2$	38	—
15	CH_3—$(CH_2)_3Br$ [a]		150 °C, 12 h		82	60: 40

[a] Used as the triphenylphosphonium salt.

pletely with excess epoxides to form ylides. They are therefore particularly suitable for quantitative investigations. The progress of the reaction can be followed by IR spectroscopy based on the decrease in the intensity of the carbonyl band in the cation (region: 1680—1735 cm^{-1}, depending on the substituent R) and the increase in the intensity of the carbonyl band of the ylide formed (1500—1600 cm^{-1}).

The investigastions carried out so far indicate that the deprotonation proceeds by two mechanisms. More weakly acidic (C—H acidic) phosphonium salts ($pK_a \geq 8.8$) are deprotonated by the 2-haloethoxide ion (or its derivatives). They include phosphonium salts such as $R_3P^+—CH_3\ X^-$, $R_3P^+—CH_2—C_6H_5\ X^-$, and $R_3P^+—CH_2—CO_2R'\ X^-$ (here and below, $R=C_6H_5$). More strongly acidic phosphonium salts ($pK_a < 8.8$), however, are presumably deprotonated by their *own anion*, and not by the relatively slowly formed alkoxide. These include $R_3P^+—CH_2—CO—CH_3\ X^-$ and $R_3P^+—CH_2—CO—C_6H_5\ X^-$.

The reaction kinetics of the more weakly acidic salts will be discussed first. The deprotonation of $R_3P^+—CH_2—C_6H_5\ Cl^-$ in epichlorohydrin as the reactant and solvent is first order with respect to the salt (and first order with respect to the epichlorohydrin, as is shown by a separate measurement in acetonitrile). Simultaneously, benzaldehyde is added to react with the ylide formed. The rate constant of the deprotonation at 43.5 °C is $k_p = 9.8 \times 10^{-3}$ $l.mol^{-1}.min^{-1}$. It agrees with the constant of the 1,2-dehydrohalogenation of 1,1,2,2-tetrachloroethane by epichlorohydrin (see Section 3), $k_d = 10.65 \times 10^{-3}$ $l.mol^{-1}.min^{-1}$, again at 43.5 °C. In both cases, the alkoxide



is formed in the slow step, and quickly reacts further, with the phosphonium ion in one case and with tetrachloroethane in the other. Here again, the deuterated compound ($R_3P^+—CD_2—C_6H_5\ Cl^-$) exhibits no kinetic isotope effect ($k_H/k_D = 1.0$). Electron-attracting residues on the epoxide ring accelerate the reaction, while electron-repelling residues retard it.

Strongly C—H-acidic phosphonium salts are deprotonated in accordance with a divergent rate equation:

$$-\frac{d[salt]}{dt} = k \cdot [epoxide]\,[salt]\,(1-\alpha)$$

This equation evidently contains the quantity of *associated* salt (ion pair) ([salt] = salt concentration according to quantities weighed out; α = degree of dissociation). This assumption is confirmed by the influence of foreign salts having the same anion on the reaction rate. The foreign halide has no effect in chloroform, since the phosphonium salt is associated in any case, as is shown by conductivity measurements. In acetonitrile, the foreign halide causes practically complete association ($\alpha = 0$) of the partly dissociated phosphonium halide[41, 42] ($K_{diss} \approx 10^{-2}$) in accordance with the law of mass action, and thus leads to a first order rate equation with respect to the salt (see Fig. 1).

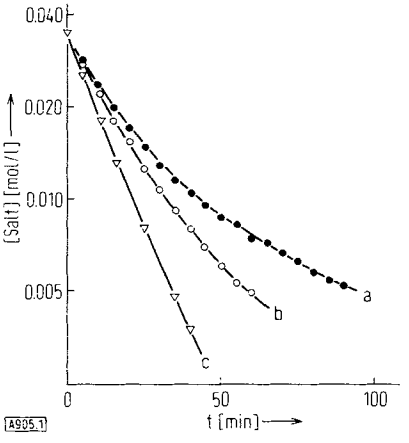
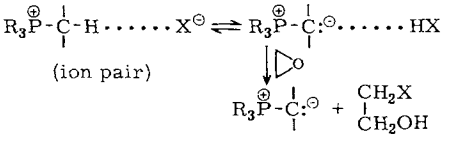
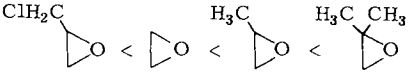


Fig. 1: Decrease in the concentration of $(C_6H_5)_3P^+—CH_2—COCH_3Br^-$ at 34.9 °C in acetonitrile ($K_{Diss} = 2 \times 10^{-2}$) a) without foreign salt, as well as in the presence of b) 0.0175 mol/l and c) 0.070 mol/l of $(n\text{-}C_4H_9)_4N^+Br^-$. [Ethylene oxide] = 4.13 mol/l (118-fold excess).

The rate constants for the deprotonation k_p increase with increasing pK_a value, and are up to 100 times as great as the rate constant of the dehydrohalogenation k_d. This rules out the alkoxide mechanism. The following course is suggested. The halide in the ion pair reversibly deprotonates the phosphonium salt, with formation of an ylide-hydrogen halide complex. Evidence of hydrogen bonding (in ion pairs) has been found by other authors in IR and NMR spectroscopic studies on phosphonium salts[43, 44]. The complex is finally converted by the epoxide into the ylide[*].



The kinetic isotope effect in this case is between 1.3 and 1.7. Effects as small as this are to be expected for the equilibrium[45] and the subsequent step[46]. Substituents on the epoxide ring have an opposite influence on the rate of ring opening in this case. Electron-repelling substituents *accelerate* the process:



This sequence is expected for *proton*-catalyzed ring cleavage[47–49].

[*] Also in accordance with the rate is the assumption of a reversible deprotonation by the epoxide itself, followed by an opening of the protonated epoxide by the ion-pair halide.

It has been shown by *Schiemenz et al.*[39] that one can make use of the basicity of the anion itself, particularly that of the fluoride ion, for the deprotonation of phosphonium salts, and the Wittig reaction, in some cases at least, can thus be carried out without an auxiliary base.

5. Deprotonation of Haloforms

Epoxides deprotonate haloforms in the presence of a catalytic quantity of a halide [reaction (9)].

$$X^{\ominus} + \triangleright O + CHX_3 \rightleftharpoons \begin{matrix} CH_2X \\ | \\ CH_2OH \end{matrix} + [CX_3^{\ominus}] \qquad (9)$$

The trihalomethyl anion formed is intercepted by electrophilic double bonds (Section 5.1) or by carbonyl compounds (Section 5.2). Its decomposition into dihalocarbene and

$$[CH_3^{\ominus}] \rightleftharpoons [CX_2] + X^{\ominus}$$

halide[50a, 50b] can be detected by addition to nucleophilic double bonds (Section 5.3)[50c], and can be used preparatively[11, 12].

Halides that are soluble in organic solvents, such as quaternary ammonium or phosphonium halides, are used as catalysts. Alkali metal halides may also be used, if cryptates are added as solubilizing agents[50d].

Our kinetic investigations on the primary step of the deprotonation are not yet complete[40].

5.1. Addition of the Trihalomethyl Anion to Polarized Double Bonds[51a]

The trihalomethyl anion formed in accordance with eq. (9) attacks the α position of α,β-unsaturated esters and nitriles[51b]. Subsequent proton uptake from the haloform leads to the final product, so that the overall process is represented by (10). The ethylene oxide and the halide ion have a purely catalytic function here, *i. e.* the production of the nucleophile CX_3^-.

$$CHCl_3 + CH_2{=}CH{-}CN \xrightarrow[(C_2H_5)_4N^{\oplus}Br^{\ominus}]{\triangleright O} CCl_3{-}CH_2{-}CH_2{-}CN \qquad (10)$$

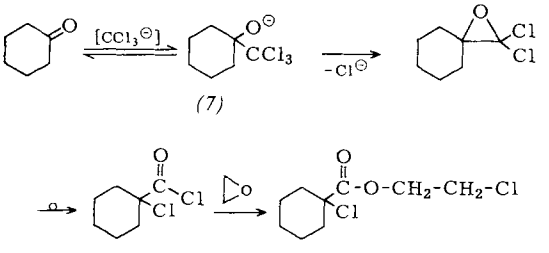
Enol esters react in accordance with eq. (11). The trihalomethyl residue becomes attached to the α position of the

$$CHBr_3 + \overset{\delta\ominus}{C}H_2{=}\overset{\delta\oplus}{C}H{-}O{-}CO{-}CH_3 \xrightarrow[(C_2H_5)_4N^{\oplus}Br^{\ominus}]{\triangleright O} CH_3{-}\underset{\displaystyle CBr_3}{\underset{|}{C}}H{-}O{-}CO{-}CH_3 \qquad (11)$$

enol ester[52], corresponding to the polarity of the latter, as was found earlier by *De Selms* and *Lin* in the reaction with sodium trichloroacetate[53]. Nucleophilic additions to the double bond of vinyl acetate have evidently not been observed before[53].

5.2. Addition of the Trihalomethyl Anion to Carbonyl Compounds[54]

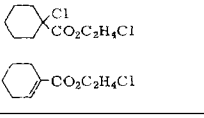
It is well known that haloforms react with carbonyl compounds in the presence of bases to give α-trihalomethyl alcohols *via* compounds of the type *(7)*[55]. The reaction proceeds further in the presence of ethylene oxide and



(7)

$(C_2H_5)_4N^+ Br^-$. Esters of α-halocarboxylic acids are formed between 50 and 150°C (Table 3). It is assumed that *(7)* first reacts by an S_Ni mechanism to give the dichloroepoxide, which isomerizes to the chloride of the α-chlorocarboxylic acid. Similar isomerizations are known[56]. The α-chloro acid chloride reacts with further ethylene oxide to form the ester[57]. Two observations support this assumption. On the one hand, the reaction can also be carried out with the alcohol corresponding to *(7)*, and on the other, 1,1,1-trichloro-2-methyl-2-propanol can be saponified with potassium hydroxide solution to give α-chloroisobutyric acid[58].

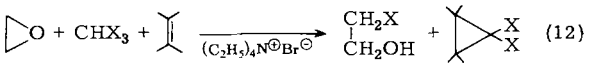
Table 3. Conversion of aldehydes and ketones into α-halocarboxylic esters with haloforms and ethylene oxide.

Carbonyl cpd.	Haloform	Final product	Yield [%]
$(CH_3)_2CH{-}CHO$	$CHCl_3$	$(CH_3)_2CH{-}CHCl{-}CO_2C_2H_4Cl$	48
$(CH_3)_2CH{-}CHO$	$CHBr_3$	$(CH_3)_2CH{-}CHBr{-}CO_2C_2H_4Br$	45
$(CH_3)_2CO$	$CHCl_3$	$(CH_3)_2CCl{-}CO_2C_2H_4Cl$	24
$(CH_3)_2CO$	$CHBr_3$	$(CH_3)_2CBr{-}CO_2C_2H_4Br$	15
	$CHCl_3$		28[a]

[a] Total yield; ratio of cyclohexane to cyclohexene compound = 1:3.

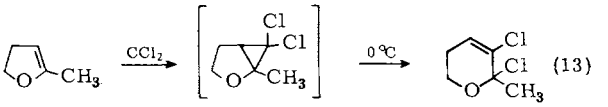
5.3. Addition of Dihalocarbenes to Olefins

The reaction proceeds in accordance with eq. (12). It is easy to carry out. Equimolar quantities of olefin and



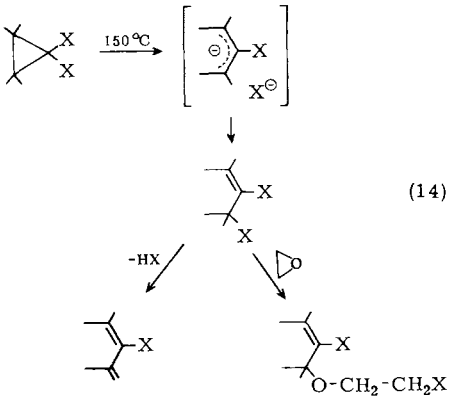
(12)

haloform are heated with excess ethylene oxide in the presence of catalytic quantities of tetraalkylammonium halide for 5 hours at 150 °C in a sealed tube or autoclave, and the dihalocyclopropanes are distilled from the crude reaction mixture. If dihalocyclopropane and 2-haloethanol have about the same boiling point, the alcohol is removed by extraction with water. As is usual in the formation of dihalocyclopropanes[59], the addition proceeds stereospecifically, despite the high reaction temperature. *cis*-2-Butene gives *cis*-1,1-dichloro-2,3-dimethylcyclopropane, while *trans*-2-butene gives the corresponding *trans* compound. Dibromo-, dichloro-, chlorofluoro-, and even difluorocarbene can be produced in this way and converted into dihalocyclopropanes[60, 61] (Table 4). Methylene chloride does not react.



(13)

On the other hand, ring cleavage frequently occurs when ethylene oxide/halide is used, since the reaction temperature is higher in this case (150 °C). This behavior is observed in reactions with highly alkylated olefins, strained olefins, and enol ethers.



(14)

Table 4. Dihalocyclopropanes [a] from ethylene oxide, haloform, and olefins; catalyst: $(C_2H_5)_4N^+Br^-$.

Olefin	Haloform	Cyclopropane	Yield [%]
$CH_2=CH_2$	$CHCl_3$	1,1-Dichlorocyclopropane	8
$CH_3-CH=CH_2$	$CHCl_3$	1,1-Dichloro-2-methylcyclopropane	26
$(CH_3)_2C=CH_2$	$CHCl_3$	1,1-Dichloro-2,2-dimethylcyclopropane	72
cis-2-Butene	$CHCl_3$	*cis*-1,1-Dichloro-2,3-dimethylcyclopropane	50
trans-2-Butene	$CHCl_3$	*trans*-1,1-Dichloro-2,3-dimethylcyclopropane	84
$CH_2Cl-C(CH_3)=CH_2$	$CHCl_3$	1,1-Dichloro-2-chlormethyl-2-methylcyclopropane	36
$CH_2=CH-CH=CH_2$	$CHCl_3$	1,1-Dichloro-2-vinylcyclopropane	61
Cyclohexene	$CHCl_3$	7,7-Dichloronorcarane	78
$(CH_3)_2C=CH_2$	$CHBr_3$	1,1-Dibromo-2,2-dimethylcyclopropane [b]	45
Cyclohexene	$CHBr_3$	7,7-Dibromonorcarane [b]	45
$(CH_3)_2C=CH_2$	$CHCl_2F$	1-Chloro-1-fluoro-2,2-dimethylcyclopropane	39
Cyclohexene	$CHCl_2F$	7-Chloro-7-fluoronorcarane	45
$(CH_3)_2C=CH_2$	$CHClF_2$	1,1-Difluoro-2,2-dimethylcyclopropane	13
Cyclohexene	$CHClF_2$	7,7-Difluoronorcarane	29

[a] Selection; for further examples see [60—62].
[b] Also ring cleavage products [61].

When ethylene oxide, chloroform, and ammonium salt are heated in the absence of an olefin, the greater part of the starting compounds is recovered on distillation. Tris-(2-chloroethyl) orthoformate is formed in 7.5% yield, presumably by attack of CCl_2 on ethylene oxide or 2-chloroethanol.

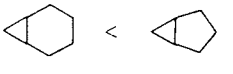
5.4. Addition of Dihalocarbenes to Highly Alkylated Olefins, Strained Olefins, and Enol Ethers

The discovery by *Doering* and *Hoffmann*[63] that dihalocarbenes can be produced from haloforms and strong bases and reacted with olefins to form dihalocyclopropanes led to a very rapid development in the field of carbene production. The dihalocyclopropanes prepared from dihalocarbenes were found to be stable under the reaction conditions (−80 to +80 °C). Ring cleavage was observed only occasionally, *e. g.* after reaction (13)[64, 65].

The cyclopropane compound is first formed from olefin, haloform, and ethylene oxide. This isomerizes *via* an ionic transition state[66] to give a dihalo compound, which either loses hydrogen halide to form a diene or reacts with excess ethylene oxide to give an allyl ether [reaction (14)][67].

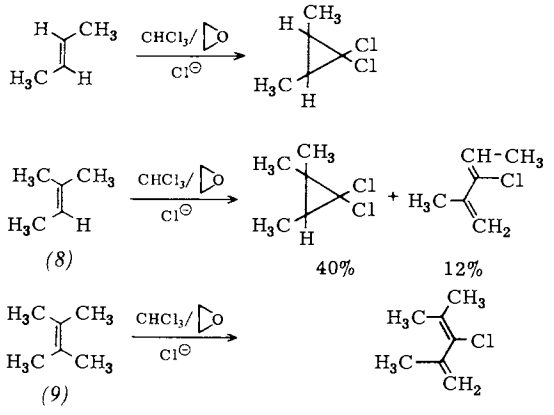
The following substituents (or arrangements) favor the isomerization[68]:

$$Br > Cl \gg F$$
$$2RO > RO \approx 4CH_3 > 3CH_3 > 2CH_3$$

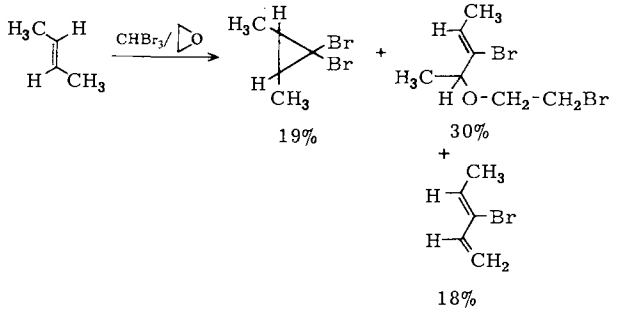


This can be illustrated by some examples. *trans*-2-Butene with chloroform/ethylene oxide gives only the cyclopropane compound, whereas 2-methyl-2-butene *(8)* gives both

the cyclopropane compound and the diene[69], and 2,3-dimethyl-2-butene *(9)* gives only the diene[1, 69].

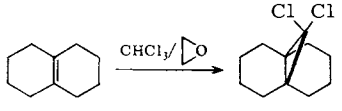


With bromoform/ethylene oxide, even *trans*-2-butene gives open-chain compounds[61].



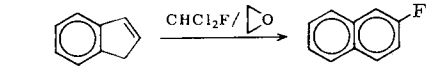
Finally, 1-hexene, as a monosubstituted olefin, gives only the cyclopropane compound both with chloroform and with bromoform.

If the environment of the cyclopropanes prevents the formation of a double bond in the transition state (Bredt's rule), even tetraalkylated cyclopropanes are stable [reaction (15)][1].

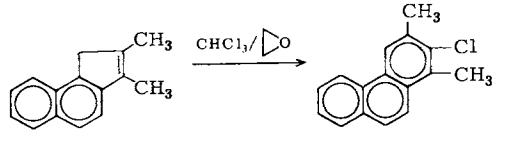


(15)

Compounds containing the cyclopentene skeleton (cyclopentene, cyclopentadiene, indene) also give isomerization products [reactions (16) and (17)]. Indenes can be smoothly converted into naphthalenes in this way[1, 11, 70–72].

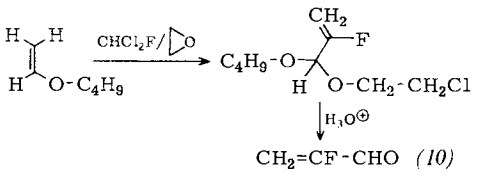


(16)

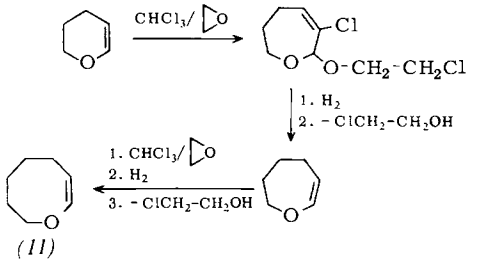


(17)

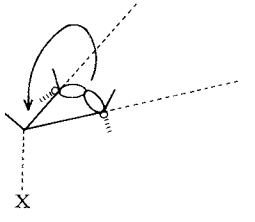
Enol ethers are extended by one C atom, with formation of unsaturated acetals[12, 73]. Let us pick out a few of the many reactions. Vinyl *n*-butyl ether is converted with dichlorofluoromethane and ethylene oxide into the acetal, and this is then converted into α-fluoroacrolein *(10)*[74], which was prepared for the first time.



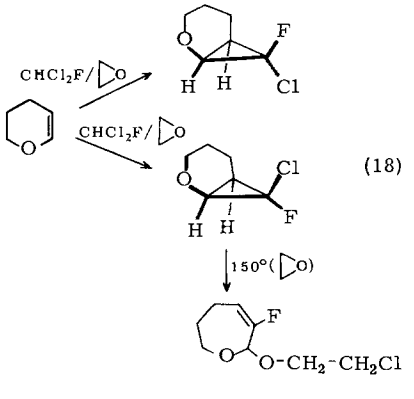
Here again, only the chlorine atom migrates, since the heterolysis of the C—Cl bond is easier than that of the C—F bond[75]. Cyclic enol ethers react similarly with ring expansion. Dihydropyran can be converted in this way into its next higher homologs, *e.g.* into 5,6,7,8-tetrahydro-4*H*-oxocin *(11)*[76], which was also unknown until then.



The thermal cleavage of the dihalocyclopropanes formed *in situ* is strictly stereospecific. The cyclopropane bond opens disrotatorily and synchronously displaces the leaving groups by backside attack (comparable with an S_N2 substitution)[77, 78].

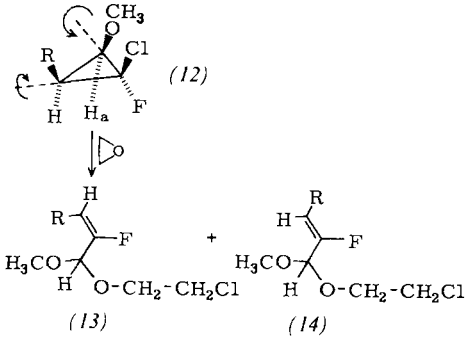


In the reaction of dihydropyran with $CHCl_2F$/ethylene oxide, the two isomeric cyclopropanes are formed first, and the *endo*-chloro isomer then undergoes cleavage [reaction (18)]. The *exo*-chloro isomer[79a] is stable, since



(18)

ring cleavage with C—Cl heterolysis would lead to a *trans* double bond in the seven-membered ring[79b]. Accordingly, the all-*cis* compound *(12)* ($R = n\text{-}C_3H_7$; $J_{F,H_a} = 12$ Hz[79a]) gives the *cis* olefin *(13)* when heated with ethylene oxide[79c]. The *trans* isomer *(14)*, which is obtained in a smaller quantity (*trans* : *cis* = 25 : 75), is evidently formed only after the stereospecific cleavage by partial *cis/trans* equilibration[79d] of the α-chloro ether formed as an intermediate.



(12)

(13) *(14)*

The reaction of aromatic compounds[1,80,81] or acetylenes[82] with haloforms/ethylene oxide again leads not to cyclopropanes or cyclopropenes but to their isomerization products.

5.5. Carbene Production with Ethylene Oxide and Halide Ions—an Alternative

The production and reaction of dihalocarbenes with ethylene oxide/halide ions require a relatively high temperature (150 °C). This is associated with a number of disadvantages and advantages. The disadvantage lies in the control of the reaction; because of the low boiling point of ethylene oxide, the reaction must be carried out in a sealed vessel. The advantage lies in the fact that instead of the initially formed dihalocyclopropanes, their ring cleavage products are obtained in many cases. In this way, suitable open-chain olefins undergo chain lengthening and cyclic olefins undergo ring expansion by one C atom. This reaction thus proves to be an alternative to the methods known until now[50c,65] for the generation of dihalocarbenes and their reaction with olefins, where the reaction temperature lies between −80 and +80 °C, and the stable dihalocyclopropanes themselves are obtained.

6. Closing Remarks

Finally, the basicity of the β-haloalkoxide ion will be compared with that of the halide ion.

Winstein, Parker, et al. investigated the behavior of halides in aprotic solvents (*e.g.* $(n\text{-}C_4H_9)_4NCl$ in acetone)[26,83] and found them to be "strong carbon nucleophiles, but very weak hydrogen bases". Nevertheless, this basicity is sufficient to eliminate hydrogen halide from reactive alkyl halides. The HX formed is trapped by addition of 2,6-lutidine (which does not influence the rate of reaction). This process presumably also takes place in the system halide/epoxide, the epoxide taking on the role of the lutidine. However, it can only be of secondary importance since, according to previous kinetic investigations, the rate equation is first order in epoxide and zero order in some haloalkanes.

It must be assumed, therefore, that the nucleophilic opening of the epoxide ring by the halide ion (to yield a strong oxygen base) proceeds much more rapidly than uptake of a proton by the halide ion.

The author is grateful to the Deutsche Forschungsgemeinschaft for its support of this work.

Received July 12, 1971 [A 905 IE]
revised: July 18, 1972
German version: Angew. Chem. *84*, 1173 (1972)
Translated by Express Translation Service, London

[1] Partly taken from the Habilitation Thesis of *J. Buddrus*, submitted to the Fakultät für Allgemeine Ingenieurwissenschaften Technische Universität Berlin 1966.

[2] a) Survey of the chemistry of epoxides: *A. Rosowsky* in *A. Weissberger*: "Heterocyclic Compounds with Three- and Four-Membered Rings". Interscience, New York 1964, Part 1; b) Review: *E. Staude, F. Patat*, and *R. J. Gritter* in *S. Pata*: The Chemistry of the Ether Linkage, Intersience, New York. 1967; c) *J. G. Buchmann* and *H. Z. Sable* in *B. S. Thyagarajan*: Selected Organic Transformations. Wiley, New York 1972, Vol. 2, p. 1.; d) *J. N. Brønsted, M. Kilpatrick* and *M. L. Kilpatrick*, J. Amer. Chem. Soc. *51*, 428 (1929).

[3] a) *D. Porret*, Helv. Chim. Acta *24*, 80 (1941); *27*, 1321 (1944); b) *A. A. Frost* and *R. G. Pearson*: Kinetik und Mechanismen homogener chemischer Reaktionen. Verlag Chemie, Weinheim 1964, p. 271.

[4] *H. Hopff*, DRP 743224 (1943), IG-Farbenindustrie AG; Chem. Abstr. *39*, 2766 (1945).

[5] *G. H. Twigg, W. S. Wise, H. J. Lichtenstein*, and *A. R. Philpotts*, Trans Faraday Soc. *48*, 699 (1952).

[6] For a summary see *M. S. Puar*, J. Chem. Educ. *47*, 473 (1970).

[7] See Ref. [2b], p. 21—80.

[8] *H. Hart* and *H. S. Elentario*, J. Amer. Chem. Soc. *76*, 1379 (1954).

[9] a) *W. Bradley, J. Forrest*, and *O. Stephenson*, J. Chem. Soc. *1951*, 1589; b) *E. Barthell* and *H. D. Schmidt-Neuhaus*, DBP 1132110 (1960); Chem. Abstr. *57*, 16877c (1962).

[10] The only success was the addition of ethylene oxide to ethyl vinyl ether in the presence of BF_3 to form 2-ethoxytetrahydrofuran, yield 5%.

[11] *J. Buddrus* and *F. Nerdel*, DBP 1198355 (1963); Chem. Zbl. *137*, 18—2333 (1966).

[12] *F. Nerdel* and *J. Buddrus*, Tetrahedron Lett. *1965*, 3585.

[13] See Ref. [2a], p. 453—456.

[14] *J. Buddrus*, Angew. Chem. *80*, 535 (1968); Angew. Chem. internat. Edit. *7*, 536 (1968).

[15] *J. Buddrus* and *W. Kimpenhaus*, Chem. Ber., in press.

[16] *D. Klamann* and *K. Ulm*, Angew. Chem. *77*, 1028 (1965); Angew. Chem. internat. Edit. *4*, 981 (1965).

[17] *J. Buddrus* and *F. Nerdel*, DBP 12986 (1966).

[18] *H. C. Chitwood* and *B. T. Feure*, J. Amer. Chem. Soc. *68*, 680 (1946).

[19] *R. E. Parker* and *B. W. Rockett*, J. Chem. Soc. *1965*, 2569.

[20] *J. K. Addy* and *R. E. Parker*, J. Chem. Soc. *1963*, 915.

[21] *E. A. S. Carell, R. E. Parker*, and *A. W. Scaplehorn*, J. Chem. Soc. *1965*, 4780.

[22] *C. A. Stewart* and *C. A. Vander Werf*, J. Amer. Chem. Soc. *76*, 1259 (1954).

[23] *L. Smith* and *S. Skyle*, Acta Chem. Scand. *5*, 1415 (1951).

[24] *A. Schaap* and *J. F. Arens*, Rec. Trav. Chim. Pays-Bas *87*, 1249 (1968).

[25] *W. Bradley, J. Forrest*, and *O. Stephenson*, J. Chem. Soc. *1951*, 1589.

[26] *G. Biale, A. J. Parker, S. G. Smith, I. R. Stevens*, and *S. Winstein*, J. Amer. Chem. Soc. *92*, 115 (1970).

[27] *S. Searles* and *M. Tamres*, J. Amer. Chem. Soc. *73*, 3704 (1951).

[28] a) *A. W. Johnson*: Ylid Chemistry. Academic Press, New York 1966; b) *H. J. Bestmann*, Angew. Chem. *77*, 651, 850 (1965); Angew. Chem. internat. Edit. *4*, 645, 830 (1965).

[29] A reaction between styrene oxide and ethoxycarbonylmethyl(tri-*n*-butyl)phosphonium bromide, which has not been investigated further,

was observed by *R. M. Gerkin* and *B. Rickborn*, J. Amer. Chem. Soc. *89*, 5852 (1967).

[30] For the reversibility of the ylide formation see *H. J. Bestmann*, Angew. Chem. *77*, 609 (1965); Angew. Chem. internat. Edit. *4*, 583 (1965).

[31] a) *S. Fliszar*, *R. F. Hudson*, and *G. Salvadori*, Helv. Chim. Acta *46*, 1580 (1963); *K. Issleib* and *R. Lindner*, Liebigs Ann. Chem. *707*, 120 (1967).

[32] *D. B. Denny*, *J. J. Vill*, and *M. J. Boskin*, J. Amer. Chem. Soc. *84*, 3944 (1962).

[33] *W. E. McEwen*, *A. P. Wolf*, *C. A. Vander Werf*, *A. Blade-Font*, and *J. W. Wolfe*, J. Amer. Chem. Soc. *89*, 6685 (1967).

[34] See *S. Trippett*, Quart. Rev. Chem. Soc. *17*, 406 (1964).

[35] *K. Friedrich* and *H.-H. Henning*, Chem. Ber. *92*, 2945 (1959).

[36] *L. Hey* and *C. K. Ingold*, J. Chem. Soc. *1933*, 531.

[37] *J. Buddrus*, German Pat. Appl. P 1768680.5 (1966), Badische Anilin- und Sodafabrik AG.

[38] *A. K. Sen Gupta*, Tetrahedron Lett. *1968*, 5205.

[39] *G. P. Schiemenz*, *J. Becker*, and *J. Stöckigt*, Chem. Ber. *103*, 2077 (1970).

[40] *J. Buddrus* and *W. Kimpenhaus*, unpublished.

[41] Cf. also *A. Höniger* and *H. Schindlbauer*, Ber. Bunsengs. Phys. Chem. *69*, 138 (1965).

[42] For a survey of recent results of conductivity measurements, see *J. Barthel*, Angew. Chem. *80*, 253 (1968); Angew. Chem. internat. Edit. *7*, 260 (1968).

[43] *G. Aksnes* and *J. Songstad*, Acta Chem. Scand. *18*, 635 (1964).

[44] *L. B. Senyavina*, *V. I. Sheichenko*, *Yu. N. Sheinker*, *A. V. Dombrovskii*, *M. I. Shevchuk*, *L. I. Barsukov*, and *L. D. Bergel'son*, J. Gen. Chem. USSR (English transl. from Zh. Obshch. Khim. *37*, 499 (1967).

[45] *D. J. Cram:* Fundamentals of Carbanion Chemistry. Academic Press, New York 1965, p. 29.

[46] *N. S. Isaacs*, Tetrahedron Lett. *1965*, 4549.

[47] For a summary see: *R. E. Parker* and *N. S. Isaacs*, Chem. Rev. *59*, 737 (1959).

[48] *J. G. Pritchard* and *F. A. Long*, J. Amer. Chem. Soc. *78*, 2667 (1956).

[49] *J. K. Addy* and *R. E. Parker*, J. Chem. Soc. *1965*, 645.

[50] a) *P. S. Skell* and *M. S. Cholod*, J. Amer. Chem. Soc. *91*, 6035, 7131 (1969), showed by competitive experiments that dichlorocyclopropanes are formed from free dichlorocarbene and olefins, irrespective of the precursors of the carbene ($LiCCl_3$; $CHCl_3$/*t*-Bu-OK; pyrolysis of $CHCl_3$ at 1500°C); b) *G. Köbrich*, *H. Büttner*, and *E. Wagner*, Angew. Chem. *92*, 177 (1970); Angew. Chem. internat. Edit. *9*, 169 (1970); c) Review of the preparation of dihalocarbenes from haloforms: *W. Kirmse:* Carbene, Carbenoide und Carbenanaloge. Verlag Chemie Weinheim 1969, p. 109; d) *B. Dietrich*, *J. M. Lehn*, and *J. P. Sauvage*, Tetrahedron Lett. *1969*, 2889.

[51] a) *F. Nerdel*, *W. Brodowski*, *J. Buddrus*, *M. Fligge*, *P. Weyerstahl*, *K. Ulm*, *C. Finger*, and *D. Klamann*, Chem. Ber. *101*, 1407 (1968); b) *H. A. Bruson*, *W. Niederhauser*, *Th. Riener*, and *W. F. Hester*, J. Amer. Chem. Soc. *67*, 601 (1945).

[52] *J. D. Roberts* and *M. C. Caserio:* Basic Principles of Organic Chemistry. Benjamin, NewYork 1965, p. 186.

[53] *R. De Selms* and *T. W. Lin*, Tetrahedron *23*, 1479 (1967).

[54] *F. Nerdel*, *J. Buddrus*, and *D. Klamann*, Chem. Ber. *101*, 1299 (1968).

[55] a) *C. Willgerodt*, Ber. dtsch. chem. Ges. *14*, 2451 (1881); b) *F. Kaspar* and *R. Wiechert*, Chem. Ber. *91*, 2664 (1958).

[56] *M. Mousseron*, *F. Winternitz*, and *R. Jacquier*, C. R. Acad. Sci. *223*, 1014 (1946).

[57] Cf. *E. L. Gustus* and *Ph. G. Stevens*, J. Amer. Chem. Soc. *55*, 378 (1933).

[58] *P. Ostropjatow*, Ber. dtsch. chem. Ges. *29* (Ref.), 908 (1897); cf. also *Ch. Weizmann*, *M. Sulzbacher*, and *E. Bergmann*, J. Amer. Chem. Soc. *70*, 1153 (1948).

[59] *H. Weitkamp*, *U. Hasserodt*, and *F. Korte*, Chem. Ber. *95*, 2280 (1962).

[60] *P. Weyerstahl*, *D. Klamann*, *C. Finger*, *F. Nerdel*, and *J. Buddrus*, Chem. Ber. *100*, 1858 (1967).

[61] *F. Nerdel*, *P. Hentschel*, *W. Brodowski*, and *J. Buddrus*, Liebigs Ann. Chem. *746*, 6 (1971).

[62] *P. Weyerstahl*, *D. Klamann*, *M. Fligge*, *C. Finger*, *F. Nerdel*, and *J. Buddrus*, Liebigs Ann. Chem. *710*, 17 (1967).

[63] *W. v. E. Doering* and *A. K. Hoffmann*, J. Amer. Chem. Soc. *76*, 6162 (1954).

[64] *S. Sarel* and *J. Rivlin*, Tetrahedron Lett. *1965*, 821.

[65] Review of the chemistry of dihalocyclopropanes: *W. E. Parham* and *E. E. Schweizer*, Org. Reactions *13*, 55 (1963); *R. Barlet* and *Y. Vo Quang*, Bull. Soc. Chim. France *1969*, 3729.

[66] For the acceleration of the isomerization by polar solvents, see *R. C. de Selms* and *C. M. Combes*, J. Org. Chem. *28*, 2207 (1963); but cf. *D. C. Duffey*, *J. P. Minyard*, and *R. H. Lane*, *ibid. 31*, 3865 (1966).

[67] *P. Bedos*, C. R. Acad. Sci. *183*, 562 (1926).

[68] Cf. also the pyrolytic decomposition series of *G. C. Robinson*, J. Org. Chem. *33*, 607 (1968).

[69] *P. Weyerstahl*, *D. Klamann*, *C. Finger*, *M. Fligge*, *F. Nerdel*, and *J. Buddrus*, Chem. Ber. *101*, 1303 (1968).

[70] See also *W. E. Parham*, *H. E. Reiff*, and *P. Swartzentruber*, J. Amer. Chem. Soc. *78*, 1437 (1956).

[71] *J. Buddrus*, Chem. Ber. *101*, 4152 (1968).

[72] *F. Nerdel*, *G. Blume*, and *P. Weyerstahl*, Tetrahedron Lett. *1969*, 3867.

[73] *F. Nerdel*, *J. Buddrus*, *W. Brodowski*, *P. Hentschel*, *D. Klamann*, and *P. Weyerstahl*, Liebigs Ann. Chem. *710*, 36 (1967).

[74] *J. Buddrus*, *F. Nerdel*, and *P. Hentschel*, Tetrahedron Lett. *1966*, 5379.

[75] *L. Ghosez*, *G. Slinckx*, *M. Glineur*, *P. Hoet*, and *P. Laroche*, Tetrahedron Lett. *1967*, 2773.

[76] *F. Nerdel*, *J. Buddrus*, *W. Brodowski*, and *P. Weyerstahl*, Tetrahedron Lett. *1966*, 5385.

[77] *C. H. DePuy*, *L. G. Schnack*, and *J. W. Hauser*, J. Amer. Chem. Soc. *87*, 4006 (1965).

[78] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969).

[79] a) Cf. also *T. Ando*, *H. Yamanaka*, and *W. Funasaka*, Tetrahedron Lett. *1967*, 2587; b) for the intermediate formation of a *trans*-cycloheptene from *exo*-7-norcaryl tosylate, see *U. Schöllkopf*, Angew. Chem. *80*, 603 (1968); Angew. Chem. internat. Edit. *7*, 588 (1968); c) *P. Hentschel*, Dissertation, Technische Universität Berlin 1969; d) *M. S. Baird* and *C. B. Reese*, Tetrahedron Lett. *1969*, 2117.

[80] *F. Nerdel*, *J. Buddrus*, *W. Brodowski*, *J. Windhoff*, and *D. Klamann*, Tetrahedron Lett. *1968*, 1175.

[81] *G. Blume* and *P. Weyerstahl*, Tetrahedron Lett. *1970*, 3669.

[82] *F. Nerdel*, *J. Buddrus*, *J. Windhoff*, *W. Brodowski*, *D. Klamann*, and *K. Ulm*, Liebigs Ann. Chem. *710*, 77 (1967).

[83] *D. J. Lloyd* and *A. J. Parker*, Tetrahedron Lett. *1971*, 637.

Industrial Application of the Semiconductor Properties of Dyes[**]

By Hans Meier, Wolfgang Albrecht, and Ulrich Tschirwitz[*]

Effects of industrial interest have been detected in investigations on the dark conductivity and photoconductivity of dyes. For example, it was found that organic dyes can be used in the same way as inorganic photoconductors in vidicon television pickup tubes for the reproduction of images. Among other things, pointers were obtained to the formation of rectifying and photoelectrically sensitive pn junctions, to relatively high thermoelectromotive forces of doped and polymeric dyes, to the possibility of use in reprography, and to a high catalytic activity connected with the conductivity, which is already being utilized in fuel cells.

1. Introduction

Though the semiconductor properties of organic compounds have been under investigation for a number of years (cf. reviews in[1-4]), the question of an industrial use of this new class of semiconductors is still in the discussion stage. On the one hand, the dark conductivity and the photoconductivity of organic compounds has long been regarded merely as a side effect, so that the search for a practical use did not seem very promising. On the other hand, too much hope was placed on attempts to produce organic semiconductor components for industrial use with compounds that were unsuitable. The superiority of inorganic materials then started to lead to a certain amount of pessimism; however, there appears to be no justification for this when one considers the decades that have gone into the development of inorganic semiconductors.

What can be said about the present position in the industrial application of the semiconductor properties of organic dyes and about future development possibilities?

2. Conduction Mechanism of Dark Conductivity and Photoconductivity

Since the discussion of the above question is closely linked to the mechanism of the dark conductivity and photoconductivity of dyes, some prefatory remarks on the conduction mechanism are appropriate.

The conductivity of organic dyes, like that of inorganic semiconductors, is attributed to electrons and defect electrons (holes). Three processes act together to produce the dark currents and the stationary photoelectric currents:

1. *Generation process:* For dyes with a difference of less than 2 eV between the ground state and the excited state, it may be assumed that, as in the case of inorganic intrinsic semiconductors, charge carriers are formed by thermal transfer of an electron from the ground state to the excited state, since measurements of the temperature dependence of the dark conductivity $\sigma\,[\Omega^{-1}\,\mathrm{cm}^{-1}]$, which follows eq. (1)

$$\sigma = \sigma_0 \exp(-\Delta E/2kT) \tag{1}$$

lead for many dyes to a thermal activation energy ΔE that agrees with the optical excitation energy found from the first absorption maximum[5]. The possibility of the formation of charge carriers by an optical excitation process of corresponding energy can also be seen from the agreement of the photoconduction and absorption spectra and of the thermal activation energy ΔE with the optical activation energy (ΔE_{opt}) deduced from the long-wave limit of the photoconductivity; for Cu-phthalocyanine (phthalocyaninatocopper(II)) for example, $\Delta E = 1.7$ and $\Delta E_{opt} = 1.63$ eV, or for indigo $\Delta E = 1.75$ and $\Delta E_{opt} = 1.79$ eV. In addition, particularly where the difference between the electronic excitation levels is greater than 2 eV, one may expect thermal excitation of defect centers (impurities, adsorbed gases, incorrectly placed counterions in the case of ionic dyes) and injection of electrons or defect electrons from the electrodes at high voltages, which leads to space charge limited currents

$$I \sim U^n (n > 1) \tag{2}$$

(I = current intensity [A], U = voltage [V]). It is also possible, particularly on excitation with high light intensities (laser light), that a detectable concentration of secondary charge carriers will be produced from excitons (by ionization of defect centers[6, 7], by annihilation processes[8, 9]).

2. *Transport of charge carriers:* As in the case of inorganic semiconductors, many organic solids may be assumed to have energy bands that arise from the discrete energy levels of the molecules by electronic interaction and allow quasi-free transport of electrons and defect electrons[10]. On the one hand this is confirmed by quantum-mechanical calculations of the energy eigenvalues belonging to the wave functions of an excess electron or defect electron of the organic solid, which give band widths of the order of kT or 10^{-2} eV[11, 12], *e.g.* 0.47 kT for metal-free phthalocyanine[13]. These band widths are characteristic of the narrow band type that explains the transport of electronic charge carriers[14], as is also shown by the mobilities of 0.1 to 10 $\mathrm{cm}^2\,\mathrm{V}^{-1}\,\mathrm{s}^{-1}$ derived with the aid of approximations and by the free paths corresponding to several lattice constants (18—80 Å for metal-free phthalocyanine[13]). On the other hand, the band model is confirmed for dyes and aromatic hydrocarbons by experimental observations. These include

[*] Prof. Dr. H. Meier, Dr. W. Albrecht, and Dr. U. Tschirwitz
Staatliches Forschungsinstitut für Geochemie
86 Bamberg, Postfach 4041 (Germany)

[**] Presented in part as a lecture to the 4th International Color Symposium in Lindau on April 11, 1971.

the electron and defect electron mobilities of 0.1 to more than $100\,cm^2\,V^{-1}\,s^{-1}$ deduced from measurements of transient currents[15], Hall effect[16, 17], thermal EMF[18], and space charge limited currents[19]; a decrease in mobility with rising temperature, which is characteristic of energy band conduction[15, 20]; the observation of an anomalous Hall effect characteristic of narrow-band conductors[14, 21]; and the detection of a charge carrier transport influenced by multiple capture in traps and quantitatively described by the energy band theory (Shockley-Read model[22])[23].

3. *Recombination of the charge carriers:* Two processes lead to recombination. One is the direct recombination of the electrons and defect electrons, which occurs in particular at high concentrations of charge carriers, and the other is the recombination *via* defect centers (recombination centers), which capture electrons or defect electrons in the first step and allow them to recombine in the second step with the defect electrons of the valence band or with electrons of the conduction band. Since the parameters of the recombination centers depend considerably on structural effects and on the chemical purity, the recombination rate and hence the lifetime τ can vary within wide limits (up to a factor of 10^{10}) in different samples of a compound.

The essential point is that the conductivity of organic dyes is determined by the interplay of the elementary processes discussed here; cf.[14]. The generation of the charge carriers is determined in the unilluminated system by the thermal activation energy ΔE and in the illuminated system by the primary quantum yield η (=number of excited charge carriers per absorbed photon). The band width and the concentration and energy of traps or defect centers are important parameters to the transport of electrons and defect electrons, which is expressed by the mobility $\mu\,[cm^2\,V^{-1}\,s^{-1}]$. On the other hand, the recombination process fixes the lifetime and hence the steady-state concentration of the charge carriers.

These processes are generally contained in the equations for the dark conductivity

$$\sigma_D = e\,(n\mu_n + p\mu_p) \tag{3}$$

and for the photoconductivity

$$\sigma_{phot} = e\,(\Delta n\mu_n + \Delta p\mu_p) \tag{4}$$

n and p are the concentrations of electrons and of defect electrons respectively in the unilluminated solid, μ_n and μ_p are the mobilities of the electrons and defect electrons, and Δn and Δp are the steady-state electron and defect electron concentrations on illumination. Δn and Δp are given by

$$\Delta n = g\tau_n; \quad \Delta p = g\tau_p \tag{5}$$

where the generation rate g (=number of charge carriers formed per cm^3 and per second) takes into account the primary quantum yield, and the lifetimes of the electrons (τ_n) and defect electrons (τ_p) take into account the concentration of defect centers (N_r) and their capture cross section (s) as follows:

$$\tau = \frac{1}{N_r \times v \times s} \tag{6}$$

(thermal velocity $v \approx 10^7$ cm/s). It can be seen from eq. (6) that changes in the defect center concentrations, which are of the order of $N_r = 10^{12}$—$10^{18}\ cm^{-3}$, the capture cross sections ranging from $s = 10^{-12}$ to $10^{-20}\ cm^2$, can strongly influence the photoconductivity [eq. (4)] *via* eq. (5).

It should be pointed out that if the concentrations and mobilities of the electrons and defect electrons are equal, one speaks of intrinsic conduction. The predominant migration of electrons in the conduction band is referred to as n conduction, and the predominance of (positive) defect electrons (or holes) as p conduction (cf. Fig. 1).

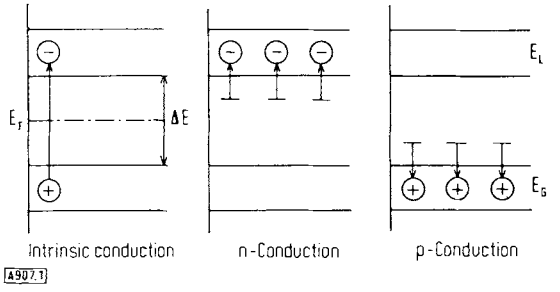


Fig. 1. Diagram of intrinsic conduction, n conduction, and p conduction. E_F = Fermi level; E_L = conduction band; E_G = valence band.

3. Possibility of Influencing the Conduction Behavior through Structure

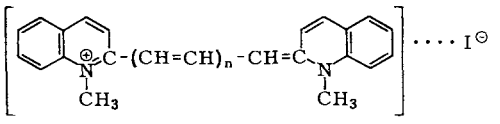
In the examination of a possible industrial application, the most important factors are the attainable orders of magnitude of the dark conductivity and of the photoconductivity.

3.1. Dark Conductivity

Organic dyes generally have only a low dark conductivity, of the order of 10^{-10} to $10^{-14}\ [\Omega^{-1}\,cm^{-1}]$, since only a few charge carriers can be excited thermally because of the relatively broad forbidden zone between the ground state band and the conduction band. However, a high conductivity is desirable for some application problems, *e.g.* for the production of thermoelectric components or rectifiers. This can be achieved in dyes, as in other organic solids, by two methods:

1. By increasing the number of delocalizable π electrons. This is possible for the following reasons. On the one hand the activation energy of the dark conduction, as the intramolecular excitation energy of the π electrons, decreases with increasing number of delocalizable π electrons[2, 24] in agreement with the electron gas theory. On the other hand the conductivity within a given semiconductor type increases with decreasing activation

energy[25,26]. These relationships are illustrated in Table 1 for polymethine dyes *(1a)*—*(1c)* that absorb at long wavelengths.



(1a), n = 1; *(1b)*, n = 2; *(1c)*, n = 3

Table 1. Relation between number of π electrons N, thermal activation energy ΔE, and dark conductivity σ_D of polymethine dyes (after [27]).

Dye	Structure	N	λ_{max} [nm]	ΔE [eV]	σ_D [Ω^{-1} cm^{-1}]
Trimethinecyanine	*(1a)*	8	605	1.8	2×10^{-13}
Pentamethinecyanine	*(1b)*	10	710	1.4—1.87	10^{-11}—10^{-9}
Heptamethinecyanine	*(1c)*	12	817	0.7—0.98	10^{-9}—10^{-7}

More highly polymeric dyes, such as the polymeric phthalocyanines, also become more conducting as the degree of polymerization increases. Thus a Cu-phthalocyanine consisting of five units, in contrast with the monomer (ΔE = 1.7 eV[2]), has an activation energy of 0.12—0.26 eV[28], the dark conductivity increasing from 10^{-14} to 0.3 Ω^{-1} cm^{-1}.

2. Another possibility for increasing the conductivity is offered by doping with special doping agents such as *o*-chloranil, tetracyanoethylene, or tetracyanoquinodimethane[26,29,30]. The conductivity increases very rapidly with the concentration of the doping agent. For example, according to eq. (7)

$$\sigma_D = a \times C^{\beta} \tag{7}$$

(C = concentration of the doping agent; a = constant), a β value of 5.3 is found on doping of phthalocyanine with

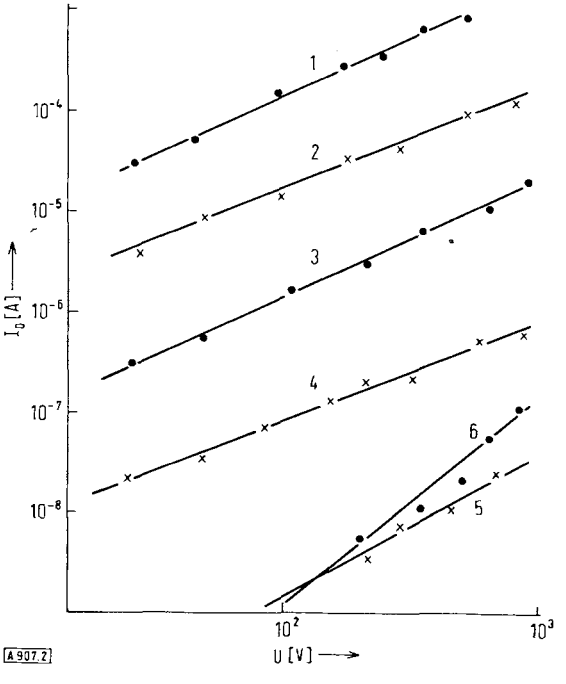


Fig. 2. Dependence of the dark conductivity on doping; plot: $\log I_D = n \log U$.
1, iodine; 2, tetracyanoethylene; 3, *o*-chloranil; 4, tetracyanoquinodimethane; 5, *p*-bromanil; 6, *p*-chloranil.

o-chloranil[26]. Figure 2 shows the increase in conductivity that can be achieved by variation of the doping agent.

By means of the above methods, the dark conductivity of p-conducting dyes can be displaced to the order of magnitude of the conductivity of inorganic materials.

3.2. Photoconductivity

Under the influence of traps and recombination centers the photoelectric current of organic dyes can become very small, particularly when unsuitable measuring arrangements are used (*e.g.* with an excessively large distance between the electrodes). This can be understood with the aid of eq. (8),

$$I_{phot} = \eta g' \times v \times e\tau\mu(E/L) \tag{8}$$

(g' = quanta absorbed per cm^3 per second), which expresses the relationship between the photoelectric current of a sample (v = volume of sample, L = distance between electrodes, E = field strength) and the lifetime τ and mobility μ of the charge carriers. A change in the defect concentration affecting the lifetime τ [according to eq. (6)] and the decrease in mobility μ caused by temporary capture in traps must, according to eq. (8), reduce the photoelectric current. I_{phot} can be increased by an increase in the field strength and a decrease in the distance between the electrodes. Above all, however, it is important that the photoconductivity can be reproducibly varied and the quantum yield G [which can be deduced from eq. (8)] increased through the elementary processes discussed in Section 2, *i.e.* by modification of η, μ, and τ.

$$G = \frac{\text{number of detectable charge carriers}}{\text{number of photons absorbed}} = \frac{I_{phot}/e}{g'v} \tag{9}$$

$$\text{or } G = \eta \times \tau \times \mu \times \frac{E}{L} = \eta \times \frac{\tau}{T} \tag{10}$$

$$\text{where } T = \frac{L}{\mu E} \tag{11}$$

(T = transit time of the charge carriers from one electrode to the other).

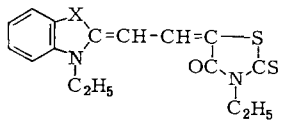
This increase in G can be achieved as follows:

1. By addition of doping agents. It can be seen from Table 2 that the photoconductivity of dyes can be increased by several orders of magnitude by doping.

The quantum yield G can even assume values >1 with suitable doping agents[31]. Figure 3 shows how strongly the photoconductivity can be influenced, as had already been described by *Hoegl*[29] in connection with an electrophotographic application of organic semiconductors, for phthalocyanine doped with *o*-chloranil.

For the doping mechanism cf.[15,26,30].

2. By specific synthesis. As in the case of the dark conductivity, relationships exist between the photoconductivity and the chemical structure that suggest the possibility of synthesizing good dye photoconductors. These structural relationships include (cf. review in[14]):



(2), X = S
(3), X = O

Table 2. Change in the photoconductivity of dyes on doping.

Dye	Doping agent	$\frac{I_{phot}\text{ (doped)}}{I_{phot}\text{ (undoped)}}$	Ref.
(2)	*o*-Chloranil	60	[31]
	Iodine	1.7×10^3	
(3)	*p*-Chloranil	6	[31]
	o-Chloranil	150	
Phthalocyanine	Tetracyanoethylene	400	[26, 32]
	o-Chloranil	10^4	[26, 32]

a) In the triphenylmethane dyes, a proportionality between the degree of methylation of the amino groups and the photoconductivity and a decrease in sensitivity on replacement of a methyl group by other substituents[1].

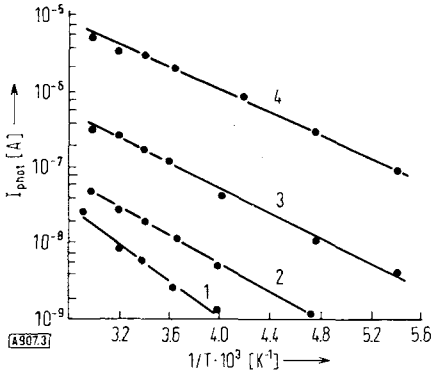
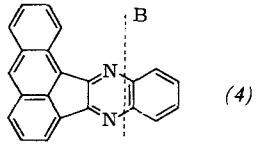


Fig. 3. Dependence of the photoconductivity on doping; plot: $\log I_{phot} = f(1/T)$.
1, Phthalocyanine, undoped; 2, *o*-CA/Phth. $= 1.26\times10^{-2}$; 3, *o*-CA/Phth. $= 1.89\times10^{-2}$; 4, *o*-CA/Phth. $= 3.15\times10^{-2}$ (*o*-CA = *o*-chloranil).

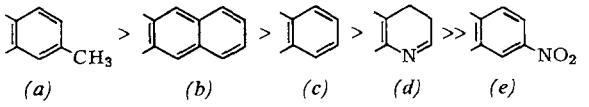
b) In cyanines and merocyanines, an increase in the photoconductivity with the number of methine groups, *i.e.* with lengthening of the conjugated chain[24, 33].

c) On modification of part B of aceanthraquinoxaline *(4)*



(4)

a variation of the action of substituents on the photoconductivity in the order[34]:



(a) *(b)* *(c)* *(d)* *(e)*

It can be concluded from this gradation that the photoconductivity is closely connected with the number and the degree of delocalization of the π electrons. An increase in the number of aromatic rings or methyl substitution increases the photoelectric sensitivity, whereas electron-accepting substituents decrease it.

This structural dependence is further illustrated in Table 3 by some I_{phot}/I_D values.

Table 3. Dependence of the photoconductivity of pyrazines on structure (after [34]).

Part B of *(4)*	I_{phot}/I_{dark}
(a)	7×10^5
(b)	7.2×10^4
(c)	2.6×10^4
(e)	4×10^2

The influence of the structure is particularly clear from Figure 4, which shows the dependence of the photoelectric current on the voltage for the case of two pyrazines *(4)* that differ by a methyl group. This example shows clearly that systematic studies can be very important for the clarification of relationships between structure and photoconductivity in the search for dye photoconductors suitable for practical use.

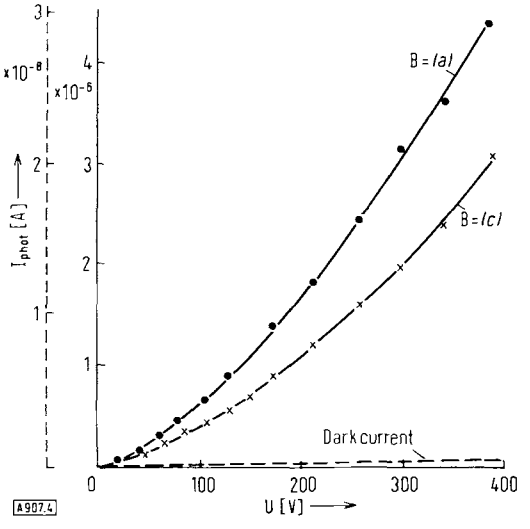


Fig. 4. Dependence of the photoconductivity on the structure for aceanthraquinoxaline *(4)*.

4. Possible Applications of the Dark Conductivity

What possible applications are presented by the conductivity of unilluminated organic dyes?

4.1. Rectifiers

Some dyes are p or n conductors in the unilluminated state, particularly in the doped form. This is confirmed by measurements of the Hall effect[35, 36] or of the thermal EMF[37]; in agreement with the rules for extrinsic semiconductors, moreover, the Fermi levels are close to the

energy bands, *e.g.* close to the ground state band for phthalocyanine doped with tetracyanoethylene, which is p conducting (cf. Fig. 5).

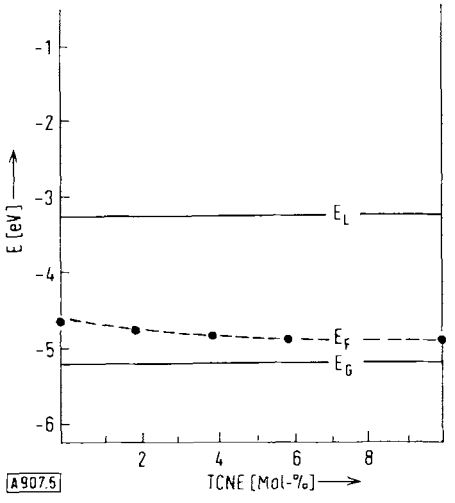


Fig. 5. Position of the Fermi level E_F in phthalocyanine doped with tetracyanoethylene (TCNE).

The use of organic dyes for the production of rectifiers therefore seems attractive. There are two possibilities:

a) The formation of pn rectifiers by contact between n- and p-conducting systems, an example being layers of p-conducting Cu-phthalocyanine and n-conducting ClIn-chlorophthalocyanine pressed together[38].

b) The formation of peak rectifiers, which are realized *e.g.* in arrangements consisting of Ag/phthalocyanine/Al point contact and prove, with a ratio of forward current to reverse current of 3000:1, to be suitable for the rectification of alternating currents up to 10^4 Hz[39]; cf. Figure 6.

4.2. Thermoelectric Components

The observation of a thermoelectromotive force that is high in comparison with that of inorganic semiconductors, and which can reach an order of magnitude of almost 3 mV/degree for organic semiconductors[40] also suggests a possible use. Under the influence of a temperature gradient, charge carriers can diffuse from the warm region to the cold; on the other hand, cooling at one electrode and warming at the other may be expected on passage of a current. The practical possibility of using such an arrangement as a thermoelectric generator or electrothermal cooling element is favored:

a) by a high differential thermoelectromotive force Q,

b) by a high conductivity σ,

c) by a low thermal conductivity κ.

Table 4 shows the quality factors or thermoelectric effectivities G_T

$$G_T = \frac{\sigma \times Q^2}{\kappa} \quad [\text{deg}^{-1}] \tag{12}$$

of some systems.

Table 4. Thermoelectric effectivities G_T of various systems.

System	σ [Ω^{-1} cm^{-1}]	Q [μV/deg]	κ [W/cm·deg]	G_T [deg^{-1}]	Ref.
Cooling system				6×10^{-3}	[41]
Bi_2Te_3	1000	200	1.6×10^{-2}	2×10^{-3}	[41]
Pyromellitonitrile		−150	5×10^{-3}	10^{-12}—10^{-8}	[42]
Phthalocyanine (doped)	10^{-7}	1000	5×10^{-3}	10^{-10}	[40]
Cu-polyphthalocyanine	0.3	3100	5×10^{-3}	5×10^{-4}	[43]

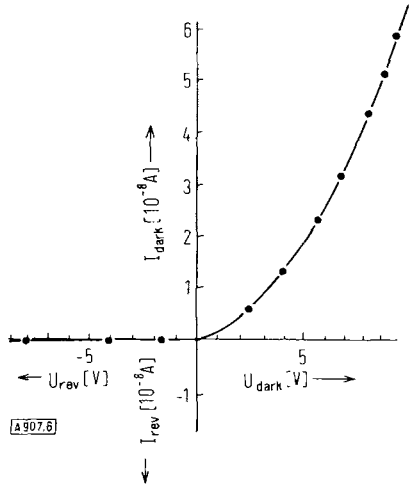


Fig. 6. Rectifier effect in the system Ag/phthalocyanine solid solution/Al point contact (after [39]).

Though pure phthalocyanines give a thermal EMF of up to 2 mV/degree, the quality factor G_T is very low because of the low conductivity. However, the conductivity can be

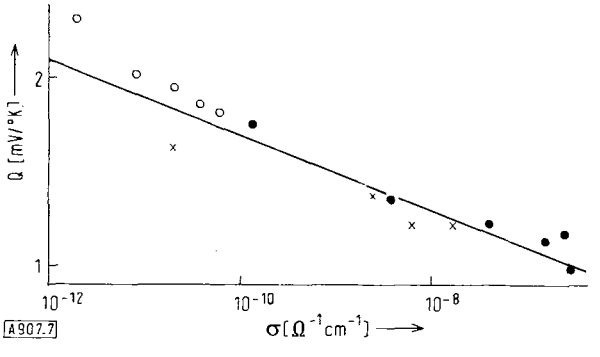


Fig. 7. Relation between thermoelectromotive force Q and conductivity σ; plot: $Q = C - (k/e \log e) \log \sigma$.
●: iodine/phthalocyanine; × = TCNE/phthalocyanine; ○: *o*-chloranil/poly-*N*-vinylcarbazole.

increased by polymerization or doping (cf. Section 3) without an excessive decrease in the thermoelectromotive force. This is demonstrated in Figure 7 for the case of doped systems.

It can be seen from Figure 7 that when the conductivity is increased to $10^{-7}\,\Omega^{-1}\,cm^{-1}$, thermoelectromotive forces of up to 1 mV/degree are still obtained. It will be necessary to look for systems having even higher conductivities, since a Peltier refrigerator, for example, becomes competitive in its power consumption only above a thermoelectric effectivity of $G_T = 6 \times 10^{-3}\,deg^{-1}$. In the example of poly-Cu-phthalocyanine[43], the quality factor should already have a remarkably favorable value of about $5 \times 10^{-4}\,deg^{-1}$.

4.3. Gas Detectors

Changes in the dark conductivity (and in the photoconductivity) of organic layers are observed on absorption and desorption of gases[1, 44, 45]. Besides oxygen and hydrogen, other gases also have characteristic reversible effects on the conductivity. As can be seen from Table 5, the conductivity changes of certain systems, *e.g.* of β-carotene[46–48], range over six orders of magnitude, depending on the type of gas.

Table 5. Dependence of the dark conductivity of β-carotene on the nature of an absorbed gas (after [48]).

Gas	$\sigma_{gas}/\sigma_{vacuum}$
NO	2
Butanol	7
Methyl acetate	10
Oxygen	10^2
SO_2	10^3
Acetone	10^4
Ethanol	10^5
NH_3	10^5
Methanol	10^6
NO_2	10^6

As in the case of ZnO[49, 50], it seems feasible to utilize this effect for the detection of gases. According to *Rosenberg*[51], odorous substances have been qualitatively separated with an instrument containing β-carotene.

4.4. Electrets

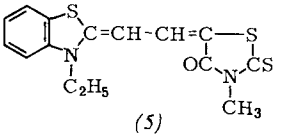
Since the electronic charge carriers injected into organic solids from ohmic contacts[14] can build up a stable space charge by combination with deep traps, some dyes assume the properties of electrets in the dark on application of an electric field. According to *Euler et al.*[52], this effect can be used for the storage of electrical energy. Thus with nigrosine paste (using silver electrodes), a storage of 1.5 mAh/cm³ and, at a mean voltage of 0.9 V with a discharge time of about 11 min, a volumetric storage capacity of 1.3 mWh/cm³ were measured. The corresponding capacity of a lead starter accumulator is 11 mAh/cm³ or 15 mWh/cm³.

5. Possible Applications of the Photoconductivity

The photoelectric sensitivity also offers possibilities for the practical use of organic dyes.

5.1. Photoresistance Cells

It is possible to use organic dyes in photoresistance cells, which are designed as surface cells (electric field normal to the direction of the light) or sandwich cells (electric field parallel to the direction of the light)[1, 2]. This possibility is supported in particular by the fact that the characteristics (dependence on intensity, voltage, *etc.*) largely agree with those of the photoconductivity of inorganic photoconductors. Moreover, the high quantum yields found for some dyes ($G > 1$) and the photoelectric current/dark current ratio of up to 7×10^4 (cf. Section 3) also suggest that a systematic examination of this possibility would be worth-



(5)

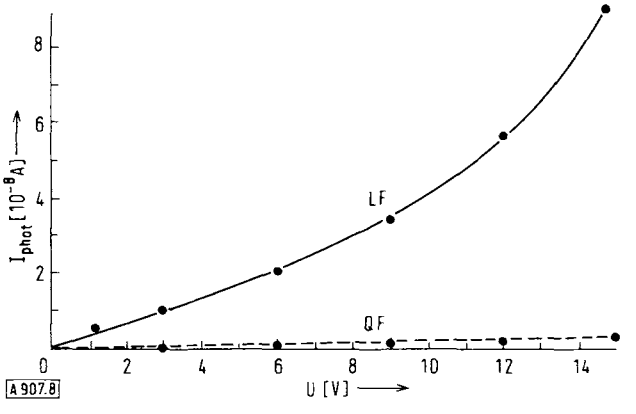


Fig. 8. Influence of the cell arrangement (LF and QF: longitudinal and transverse field cells respectively) on the magnitude of the photoelectric current of the merocyanine dye FX 79 *(5)*.

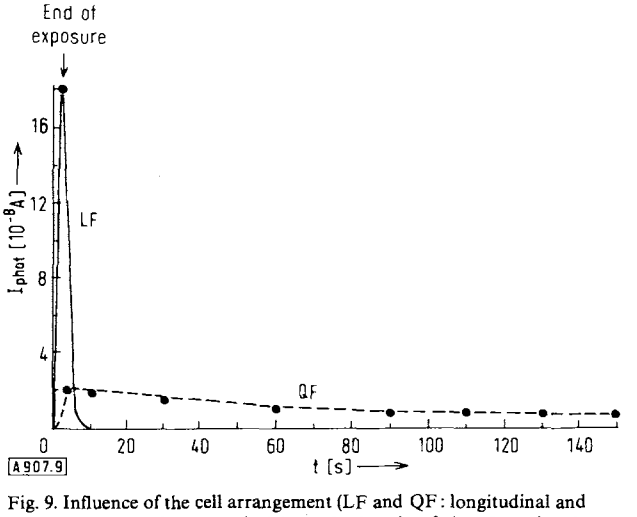


Fig. 9. Influence of the cell arrangement (LF and QF: longitudinal and transverse field cells respectively) on the inertia of the photoelectric current of malachite green; plot: $I_{phot} = f$ (exposure time).

while. With merocyanine dyes it was even possible to construct photoresistance cells that gave photoelectric currents of up to 10^{-4} A with an external voltage of 100 V and a light intensity of 1 mW/cm^2[1]. It is important for measuring cells of this type that the distance between the electrodes be as small as possible. On the one hand, a short distance between the electrodes can compensate for a low mobility and a short charge-carrier lifetime due to high defect concentrations in accordance with eq. (8) (cf. Fig. 8). On the other hand, the effect of the traps in delaying the start and the decay of the photoelectric current can be largely eliminated[14], as is shown by a comparison of the photoelectric currents measured for malachite green in the longitudinal and transverse field arrangements (Fig. 9).

5.2. Photoelectric Cells

The photoelectric sensitivity in conjunction with n and p conduction allows the production of photoelectric cells that give photoelectric currents and photoelectric voltages with no applied EMF[1, 53, 54]. The essential arrangement here is the combination of an n-conducting dye such as malachite green or Rhodamine B with a p-conducting dye, which may be *e.g.* a phthalocyanine or a merocyanine[55]. The directional and intensity dependence of the photoelectric current (cf. Fig. 10) show that the photovoltaic effect is due to a p-n junction between the compounds in contact.

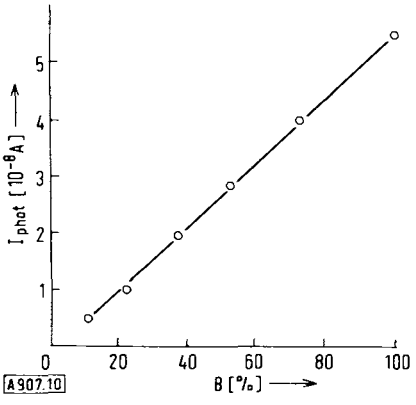


Fig. 10. I_{phot} = f(irradiation intensity B); system: malachite green (n) + merocyanine FX 79 (p) *(5)* (λ = 6200 Å, 100% corresponds to 3.7×10^{15} quanta/cm^{2}s; cell dimensions: distance between electrodes approx. 10^{-4} cm, illuminated area 1 cm^2).

An organic component can therefore also be replaced by an inorganic photoconductor of the corresponding conduction type (*e.g.* Rhodamine B (n) by CdS (n)[15, 24, 56, 57]). Table 6 shows the outputs obtained so far for some organic pn photoelectric cells.

Since the photoelectric currents and no-load voltages can be increased by doping, and there is evidence of the formation of pn junctions in homogeneous bodies[62], an improvement on the outputs N_{max} obtained so far seems possible. It should also be mentioned that dyes can be used in two-layer photocondensers (consisting *e.g.* of phthalocyanine and a ferroelectric ceramic), which are very sensitive to light and have a response time of 10^{-4} to 10^{-3} s[63].

5.3. Spectrally Sensitive Detectors

In addition to the photoelectric effects due to a pn boundary layer or to a difference in the mobilities of the charge carriers (Dember effect), the photovoltaic effects due to metal/semiconductor or metal/gas/semiconductor interfaces could possibly also be of practical importance. The photoelectric currents of these systems reach an order of magnitude of only about 10^{-10} A/cm^2, but they are characterized by the dependence of their direction on the wavelength. For example, the measurements in Figure 11 for Orthochrome T[64] and β-carotene[65] show that the photoelectric currents and voltages change their sign on transition from short to long wavelengths. The approximate wavelength of the light falling on the dye can therefore be read off simply from the direction of the photoelectric current.

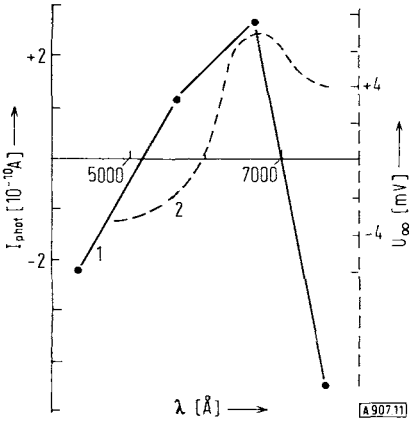


Fig. 11. Dependence of photoconductivity on wavelength.
1: Orthochrome T; I_{phot} = f(λ) [64].
2: β-Carotene; U_∞ = f(λ) [65].
Exposure conditions: curve 1: 10^3 μW/cm^2; curve 2: 3.9×10^{15} quanta/cm^{2}s.

It would be important to increase the sensitivity of the photoelectric effect.

Table 6. Outputs N_{max} of organic pn photoelectric cells.

System n	p	U_∞ [mV]	I_0 [A]	N_{max} [W]	Ref.
Malachite green	Phthalocyanine	100	10^{-8}	10^{-9}	
CdS	Phthalocyanine	300	10^{-8}	3×10^{-9}	
Triphenylmethane dyes	Phthaleins	100	0.5×10^{-9}	6×10^{-10}	[58]
Tetramethyl-*p*-phenylenediamine	Mg-Phthalocyanine	200		3×10^{-12}	[59, 60]
Ion exchange membrane with thionine/ascorbic acid		15	1.6×10^{-6}	2×10^{-8}	[61]

5.4. Use in Vidicon Television Pickup Tubes

Because of the photoelectric sensitivity and the frequently high I_{phot}/I_D ratio, organic dyes of various classes can be used as targets in vidicon television pickup tubes for image reproduction[66]. In principle, the dye is arranged in these camera tubes as in a longitudinal field cell (cf. Fig. 12). In the vidicon, however, one electrode is replaced by an electron beam, which brings the dye layer to the potential of the beam system cathode by scanning. Since the transparent electrode carrying the dye is slightly charged, light falling on the dye produces a photoelectric current, which can be measured in a galvanometer and recorded on the television screen.

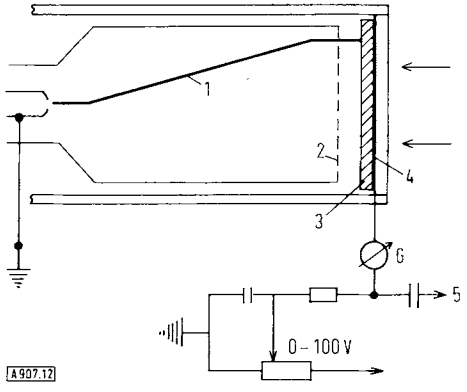


Fig. 12. Diagram of the vidicon measuring tube (for details see [66]). 1, Scanning beam (emerging from the beam system cathode with a potential $V=0$ volt); 2, gauze; 3, dye layer; 4, transparent electrode (potential up to about +30 volt); 5, amplifier; G, galvanometer.

Some characteristics of the organic vidicon are:

a) A sensitivity of about 10—100 μA/lm (or 100 nA/lx) which extends to the order of magnitude of inorganic vidicons.

b) A variation of the photoelectric current with voltage, irradiation intensity, and beam current corresponding to that of inorganic targets. Figure 13 shows this agreement for the intensity dependence of the vidicon photoelectric currents of phthalocyanine and of Sb_2S_3.

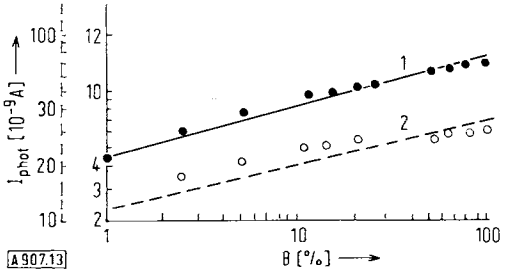


Fig. 13. Photoelectric currents of Sb_2S_3 and phthalocyanine in the vidicon arrangement; plot: $\log I_{phot} = f(\log \text{irradiation intensity})$. 1, Sb_2S_3; 2, phthalocyanine ($\lambda = 5500$ Å).

c) The fundamental possibility of reproducing several colors with a single target containing photoconductor points that absorb differently.

d) Appreciable storage in the case of layers that are rich in traps. It should be the aim of further systematic studies to test as many dyes as possible for use in television image reproduction. The results are of interest *e.g.* for color television, for medicinally important IR vidicons[1, 67], and for the production of storage vidicons[*].

5.5. Use in Reprography

There is a real chance for the use of organic photoconductors on an industrial scale in the near future in the reproduction methods based on photoelectric and electrostatic processes (cf. review in[14]).

Even in the general electrophotographic processes (cf.[1, 14, 68–70]) organic systems offer advantages over inorganic photoconductors. For example, the sensitivity of polyvinylanthracene is higher than that of sensitized ZnO materials by a factor of 1.7[71]. Compounds having a dye structure are also important. Thus the utilizability of photoconducting polymers with a phthalocyanine structure that are easily applied to a substrate has been established[72], and the feasibility of using photoconducting leuco bases of triarylmethane dyes as components of transparent electrophotographic recording materials, which allow *e.g.* the electrophotographic production of microfilms, has been described[73].

Above all, the development of new reproduction processes based on the electrophotographic principle is made possible by organic photoconductor systems (cf.[14]). Dyes play an important role here, not only as spectral sensitizers of the organic photoconductor[29, 74, 75]. Photoelectric effects of the dye can also be utilized directly. Examples that could be mentioned include:

a) the use of the memory effect observed *e.g.* for dyes after exposure to light (persistent photoconductivity[76, 77]), by means of which several copies of equal quality can be obtained from one original after exposure to light without a corona discharge[78];

b) the use of the photoelectric sensitivity of dyes of the triphenodioxazine class[79], of metal-free phthalocyanine (α form), azo pigments, *etc.*[80] in a polychromatic photoelectrophoretic image reproduction process.

6. Connections with Industrial Processes

6.1. Questions of Lightfastness

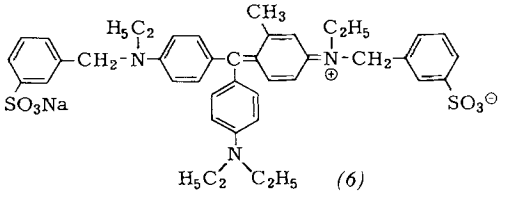
In the discussion of the application of photoconduction measurements to the lightfastness testing of dyes (cf.[81]), it must be noted that the photoconductivity is not due to intermolecular or intramolecular bleaching processes. Only the start of the photochemical decomposition of the dye is recorded, since it is associated with a decrease in conductivity. For example, it was found for the triphenylmethane dyes used as standards in the ISO lightfastness

[*] We are grateful to AEG-Telefunken, Ulm, and particularly to Dr. *A. Bogenschütz*, for valuable technical support.

test method[81] that the conductivity decreases with the photochemically induced transition of the dyes into the leuco form[82]. It is not yet known to what extent negative photoelectric effects[83] of colored fibers can be correlated with their lightfastness[84, 85]. However, the relation found for the ISO standards between lightfastness and the thermal activation energy of the photoconductivity (ΔE_{phot}) determined from eq. (13)

$$\sigma_{phot} = \sigma'_0 \exp(-\Delta E_{phot}/kT) \tag{13}$$

could be of importance for lightfastness measurements[82]. According to this relation, ΔE_{phot} increases with the lightfastness for the standard dyes CI Acid Blue 104, 109, and 83 (see Table 7, and, for interpretation[81]).



(6)

Table 7. Relation between ΔE_{phot} and time t_B until the start of bleaching (after [82]).

Dye	t_B [min]	ΔE_{phot} [eV]
CI Acid Blue 104 *(6)*	9	0.39
CI Acid Blue 109	25	0.48
CI Acid Blue 83	60	0.58

However, only structurally similar dyes can be used for such comparisons.

6.2. Spectral Sensitization

In the case of an electron transfer mechanism for the spectral sensitization of the photographic process and the photoconduction of inorganic semiconductors[1, 24, 86–88], a relationship can obviously be assumed between the electric behavior of a dye and its sensitizing effect. According to a modified mechanism[24, 27, 89], the spectral sensitization is regarded as a type of pn or nn' photoelectric effect, in which two effects act together. One of these effects is the build-up of a space charge in the unilluminated state in the interfacial zone between the dye and the semiconductor as a result of an electron transfer leading to the balancing out of different chemical potentials of the electrons. The second is a separation under the action of the space charge field of the electrons and defect electrons formed in the dye on exposure to light.

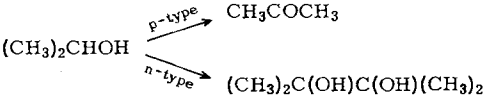
Photovoltaic effects in model arrangements of sensitized systems are in agreement with this mechanism[24]. However, it is not yet certain how far these findings can be utilized for the production of particularly effective sensitizing dyes.

6.3. Catalytic Effect

It can be concluded from various experiments that a correlation exists between electrical and catalytic data for organic solids if the catalytically active substances to be compared are very similar in their specific chemical and structural properties[14, 90, 91]. Thus in the oxidation of acetaldehyde ethylene acetal to ethylene glycol monoacetate with Fe-M polyphthalocyanines (M: V, Cr, Cu, *etc.*) as catalysts, a linear relation exists between catalytic activity K_a and the thermal activation energy of the dark conductivity ΔE_{therm}[92]:

$$K_a \sim \frac{1}{\Delta E_{therm}} \tag{14}$$

Mention should also be made of the increase in the catalytic activity of Cu-phthalocyanine samples for the decomposition of H_2O_2 with increasing conductivity and decreasing activation energy[93], and of the observed increase in the catalytic activity, *e.g.* in the oxidation of cumene in the presence of Cu-phthalocyanine, on transition from the monomer to the polymer[94]. The catalytic activity is also related to the type of conduction. For example, the decomposition of HCOOH is catalyzed more strongly by n-conducting poly-Cu-phthalocyanine than by p-conducting Cu-phthalocyanine[95]. *Inoue et al.*[96] found, moreover, that dye photoconductors of the p type (eosin, fluorescein, acridine, *etc.*) catalyze the photooxidation of isopropyl alcohol with O_2 to acetone, while semiconductors of the n type (Crystal Violet, Rhodamine, *etc.*) are either inactive or cause pinacol formation.



This reaction shows an important characteristic of organic catalysts, *i.e.* their high selectivity.

The relations between structure, conductivity, and catalytic activity are of interest particularly in connection with the use of organic dyes for the reduction of oxygen in fuel cells. Since *Jasinski*'s discovery[97, 98] that Co-phthalocyanine can be used for the reduction of oxygen in fuel cell cathodes instead of the usual platinum, which is uneconomical because of its high price, several investigations have been concerned with this question[99, 100–103]. *Jahnke*[103] was able to show that the catalytic reduction of oxygen in H_2SO_4 depends on the nature of the central atom and particularly on the degree of polymerization. This last finding (cf. also[99]) probably suggests a relationship similar to that between the conductivity and the catalytic activity of the phthalocyanines. It should be stressed that poly-Fe-phthalocyanines exhibit a higher activity than platinum metal alloys in sulfuric acid-methanol cells[103]. The stability of the phthalocyanine catalysts is probably not yet ideal, but the results obtained so far should allow

an optimistic prognosis regarding the possibility of using fuel cells with high-conductivity dye catalysts, which could be used *e. g.* in heart pacemakers[104].

We are grateful to the Deutsche Forschungsgemeinschaft and to the Fonds der Chemischen Industrie for their support of this work.

Received: August 2, 1971 [A 907 IE]
German version: Angew. Chem. *84*, 1077 (1972)
Translated by Express Translation Service, London

[1] *H. Meier:* Die Photochemie der organischen Farbstoffe. Springer-Verlag, Berlin 1963.

[2] *H. Meier*, Angew. Chem. *77*, 633 (1965); Angew. Chem. internat. Edit. *4*, 619 (1965).

[3] *F. Gutmann* and *L. E. Lyons:* Organic Semiconductors. Wiley, New York 1967.

[4] *E. Rexer:* Organische Halbleiter. Akademie-Verlag, Berlin 1966.

[5] *H. Meier*, Z. Phys. Chem. (Leipzig) *208*, 325 (1958).

[6] *L. E. Lyons*, J. Chem. Phys. *23*, 220 (1955).

[7] *V. A. Benderskii, M. I. Fedorov*, and *N. N. Usov*, Doklady Akad. Nauk SSSR *183*, 1117 (1968).

[8] *M. Silver, D. Olness, M. Swicord*, and *R. C. Jarnagin*, Phys. Rev. Lett. *10*, 12 (1963).

[9] *N. N. Usov* and *V. A. Benderskii*, Phys. Status Solidi *37*, 535 (1970).

[10] *H. Meier*, Dissertation, Universität Mainz 1954, pp. 107ff.

[11] *O. H. Le Blanc*, J. Chem. Phys. *35*, 1275 (1961); *36*, 1082 (1962).

[12] *R. Stilbey, J. Jortner, S. Rice*, and *M. T. Vala:* J. Chem. Phys. *42*, 733 (1965); *43*, 2925 (1965).

[13] *M. Sukigara* and *R. C. Nelson*, Mol. Phys. *17*, 387 (1969).

[14] *H. Meier:* Organic Semiconductors. To be published.

[15] *H. Meier* and *W. Albrecht*, Z. Naturforsch. *24a*, 257 (1969).

[16] *G. Delacote* and *M. Schott*, Phys. Status Solidi *2*, 14, 60 (1962); Solid State Commun. *4*, 177 (1966).

[17] *H. Heilmeier* and *S. E. Harrison*, Phys. Rev. *132*, 2010 (1963).

[18] *C. Hamann* and *M. Starke*, Phys. Status Solidi *4*, 509 (1964).

[19] *C. R. Westgate* and *G. Warfield*, J. Chem. Phys. *46*, 94 (1967).

[20] *R. G. Kepler*, Phys. Rev. *119*, 1226 (1960); in *J. J. Brophy* and *J. W. Buttrey:* Organic Semiconductors. Macmillan, New York 1962, pp. 1ff.

[21] *O. H. Le Blanc*, J. Chem. Phys. *39*, 2395 (1963).

[22] *W. Shockley* and *W. T. Read*, Phys. Rev. *87*, 835 (1952).

[23] *A. Schmillen* and *W. W. Falter*, Z. Phys. *218*, 401 (1969).

[24] *H. Meier:* Spectral Sensitization. Focal Press, London 1968.

[25] *K. Ulbert*, J. Polymer. Sci. *C 22*, 881 (1969).

[26] *H. Meier, W. Albrecht*, and *U. Tschirwitz*, Ber. Bunsenges. Phys. Chem. *73*, 795 (1969).

[27] *M. Heider, P. Lochon*, and *J. Néel:* C.R. Acad. Sci. Paris *267 C*, 797 (1968).

[28] *A. Epstein* and *B. S. Wildi* in *H. Kallmann* and *M. Silver:* Electrical Conductivity in Organic Solids. Interscience, New York 1961, pp. 337ff.

[29] *H. Hoegl*, J. Phys. Chem. *69*, 755 (1965).

[30] *U. Tschirwitz*, Dissertation, Universität Erlangen-Nürnberg 1970.

[31] *H. Meier* and *W. Albrecht*, Z. Phys. Chem. (Frankfurt am Main) *39*, 17 (1963).

[32] *D. R. Kearns, G. Tollin*, and *M. Calvin*, J. Chem. Phys. *32*, 1020 (1960).

[33] *W. Albrecht*, Dissertation, Universität Erlangen-Nürnberg 1964.

[34] *A. Golubovic*, J. Phys. Chem. *73*, 1352 (1969).

[35] *G. H. Heilmeier* and *S. E. Harrison*, Phys. Rev. *132*, 2010 (1963).

[36] *M. Delacote* and *M. Schott*, Phys. Status Solidi *2*, 1460 (1962).

[37] *C. Hamann* and *M. Starke*, Status Solidi *4*, 509 (1964).

[38] *C. Hamann* and *I. Storbeck*, cited in [39].

[39] *C. Hamann*, Phys. Status Solidi *4*, K 97 (1964).

[40] *H. Meier, W. Albrecht*, and *U. Tschirwitz*, Ber. Bunsenges. Phys. Chem. *74*, 938 (1970).

[41] *U. Birkholz* in *F. Sauter:* Halbleiterprobleme VI. Vieweg, Braunschweig 1961, pp. 206ff.

[42] *J. E. Katon* and *B. S. Wildi*, J. Chem. Phys. *40*, 2977 (1964).

[43] *G. Kossmehl*, Umschau *67*, 636 (1967).

[44] *H. Meier*, Z. Phys. Chem. (Leipzig) *212*, 73 (1959).

[45] *H. Meier*, Z. Wiss. Photogr. Photophys. Photochem. *53*, 1 (1958).

[46] *R. J. Cherry* and *D. Chapman*, Nature *215*, 956 (1967).

[47] *T. Misra, B. Rosenberg*, and *R. Switzer*, J. Chem. Phys. *48*, 2096 (1968).

[48] *B. Rosenberg, T. Misra*, and *R. Switzer*, Nature *217*, 423 (1968).

[49] *T. Seiyama, K. Fujiishi, M. Nagatani*, and *A. Kato*, Kogyo Kagaku Zasshi *66*, 652 (1963).

[50] *T. Seiyama* and *S. Kagawa*, Anal. Chem. *38*, 1069 (1966).

[51] *J. O. Williams* and *B. Rosenberg*, Umschau *69*, 348 (1969).

[52] *K. J. Euler, G. Ryhiner*, and *F. Scholz*, Z. Angew. Phys. *24*, 32 (1967).

[53] *H. Meier* and *A. Haus*, Angew. Chem. *72*, 631 (1960); Umschau *61*, 183 (1961).

[54] *W. Noddack, H. Meier*, and *A. Haus*, Z. Wiss. Photogr. Photophys. Photochem. *55*, 7 (1961).

[55] *H. Meier*, J. Phys. Chem. *69*, 719 (1965).

[56] *H. Meier* and *W. Albrecht*, Ber. Bunsenges. Phys. Chem. *68*, 64 (1964),

[57] *H. Meier* and *W. Albrecht*, Ber. Bunsenges. Phys. Chem. *69*, 160 (1965).

[58] *J. Kostelec*, US-Pat. 3009006 (1961).

[59] *D. Kearns* and *M. Calvin*, J. Chem. Phys. *29*, 950 (1959).

[60] *M. Calvin* and *D. R. Kearns*, US-Pat. 3057947 (1962).

[61] *M. Yoshida*, Bull. Kobayashi Inst. Phys. Res. *13*, 109 (1963).

[62] *E. Krikorian*, U. S. Clearinghouse Fed. Sci. Tech. Inform. AD *1968*, AD-679601.

[63] *Yu. A. Vivadi, L. D. Rozenshtein*, and *E. A. Chistyakov:* Sov. Phys.-Semicond. *1*, 1049 (1968).

[64] *H. Meier*, Z. Wiss. Photogr. Photophys. Photochem. *53*, 117 (1959).

[65] *B. Rosenberg, R. J. Heck*, and *K. Aziz*, J. Opt. Soc. Amer. *54*, 1018 (1964).

[66] *H. Meier* and *W. Albrecht*, Ber. Bunsenges. Phys. Chem. *73*, 86 (1969).

[67] *P. Delius*, Brit. J. Photogr. *111*, 278 (1964).

[68] *J. H. Dessauer, G. R. Mott*, and *H. Bogdonoff* (Translation by *A. Büchler* and *J. Eggert*), Schweiz. Photo-Rundschau No. 1—3, 1 (1957).

[69] *K. Hauffe*, Naturwissenschaften *54*, 181 (1967).

[70] *R. M. Schaffert:* Electrophotography. Focal Press, London 1965.

[71] *H. Kokado*, Rev. Progr. Photogr. Japan No. 19, 69 (1969).

[72] *D. E. Kramm, L. Light*, and *J. F. Light*, US-Pat. 3498784, March 3, 1970.

[73] *C. V. Wilson*, DBP 1237900, October 19, 1967.

[74] *H. Meier, W. Albrecht*, and *U. Tschirwitz*, Lecture at 2. Elektrophotographisches Kolloquium, München, May 10, 1969.

[75] *H. Meier, W. Albrecht*, and *U. Tschirwitz*, Report on Int. Congr. Photogr. Sci. Moscow, Ser. E *1970*, pp. 264ff.

[76] *H. Meier*, Z. Phys. Chem. (Leipzig) *208*, 340 (1958).

[77] *Y. Hayashi, M. Kuroda*, and *A. Inami:* Bull. Chem. Soc. Jap. *39*, 1660 (1966).

[78] *P. M. Cassiers*, J. Photogr. Sci. *10*, 57 (1962).

[79] *L. Weinberger*, US-Pat. 3442781, January 6, 1966.

[80] *J. W. Weigl*, DOS 1947105 (1970).

[81] *H. Meier* in *K. Venkataraman:* The Chemistry of Synthetic Dyes. Academic Press, New York 1971, p. 389.

[82] *D. Patterson* and *B. Pilling*, Trans. Faraday Soc. *62*, 1976 (1966).

[83] *H. Meier*, Z. Wiss. Photogr. Photophys. Photochem. *53*, 117 (1959).

[84] *R. W. Moncrieff*, Text. Mfr. *92*, 462 (1966).

[85] *I. P. Fedotov* and *B. M. Yavorskii*, Izv. Vyssh. Ucheb. Zaaved. Tekhnol. Tekstil'noi Prom. No. 2, 115 (1966).

[86] *W. Noddack, G. Eckert*, and *H. Meier*, Z. Elektrochem. *56*, 735 (1952).

[87] *W. F. Berg, V. Mazzucato, H. Meier*, and *G. Semerano:* Dye Sensitization—Symposium Bressanone. Focal Press, London 1970.

[88] *F. Dörr* in *H. Frieser, G. Haase*, and *E. Klein:* Grundlagen der Photographischen Prozesse mit Silberhalogeniden, Vol. 3. Akademische Verlagsgesellschaft Frankfurt/M. 1968, p. 603.

[89] *H. Meier*, Chimia *18*, 170 (1964).

[90] *W. Hanke*, Z. Chem. *9*, 1 (1969).

[91] *S. Z. Roginskii* and *M. M. Sakharov*, Russ. J. Phys. Chem. *42*, 696 (1968).

[92] *H. Inoue, Y. Kida*, and *E. Imoto*, Bull. Chem. Soc. Jap. *41*, 684 (1968).

[93] *S. Z. Roginskii, A. A. Berlin, D. A. Galovina, E. S. Dokukina, M. M. Sakharov,* and *L. G. Cherkashina,* Kinet. Katal. *4,* 431 (1963).

[94] *W. Hanke,* Z. Anorg. Allg. Chem. *347,* 67 (1966).

[95] *W. Hanke* and *W. Karsch,* Monatsber. Deut. Akad. Wiss. Berlin *9,* 323 (1967).

[96] *H. Inoue, S. Hayashi,* and *E. Imoto,* Bull. Chem. Soc. Jap. *37,* 326 (1964).

[97] *R. Jasinski,* Nature *201,* 1212 (1964); J. Elektrochem. Soc. *112,* 526 (1965).

[98] *R. Jasinski,* US-Pat. 3410727, November 12, 1968.

[99] Siemens AG, French Pat. 1591825 (1970).

[100] *H. Jahnke,* Ber. Bunsenges. Phys. Chem. *72,* 1053 (1968).

[101] R. Bosch GmbH, French Pat. 1538821 (1967).

[102] *H. Jahnke* and *M. Schönborn,* Proc. Joint Int. Etud. Piles Combust. Brussels 1969, p. 60.

[103] *H. Jahnke,* Report on 3. Int. Farbensymposium Lindau 1970, p. 86.

[104] *M. Schaldach,* Umschau *70,* 857 (1970).

Biochemistry of the Pteridines

By Heinz Rembold and William L. Gyure[*]

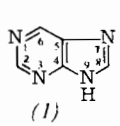
Biochemical information about the ubiquitous pteridines has become generally available only within the last fifteen years. This delay can be traced to the chemical lability of these compounds and their small concentrations in organisms. New methods of isolation and isotopic techniques have provided data on the biosynthesis, anabolism, and catabolism of this class of compounds. Hydrogenated pteridines are recognized today as cofactors for various mixed function oxygenases and are involved in cellular electron transport. Further unknown catalytic functions for pteridines in cellular metabolism are indicated by their physiological activity, negative redox potentials, and histoautoradiographic data.

1. Introduction

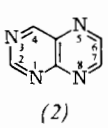
At the end of the last century *Hopkins* reported on a crystalline pigment which he had extracted from the wings of a butterfly[1]. This finding formed the basis for later investigations by *Wieland* and his co-workers who succeeded in isolating first a yellow[2] and then a white pigment[3]. After much experimental difficulty *Purrmann* was finally able in 1940 to determine the structure of these natural pigments, which were named xanthopterin *(35)* and leucopterin *(37)*. At the same time he also elucidated the structure of a related pigment called isoxanthopterin *(38)*[4].

For the bicyclic ring system of these new butterfly pigments *Wieland* chose the name "pteridine" while the designation "pterin" was originally used as a general term for all insect pigments. Today pyrazino[2,3-*d*]pyrimidine is called pteridine *(2)*. The naturally occurring pteridines are commonly called pterins when they are derivatives of the parent compound 2-amino-4-oxodihydropteridine *(3)* and lumazines when they are derivatives of 2,4-dioxotetrahydropteridine *(4)*.

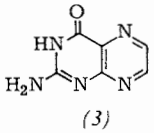
As a simple approach pteridines *(2)* may be considered related to the purines *(1)* to which they bear a structural resemblance. Both classes of compounds have many properties in common such as low solubility at neutral pH values, well defined ultraviolet absorption spectra, ability to form chelates with metal ions, and the property of forming precipitates with mercury and silver salts. In addition to the purine-like properties, fully oxidized, or



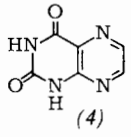
(1)



(2)



(3)



(4)

aromatic, pteridines exhibit strong blue to red fluorescence when irradiated with ultraviolet light. This fact aids their purification from sources containing only trace amounts of these compounds.

Reviews of the chemistry of the pteridines are available[5, 6]. One property of pteridines is especially important from a biochemical standpoint and that is their ability to form dihydro and tetrahydro derivatives. These reduced forms are very reactive and not only can they serve as specific reductants but they can also participate in electron transport reactions. It is precisely because these reduced forms are so reactive that working with them is difficult. The aromatic structures are already photolabile while the reduced forms are even more photolabile and subject to oxidative degradations. As an example of this lability,

[*] Prof. Dr. H. Rembold and Dr. W. L. Gyure
(American Cancer Society Postdoctoral Fellow)[**]
Max-Planck-Institut für Biochemie
8033 Martinsried bei München (Germany)

[**] Present address:
University Hospital BB-203
University of Washington
Seattle, Washington 98105 (USA)

reduced biopterin and neopterin can respectively lose their dihydroxypropyl and trihydroxypropyl side chains simply upon heating in neutral aqueous solution in the presence of air[7].

2. Isolation

The naturally occurring pteridines are found throughout the plant and animal kingdoms. Several reviews discuss the pteridines found especially in insects[8], in microbes[9], and in amphibia and fish[10]. Normally pteridines are found in only trace amounts in biological material. Biopterin *(6b)* occurs, for example, in concentrations of less than 10 mg/kg and other pteridines are often present in even lower amounts. In Table 1 the results of an analysis of honeybees clearly illustrates this general fact.

Pierid butterflies, utilized in *Wieland's* original studies, contain relatively high concentrations of pterins. Along with other compounds, xanthopterin *(35)*, isoxanthopterin *(38)*, and leucopterin *(37)* serve these insects as pigments. However, disregarding a few exceptions among fish and amphibians, pteridines generally occur in very small concentrations. Examination of the values in Table 1 shows that many pteridines must be enriched 10^9 fold in order to reach an analytically pure state.

A variety of methods are available for the isolation of these compounds from natural sources; the choice of which to use depends upon the solubility and lability of the pteridine in question (Table 2). Relatively soluble pteridines such as the 6-polyhydroxyalkyl derivatives [biopterin *(6b)*, neopterin *(6a)*, sepiapterin *(7b)*, *etc.*] can be isolated from trichloroacetic acid extracts. These extracts are free of most protein and peptide materials and labile hydrogenated pteridines are stabilized under the acidic conditions. Acid extraction however cannot be used in a quantitative sense for such acid-insoluble pteridines and lumazines as isoxanthopterin, leucopterin, and 7-hydroxylumazine. Often pteridines occur in association with other molecules such as protein, peptides, and nucleic acids[13, 14]. In order to isolate these complexed pteridines and to solubilize the acid-insoluble pteridines, basic solvents are useful and when used in conjunction with an alkaline precipitation

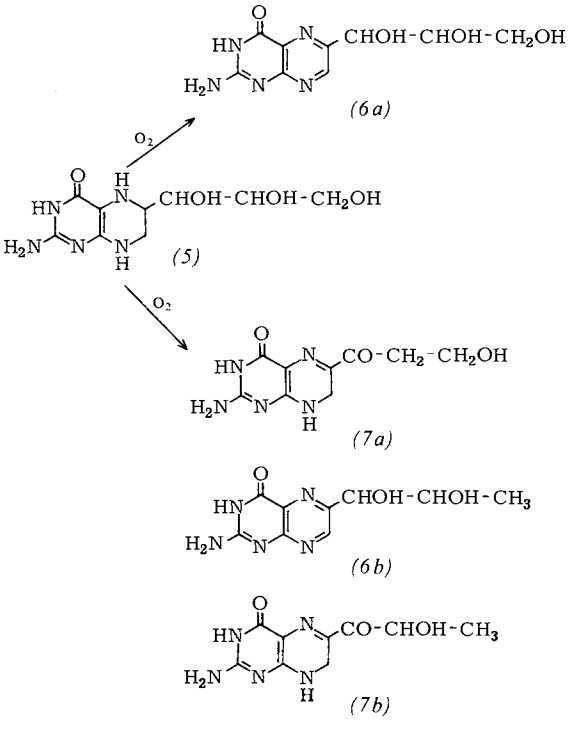


Table 1. The pteridines listed as occurring in the honeybee [11, 12], *Apis mellifica* L., are given in micrograms per animal. The average weight of a bee is 150–200 mg.

Pteridine	Pupa	Flight bee
Biopterin *(6b)*	0.2	0.2
Neopterin *(6a)*	0.015	0.005
7-Hydroxylumazine *(30)*	0.25	0.4
Isoxanthopterin *(38)*	0.009	0.23
Pterin *(3)*	0.02	0
6-Pterincarboxylic acid	0.013	0.01
6-Isoxanthopterincarboxylic acid	0	0.004

Table 2. Procedures for isolating and identifying pteridines from biological material.

1. Extraction

Type of pteridine	Extraction medium	Protein and peptide removal
acid-soluble pteridines	water or 5% trichloroacetic acid	trichloroacetic acid [17]
alkaline-soluble pteridines	2 N NH_4OH	$Al_2(SO_4)_3/Ba(OH)_2$ [15]
labile reduced pteridines	water or 5% trichloroacetic acid	trichloroacetic acid [18] or sephadex [19]
	2 N NH_4OH with mercaptoethanol	$Al_2(SO_4)_3/Ba(OH)_2$ [15]

2. Purification

Column chromatography (Dowex 1 and 50 [17], phosphocellulose [17], ecteola cellulose [17], cellulose [20], Florisil [9]); paper chromatography [21]; thin layer chromatography [22]; paper electrophoresis [23]; electrophoresis on cellulose acetate [24]; isoelectric focusing [25]

3. Identification

UV absorption spectra; fluorescence emission spectra; chromatographic behavior; *Crithidia* growth tests [26]; color tests [15, 27]; enzyme tests [28]; gas chromatography [29, 30]

4. Quantitative determinations

UV extinction coefficient; measurement of fluorescence on paper [31] or in solution [32]; *Crithidia* growth [26]; isotopic dilution [18]; color tests [15, 27]; enzyme tests [28]; gas chromatography [29, 30]

method give quantitative results[15]. Alkaline extraction methods necessitate precautions, such as the addition of mercaptoethanol to the solvent, to prevent the degradation of the labile reduced pteridines.

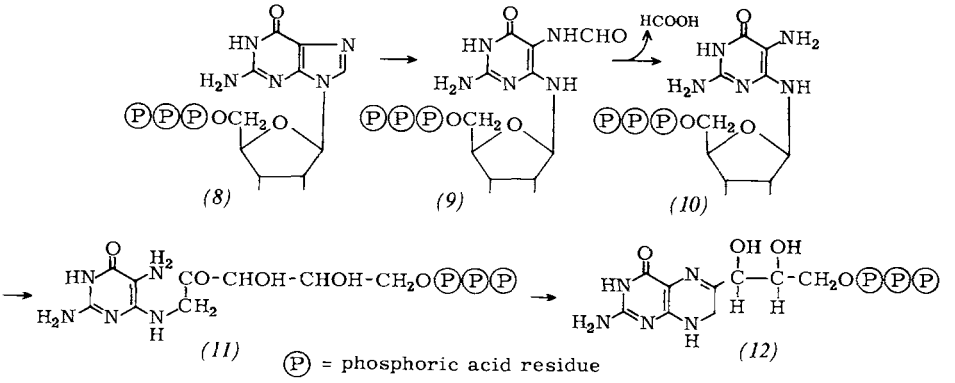
Depending on the conditions used the structure of the reduced pteridines can be changed during isolation. As an example, tetrahydroneopterin *(5)* can be adsorbed on a column of phosphocellulose and eluted with dilute formic acid in the presence of mercaptoethanol. After evaporation, renewed chromatography of the eluate on the same column yields two bands upon elution with water. Structural analysis[16] showed that tetrahydroneopterin is oxidized in the process producing neopterin *(6a)* and a yellow pterin 6-(3-hydroxypropionyl)-7,8-dihydropterin *(7a)*. When the original tetrahydroneopterin is chromatographed in the absence of mercaptoethanol, the dihydropterin is formed on the column.

Once the pteridines have been extracted, they can be purified, identified, and assayed by the methods in Table 2. Nuclear magnetic resonance, mass spectroscopy, and elemental analysis are additional methods which aid in identification; however they are of limited value due to the low solubility and volatility of most pteridines. After preparation of trimethylsilyl derivatives even very polar pteridines are volatile enough to be separated by gas chromatography and identified by mass spectral fragmentation[29, 30].

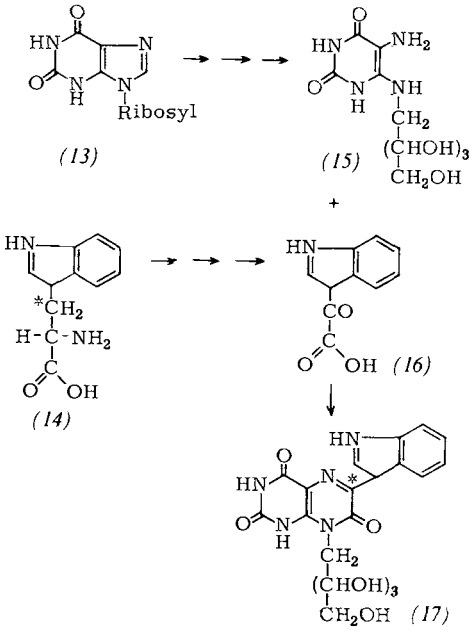
3. Metabolism

3.1. Biosynthesis of the Pteridine Ring

Because of structural similarities purines and pyrimidines were early considered as potential starting materials for pteridine biosynthesis. Numerous studies indicated that purines are utilized for pteridine ring formation in bacteria, fungi, amphibia, and insects[33]. Direct proof of this conversion has been offered by *Brown et al.*[34] who have isolated the enzyme GTP-cyclohydrolase from *Escherichia coli*. This enzyme catalyzes the conversion of guanosine-5'-triphosphate *(8)* into D-*erythro*-7,8-dihydroneopterin-3'-triphosphate *(12)*. *Shiota* has isolated a similar enzyme from *Lactobacillus plantarum*.



Many reports tend to support this set of reactions and these have been discussed by *Shiota*[33] and by *Brown*[34] in their reviews on the biosynthesis of folic acid. Recent data however cautions against accepting the Brown-Shiota pathway as the sole mode of pteridine synthesis. A cyclic dihydroneopterin phosphate has been found by *Cone* and *Guroff*[102] to be the end product of GTP conversion in *Comamonas*. In addition *Forrest*[9] rightly discusses the possibility of alternate pathways for pteridine biosynthesis, such as from a pyrazine compound. Another possibility has been put forward by *Takeda*[35] in his studies on the formation of indolyl- and hydroxyphenylpteridines by *Achromobacter petrophilum*. Although GTP *(8)* and xanthine derivatives *(13)* were utilized by the microbe for the formation of the pteridines, radioactivity was incorporated into the ring system when [3-^{14}C]tryptophan was added to the culture medium. *Takeda* discusses the following biosynthetic route to *(17)*[*]:



Data on pterin biosynthesis in the rat is also difficult to resolve utilizing the Brown-Shiota scheme. In studies on possible precursors in the rat, *Remboldet al.* have established that biopterin excretion per day is constant at about 30 µg even when several generations are fed on a biopterin free diet[36]. This indicates biopterin formation in a mammal which is incapable of forming folic acid. When purine precursors, such as formate and glycine, or possible pteridine

[*] *Note added in proof* (October 12, 1972): 6-(3-Indolyl)-7-oxo-8-(1-D-ribityl)lumazine *(17)* has also been isolated from a culture of *Pseudomonas ovalis*[113]. This fact shows that *Takeda*'s scheme of pteridine biosynthesis may also occur in *Pseudomonas*.

precursors, such as adenine, guanine, guanosine, guanylic acid, or GTP, were injected or fed to rats only trace amounts were converted to biopterin. The formation of biopterin was somewhat increased when nucleic acid synthesis was inhibited by injection of actinomycin D and the accompanying flow of purine precursors into nucleic acid biosynthesis was decreased[37]. The injection of radioactive neopterin *(6a)* or radioactive tetrahydroneopterin *(5)* did not result in incorporation of label into the biopterin excreted over the next four days[38]. *Fukushima*[39] described a very low incorporation of radioactivity into biopterin by tadpoles of *Rana catesbeiana* after injection of dihydroneopterin or its triphosphate derivative. These results in the rat and tadpole make it difficult to postulate the involvement of neopterin or one of its derivatives as an intermediate in biopterin synthesis.

3.2. Anabolism

Once the pteridine ring has been formed by an organism a considerable number of subsequent reactions must occur in order to account for the great diversity of naturally occurring pteridines. The first results in the clarification of the metabolic steps are now beginning to appear. Table 3 is a summary of the investigated enzymes and their reactions.

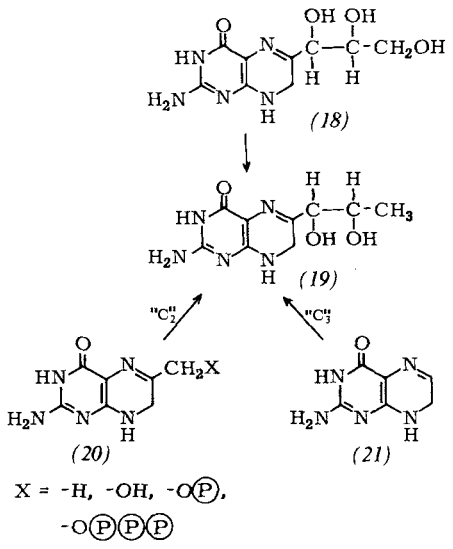
In spite of the great effort expended the direct relationship between neopterin *(6a)* and the other pteridines found in nature is not yet clear, the intermediates in folic acid biosynthesis being excluded. This is remarkable since neopterin is the parent and first pteridine formed according to the Brown-Shiota scheme. The unknown relation between neopterin and biopterin *(6b)* has already been mentioned. In this connection recent work by *Dayman* and *Guroff*[111] has shown the presence of a neopterin cyclic phosphate phosphodiesterase in *E. coli*, in *Comamonas*, and in the rat. This enzyme catalyzes the hydrolysis of neopterin cyclic phosphate to neopterin phosphate. *Guroff*[102] suggests that in this hydrolysis the neopterin side chain is inverted from the D-*erythro* to the L-*threo* configuration. Such a coupled reaction, *i.e.* hydrolysis and inversion, can explain why neither D-*erythro*-neopterin nor its non-cyclic phosphate derivative can be converted to biopterin.

Even more fundamental and still debated is the origin of the carbon chain on C-6 of the pteridine ring. Three hypotheses have been advanced concerning the chain[33]. The first one states that it is formed by a simple rearrangement of the intact neopterin side chain in which the hydroxyl groups are enzymatically epimerized. This hypothesis is the basis for *Guroff*'s suggestion as described above. This statement assumes that 7,8-dihydroneopterin *(18)*, or one of its phosphate derivatives, is the parent compound for the whole series of 6-(polyhydroxyalkyl)pteridines, including biopterin. The second hypothesis states that 6-substituted pteridines arise by an addition of carbon units to a 6-methylpteridine *(20)*. This statement assumes nothing about the origin of the 6-methylpteridine nor of the carbon units attached to it. According to the third hypothesis carbon units are attached directly to the pteridine ring *(21)*—in the case of biopterin a three-carbon unit is attached. These three suggestions are illustrated for the formation of 7,8-dihydrobiopterin *(19)*.

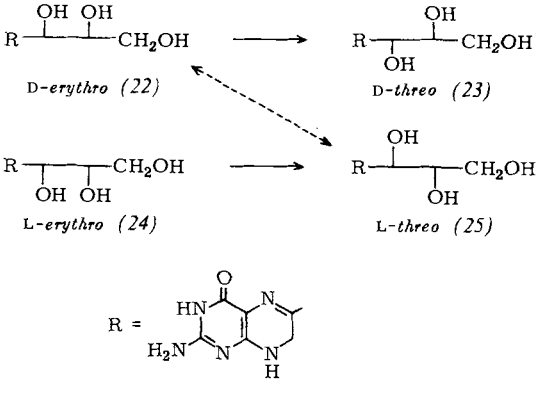
From the available data there is much that could be said for and against each hypothesis and it may well be that each plays its own role depending on the particular pteridine.

Table 3. Summary of enzymes involved in pteridine metabolism.

Type of reaction	Enzyme (source)	Substrate	Product
Biosynthesis	GTP cyclohydrolase [41, 102] *(E. coli, Comamonas sp.)*	GTP	dihydroneopterin triphosphate and cyclic phosphate
	dihydroneopterin-triphosphate synthetase [48] *(L. plantarum)*	GTP	dihydroneopterin triphosphate
Anabolism folic acid formation	dihydroneopterin aldolase [49] *(E. coli)*	dihydroneopterin	6-hydroxymethyl-dihydropterin
	hydroxymethyldihydropteridine pyrophosphorylase [50, 51] *(E. coli, L. plantarum)*	6-hydroxymethyl-dihydropterin	6-hydroxymethyl-dihydropterin pyrophosphate
	dihydropteroate synthetase [52] (pea seedlings)	6-hydroxymethyldi-hydropterin	6-hydroxymethyl-dihydropterin pyrophosphate
	dihydropteroate synthetase *(E. coli* [50], *L. plantarum* [51], pea seedlings [52])	6-hydroxymethyl-dihydropterin pyrophosphate	dihydropteroate
erythropterin synthesis	erythropterin synthetase [32] *(Oncopeltus fasciatus)*	dihydroxanthopterin	erythropterin
biopterin and sepiapterin synthesis	sepiapterin reductase [54, 98] (rat liver, horse liver)	sepiapterin	dihydrobiopterin
	dihydrofolate reductase [108]	sepiapterin, dihydrobiopterin	reduced sepiapterin, tetrahydrobiopterin
	dihydropterin reductase [73, 114] (sheep liver, rat liver)	quinonoid dihydrobiopterin	tetrahydrobiopterin
neopterin synthesis	neopterin cyclic phosphate phosphodiesterase [111] *(Comamonas)*	neopterin cyclic phosphate	neopterin phosphate



According to the Brown-Shiota scheme D-*erythro*-neopterin is the parent compound formed in *E. coli*[40, 41]. L-*threo*-Neopterin is however found in various organisms and indeed it is the chief pteridine found in *E. coli* itself[42]. *Brown*[43] has reported on neopterin epimerase activity found in this bacterium. His preliminary results, which ought to be further tested, indicate an alteration of the optical configuration of the intact dihydroneopterin side chain.

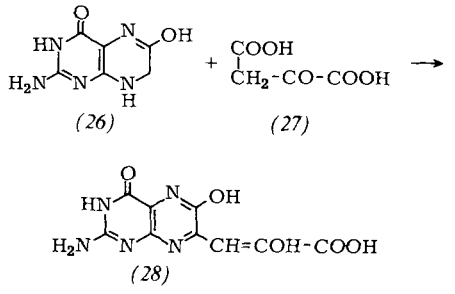


This scheme is based on the assumption of the validity of the first hypothesis on the origin of the side chain.

The characteristics of the four optical isomers of neopterin[44] and of biopterin[45] are listed in Table 4. Conveniently the *erythro* and *threo* isomers can be chromatographically separated from one another, while further determination of an unknown isomer by the *Crithidia* test is only applicable to the *erythro* series. In the case of the *threo* series optical rotations must be measured, a necessity not always met for the natural *threo* isomers listed in the literature. Because of the similarities of the isomers, all four optical forms should be tested for their cofactor activity in enzymatic reactions.

Table 4. Characteristics of the four optical isomers of neopterin [44] and biopterin [45]. R_f values measured in isopropanol/5% boric acid solution (4:1).

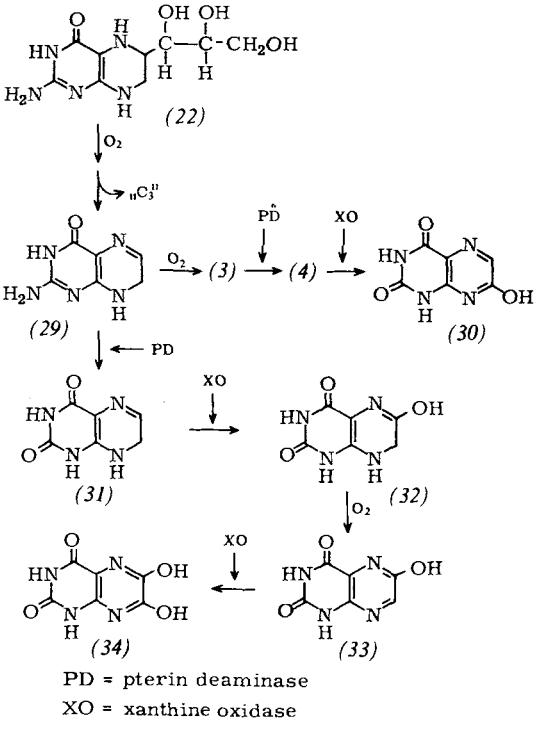
	R_f values	*Crithidia* half optimal growth concentration (ng/ml medium)	$[\alpha]_D^{25}$ [°]
Neopterin *(6a)*			
D-*erythro*	0.21	10	+45±3
L-*erythro*	0.21	0.03	−44±3
D-*threo*	0.12	10	−92±3
L-*threo*	0.12	2	+97±3
Biopterin *(6b)*			
D-*erythro*	0.30	0.7	+61
L-*erythro*	0.30	0.006	−62
D-*threo*	0.26	0.5	−94
L-*threo*	0.26	0.2	+95



The direct addition of a complete carbon chain to position 7 of the pteridine ring is illustrated by the synthesis of erythropterin. In the butterflies *Colias eurytheme* and *Colias croceus* xanthopterin *(35)* and, even better, dihydroxanthopterin *(26)* are directly incorporated into erythropterin *(28)*[46, 47]. With xanthopterin as a cosubstrate, *Forrest*[32] found that in the eggs of *Oncopeltus fasciatus* oxaloacetic acid *(27)* is utilized for the formation of the erythropterin side chain.

3.3. Catabolism

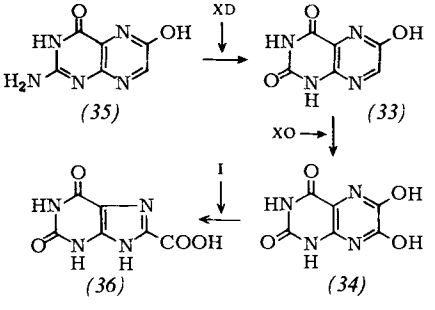
The degradation of pteridines is now better understood than any other part of their biochemistry. In a series of studies *Rembold et al.* have shown that tetrahydrobiopterin



(42) and tetrahydroneopterin *(22)* are degraded similarly *in vitro* by rat liver homogenates and *in vivo* after intraperitoneal injection into the rat[7, 55, 56]. The main pathway leading to the formation of simple lumazines is shown in the formula scheme.

After the polyhydroxyalkyl chain is oxidatively cleaved in a non-enzymatic reaction to form an aldehyde, the remaining 7,8-dihydropterin *(29)* is used as a substrate in either of two enzyme-catalyzed reactions. The pterin can be oxidized to dihydroxanthopterin *(26)* by xanthine oxidase[57] or it can serve as a substrate for the highly specific enzyme pterin deaminase. In the last case, which is illustrated in the above scheme, either 7,8-dihydrolumazine *(31)* or lumazine *(4)* is formed, depending on the state of oxidation of the substrate of the deaminase. The products in both cases serve as further substrates for xanthine oxidase and the end result is the formation of either 6,7-dihydroxylumazine *(34)* or 7-hydroxylumazine *(30)*.

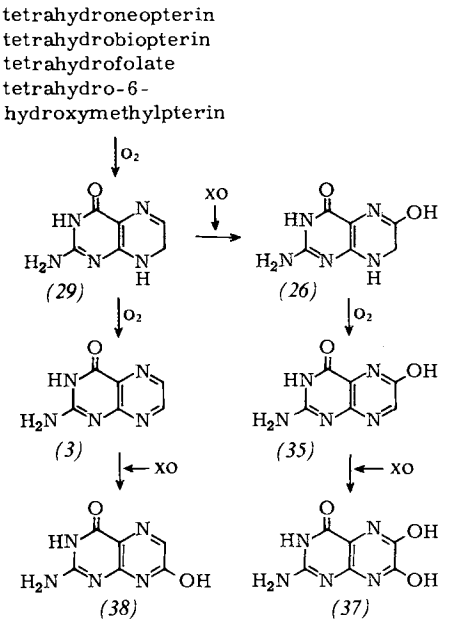
Levy and *McNutt*[58, 59] examined the degradation of pteridines by the organism *Alcaligenes faecalis* and found that starting with the simple pteridines isoxanthopterin *(38)* and xanthopterin *(35)* a series of deaminations and oxidations yielded the same lumazine derivatives as noted in the studies conducted with rats. However, *Alcaligenes* was able to proceed one step further and convert the 6,7-dihydroxylumazine *(34)* into its isomer xanthine-8-carboxylic acid *(36)*, *i.e.* the pteridine ring was converted into a purine ring.



XD = xanthopterin deaminase
XO = xanthine oxidase
I = isomerase

Ring-hydroxylated pterins are formed in a manner completely analogous to the reactions in the lumazine series[56]. Depending upon the presence or absence of the different pteridine deaminases, the catabolism of pteridines results in either simple pterins or simple lumazines. Pterin *(3)* and lumazine *(4)* undergo the same reaction in the presence of xanthine oxidase: both pteridines are hydroxylated at C-7[60, 61]. The 7,8-dihydro derivatives however are attacked at C-6[57].

Forrest et al.[62] found that pterin *(3)* occurs in the ry^2 mutant of *Drosophila melanogaster* which lacks xanthine oxidase while the wild strain has isoxanthopterin *(38)* in its place. After injection of radioactive pterin into pupae of the butterfly *Colias croceus*, *Descimon*[64] showed that radioactive isoxanthopterin was accumulated while injection of tetrahydropterin led to accumulation of labeled isoxanthopterin *(38)*, xanthopterin *(35)*, and leucopterin *(37)*. *Harmsen*[65] raised pupae of the butterfly *Mylothris chloris* at different oxygen partial pressures and showed that reducing conditions favored the formation of xanthopterin *(35)* and other 6-substituted pterins in the adult while high oxygen partial pressure favored the formation of pterins oxidized at position 7. *Dustmann*[63] found 6-hydroxylumazine *(33)* and 6,7-dihydroxylumazine *(34)* in drone honeybees while *Rembold* and *Buschmann*[12]



XO = xanthine oxidase

found that worker bees accumulated 7-hydroxylumazine (see Table 1). Drone honeybees apparently utilize 7,8-dihydrolumazine while worker bees use lumazine to form their end products.

The question arises whether the simple oxidized pterins and lumazines are in general further degraded by organisms or represent true terminal catabolites. This problem was studied by *Gyure* and *Corrigan*[15] in several species of insects. In the case of the silkworm *Bombyx mori*, homogenates deaminated isoxanthopterin *(38)* by a highly specific deaminase. The product, 7-hydroxylumazine *(30)*, was not further metabolized. When synthetic 6-hydroxylumazine was added to the homogenates, 6,7-dihydroxylumazine *(34)* was formed by the catalytic action of xanthine oxidase. The 6,7-dihydroxylumazine was not further catabolized by the homogenates.

The same results were obtained with the cockroach *Periplaneta americana* and the silkworms *Hyalophora cecropia* and *Rothschildia orizaba*. When the cockroach *Brysotria fumigata* and the firebug *Pyrrochoris apterus* were studied they were found to perform the same or similar reactions; however they possessed pterin deaminase activity similar to that found in rat tissues. In all these insects 7-hydroxylumazine was formed but not further catabolized. Since 7-hydroxylumazine is naturally found in *Bombyx mori*, *Hyalophora cecropia*, *Rothschildia orizaba*, and *Pyrrochoris apterus* it is most probably a terminal catabolite in these organisms.

Homogenates prepared from the relatively pteridine-rich butterflies *Pieris rapae* and *Colias eurytheme* did not degrade

isoxanthopterin, leucopterin, 7-hydroxylumazine, or 6,7-dihydroxylumazine. Since pterin deaminase activity was not observed, isoxanthopterin and leucopterin appear to be the terminal catabolites in these two insects. These data show that among the organisms studied only the bacterium *Alcaligenes* was capable of fully degrading the pteridine ring while the rat and the insects described end their catabolism at the stage of simple pteridines and lumazines.

The properties of the pteridine deaminases listed in Table 5 are very similar to one another with the exception of sepiapterin deaminase. Comparison with the properties of guanine deaminase (guanase) indicates that there are similarities here too. Guanase has the same pH optimum,

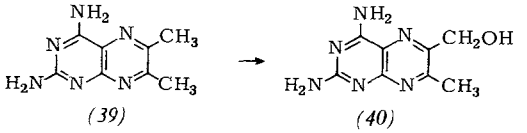
Table 5. Comparison of the characteristics of different pteridine deaminases.

Characteristic	*A. faecalis* pterin deaminase [66]	Rat liver pterin deaminase [55]	*P. americana* isoxanthopterin deaminase [15]	*B. mori* isoxanthopterin deaminase [15]	*B. mori* sepiapterin deaminase [53, 67]
pH optimum	6.3—6.7	6.5	6.6	6.6	8.0
Stability	unstable at pH 7 and 0 °C; stable at pH 9 and 0 °C	unstable at pH 6.5 and 4 °C; activity decreases 50% in 5 days	unstable at pH 7 and 0 °C	unstable at pH 7 and 0 °C; activity decreases 50% in 7 days	stable
K_M		3×10^{-5} mol/l		1.2×10^{-5} mol/l	5.9×10^{-4} mol/l
Specificity	pterin and all 6-substituted derivatives	tetrahydropterin >pterin >iso-xanthopterin	isoxanthopterin	isoxanthopterin	sepiapterin and isosepia-pterin
Inhibitors	*p*-chloromercuri-benzoate, NaF	KCN, lumazine, azaguanine	KCN, KF, xanthopterin, azaguanine	KCN, KF, xanthopterin, guanine	pterin biopterin, xanthopterin

it catalyzes an irreversible deamination reaction, and it is also inhibited by xanthopterin[15]. These similarities may point to a common mechanism of action.

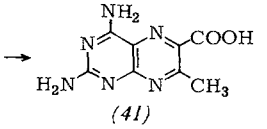
In contrast to these enzymes, sepiapterin deaminase from *Bombyx mori* has very different properties. However it must be noted that its substrate is a 7,8-dihydropterin while the other deaminases utilize the oxidized, or aromatic pteridines. Exceptions are the pterin deaminases from rat liver[55] and *Drosophila melanogaster*[15] which can catalyze the deamination of both aromatic and reduced pterins. The substrate specificity of the deaminases for the pteridines alone is in marked contrast to xanthine oxidase which catalyzes oxidations of both purines and pteridines. Guanase and uricase from bacteria, fungi, insects, and mammalian sources utilize no pteridine as substrate; conversely no purine acts as substrate for the pterin deaminases[15].

Numerous synthetic pteridines possess diuretic action. In investigations with the diuretic 2,4-diamino-6,7-dimethyl-



(39)

(40)



(41)

pteridine *(39)* *Eder* and *Rembold*[68, 69] noted that, after intraperitoneal injection into the rat, this pteridine was quickly detoxified by catabolism to the 6-hydroxymethyl *(40)* and the 6-carboxylic acid derivative *(41)*.

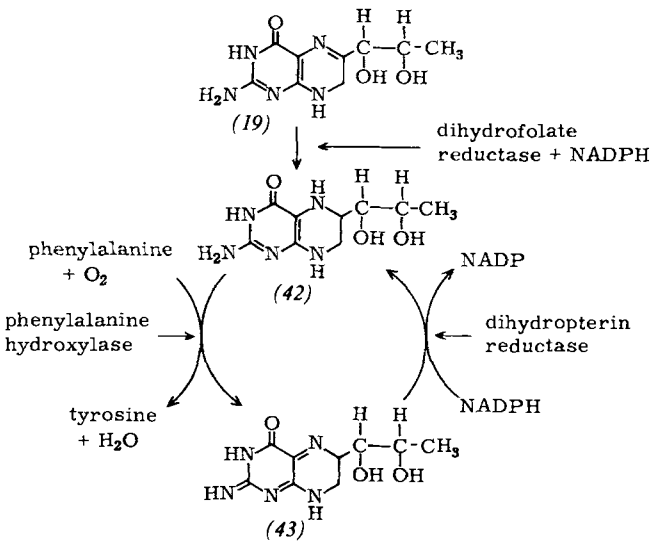
The first oxidation product *(40)* has only weak diuretic action while the second *(41)* is pharmacologically inactive. The enzymatic reaction is another example of the importance of position 6 of the pteridine ring. This position is attacked in preference to position 7. Such an importance can also be seen in the fact that biopterin is a growth factor for *Crithidia fasciculata* while the isomer of biopterin bearing the side chain in position 7 is completely without activity[70].

4. Cofactor Functions

Reduced pterins play a functional role in nature by acting as cofactors in a number of oxygenase reactions. *Kaufman*[71] was the first to show this when he reported that reduced biopterin serves as the natural cofactor in the hydroxylation of phenylalanine[103]. The reduced pterin in its inactive 7,8-dihydro form *(19)* is converted into the tetrahydro form *(42)* and after releasing two reducing equivalents it is converted to a quinonoid-dihydro form *(43)*[72]. The tetrahydropterin structure is regenerated from the quinonoid form by the action of an NADPH-dependent dihydropterin reductase.

The pteridine in this hydroxylation reaction has been shown to be specific since other reductants, such as ascorbate, glutathione, ferrous ions, *etc.*, are incapable of replacing the reduced pterin. The pterin functions catalytically, *i.e.* when a regenerating system is present a small amount of tetrahydrobiopterin will serve to catalyze the oxidation of greater amounts of substrate. Reduced biopterin has also been shown to be consumed stoichiometrically in the reaction and this utilization is substrate and enzyme dependent[73]. Further studies by *Osanai* and *Rembold*[74] have demonstrated that of the four isomers of biopterin the L-*erythro*-tetrahydrobiopterin isomer is by far the best cofactor in the rat liver system.

A reduced pteridine also functions as a cofactor for *Pseudomonas* phenylalanine hydroxylase[75]. The structure of the natural cofactor in this system has not yet been identi-



fied but it is known that *Pseudomonas* can accomplish the *de novo* synthesis of the pteridine ring and the necessary cofactor for the reaction[76]. When pteridines are extracted from this organism L-*threo*-neopterin occurs in the greatest amount followed by 6-pterincarboxylic acid, pterin, and xanthopterin. No biopterin was observed. Since reduced neopterin functions as well as tetrahydrobiopterin in the *Pseudomonas* system it may represent the natural cofactor.

Tyrosine hydroxylase has been highly purified from bovine adrenal medulla[77]. Tetrahydrobiopterin also seems to be the natural cofactor for this enzyme[110]. In all other oxygenase systems in which reduced pteridines have been suggested as cofactors the natural cofactor has not been identified or proved to be a pteridine. However, at least one of these other systems has been shown to utilize reduced pteridines specifically, catalytically, and also stoichiometrically. This system is the rat liver enzyme preparation which catalyzes the conversion of long chain alkyl ethers of glycerol to fatty acids and glycerol[78].

Other less well characterized reactions nevertheless showing considerable dependence on reduced pteridines are listed in Table 6. More studies are necessary to validate these

Table 6. Enzyme reactions reported to involve pteridine cofactors.

Enzyme	Reaction	Ref.
Tryptophan 5-hydroxylase	tryptophan to 5-hydroxytryptophan	[84, 115]
Cinnamic acid hydroxylase	cinnamic acid to *p*-cumaric acid	[85]
Anthranilic acid hydroxylase	anthranilic acid to hydroxyanthranilic acid	[86]
Progesterone 17-hydroxylase	progesterone to 17-hydroxyprogesterone	[87]
Proline hydroxylase	proline to hydroxyproline	[88]
Prostaglandin synthetase	prostaglandin biosynthesis	[89]
Pseudomonas alcohol dehydrogenase	ethanol to acetaldehyde	[90]

reported pteridine-dependent reactions, especially since it has been shown that reduced pteridines can stimulate an enzyme-catalyzed reaction by protecting the enzyme from inactivation[79].

Because reduced pteridines are active reagents in their own right, it is not surprising that recent reports have demonstrated that in the presence of Fe^{2+} tetrahydropterins in molar excess can act as non-specific hydroxylation agents for aromatic amino acids[80, 81, 112]. With these pteridine characteristics in mind the reactions in Table 6 should be restudied. Nevertheless it is significant that when *Rembold* and *Hanser* injected labeled biopterin and neopterin into bee pupae[82] and into the rat[37] radioactivity was found in cells of high metabolic activity such as bee cuticle at the time of sclerotization, bee fat body, rat liver, and the peripheral ganglion sheath of the rat central nervous system. These are exactly the locations required of cofactors for tyrosine hydroxylase, phenylalanine hydroxylase, and the alkyl ether hydroxylase. Similar findings have been reported by *Kokolis* and *Ziegler*[83] who noted that high concentrations of tetrahydrobiopterin *(42)* were localized in regenerating portions of the tails of *Triturus cristatus*.

5. Hydrogenated Pterins in Cellular Electron Transport

Recent studies, especially those on redox potentials, point to the probable importance of pteridines in cellular electron transport[91]. The polarographic halfwave potentials of the aromatic pteridines are similar to those of the pyridine nucleotides[92]. The standard halfwave potential of 6,7-dimethyltetrahydropterin is +150 mV[93], which is similar to those of the cytochromes (Table 7). EPR measurements show the possibility that this tetrahydropterin can form a cationic radical under physiological conditions[94].

Table 7. Standard redox potentials E_0' of components of the respiratory chain compared with 6,7-dimethyltetrahydropterin (DMTH).

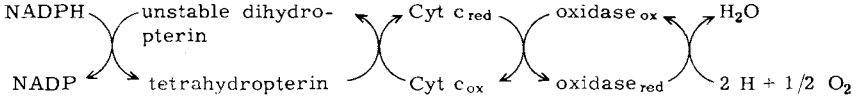
Compound	E_0' [V]
Cytochrome a/a_3	+0.29
Cytochrome c	+0.25
Cytochrome c_1	+0.23
DMTH	+0.15
Cytochrome b	+0.04
Flavoproteins	−0.05

These findings, although not conclusive, support the hypothesis of *Fuller* and *Nugent*[95] that pteridines are primary electron receptors in photosynthesis. According to these authors, a trihydropteridine radical is the electron receptor in the photosynthetic light reaction, and a tetrahydropteridine is thereby formed which then reduces ferredoxin. The hypothesis is not supported by the fact that the standard potential for tetrahydropterins is +0.15 V while for ferredoxin it is −0.42 V. From these potentials a reverse sequence of electron flow, *i.e.*, the reduction of an oxidized pterin by a reduced ferredexin, would be the expected reaction. Further studies will help to solve this question.

The occurrence of pteridines in chloroplasts has not been clearly demonstrated. It is possible that the few simple pteridines isolated from plants are decomposition products

of folic acid or riboflavin. The function of pteridines in mitochondria is much clearer. By isotopic dilution methods a significant amount of tetrahydrobiopterin *(42)* has been detected in these organelles[18]. Reduced pteridines in physiological concentrations stimulate mitochondrial respiration and the utilization of oxygen has been found to be linearly proportional to the amount of tetrahydropteridine present. At a concentration of reduced pterin which is five times higher than the physiological concentration the linearity of the oxygen utilization levels to a plateau.

Low temperature difference spectra show the reduction of the respiratory chain at the cytochrome c and a/a_3 sites. Cytochrome c_1 is not reduced even though its redox potential makes it appear a likely candidate (Table 7). It is noteworthy that respiration is not coupled to ATP production in the presence of tetrahydropterins. Obviously the electrons must flow from the tetrahydropteridine, *via* cytochrome c, directly to cytochrome oxidase[91]. A soluble electron transport system can be formed (Scheme 1).



Scheme 1.

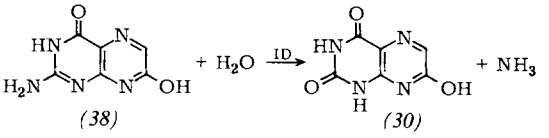
For an optimal oxidation of the reduced pyridine nucleotide, NADPH, every component of the system is essential. Tetrahydropterin can also be non-enzymatically regenerated in the system by NADPH probably from an unstable radical. The system can reduce more material than the amount of component tetrahydropterin and is limited only by the NADPH concentration. Therefore tetrahydropterin has a distinct catalytic effect in the system[16, 96]. The exact significance of tetrahydrobiopterin *(42)* and similar pteridines in cellular electron transport will have to be clarified in further studies.

6. Physiological Aspects

Once pteridines have been synthesized by an organism they can be utilized *in situ* or they can be transported to other tissues to be used directly or stored for later needs. The mechanisms of pteridine transport and storage are not yet well understood but investigations by *Gyurè*[15] on pteridines in the silkworm *Bombyx mori* give an insight into the general physiological process in insects. The results of the study will therefore be given in detail.

7-Hydroxylumazine *(30)* occurs in *Bombyx* eggs in very small amounts, its presence presumably arising from the maternal tissues. At the time of hatching the enzyme isoxanthopterin deaminase becomes active. This enzyme in *Bombyx* has been shown to be responsible for catalyzing the synthesis of 7-hydroxylumazine *(30)* from isoxanthopterin *(38)*.

Parallel to the deaminase activity, 7-hydroxylumazine is found throughout larval development, especially localized in the integument. *Tsujita* and *Sakurai*[97] have shown that in *Bombyx* larvae pteridines and purines are bound to specific proteins and are localized in integument pteridine granules. There are specific binding proteins for uric acid, sepiapterin *(7b)*, and isoxanthopterin *(38)*. It is not yet



ID = isoxanthopterin deaminase

known if such proteins exist also for deaminated sepiapterin and for 7-hydroxylumazine which are the other two pteridines found in *Bombyx*. Presumably there is either a specific carrier protein for 7-hydroxylumazine or the carrier for isoxanthopterin serves also to bind 7-hydroxylumazine. Because isoxanthopterin deaminase is mainly found in larval integument, it is clear that 7-hydroxylumazine is produced and stored in this tissue.

At the beginning of the spinning phase, which occurs at the start of metamorphosis from larval to pupal form, the integument loses its creamy white color. It now becomes clear due to the breakdown of the membrane of the pteridine granules which in turn releases purines and pteridines to the cytoplasm and insect hemolymph. That the poorly soluble 7-hydroxylumazine can be so suddenly accommodated and transported by the hemolymph is probably an indication that it is again complexed to a protein.

As *Bombyx* pupal tissues form, the concentration of hemolymph 7-hydroxylumazine rapidly decreases, a portion being excreted while the rest is stored in the fat body. New 7-hydroxylumazine is not formed in the fat body and the observable lumazine in this organ represents a transported and stored compound. This can be deduced from observations on the behavior of isoxanthopterin deaminase. This enzyme disappears from *Bombyx* at the time of the breakdown of larval pteridine granules and at no time does it ever occur in the fat body. 7-Hydroxylumazine is stored in the fat body only during the first half of pupal development; during the second half it collects in the meconium. After emergence of the moth a great part of the lumazine is excreted while the rest remains attached to the meconial sac membranes. In the last few days of imaginal development, newly forming female wings and integument abruptly start fresh synthesis of 7-hydroxylumazine. This is accompanied by an equally abrupt appearance of isoxanthopterin deaminase activity in the same tissues. This effect is not observed in male silk moths, probably for genetic reasons.

Similar findings to those in *Bombyx* have been reported for other insects, fish, and amphibia. *Hama*[101] has des-

cribed the pteridine granules in various fish, reptiles, and amphibia. *Obika*[99] isolated pterinosomes from lower vertebrates and found that about 60% of all pteridines were bound to cell particles. Isoxanthopterin deaminase and 7-hydroxylumazine display the same localization patterns in the wild silkmoths *Hyalophora cecropia* and *Rothschildia orizaba* as found in *Bombyx mori*[115]. *Hanser* and *Rembold*[82,100] found that after injection of labeled biopterin into bee pupae radioactivity was located in the meconial sac membranes.

Worthy of further mention are the studies of *Harmsen* on the cabbage butterfly, *Pieris brassicae*[101]. During the larval and early pupal stages much the same results as found in *Bombyx mori* were observed. However, at the time of the development of adult tissues in the pupae, pteridines were noted to be synthesized in relatively large amounts. In this regard Pierids differ from other lepidoptera. For example, in this species the isoxanthopterin concentration in the adults is thirty times that found in *Bombyx*. *Ziegler* and *Harmsen*[8] assumed that the large amounts of pteridines in *Pieris brassicae* adult wings arise in part from *de novo* synthesis in the wings and in part by transport from the fat body. The results of studies by *Watt*[46] with the butterfly *Colias eurytheme* support this assumption. He found that incubation of isolated developing wings of this butterfly with labeled guanine precursors led to formation of radioactive wing pteridines. On the other hand *Descimon*[47] has found that synthetic 6-hydroxymethylpterin injected into *Colias croceus* pupae could be recovered from the adult wings. Since this pteridine does not normally occur in *Colias* wings it must have been transported from the site of injection and stored in the developing wings. *Lafont*[109] has noted that, after injection of radioactive isoxanthopterin into *Pieris brassicae* pupae, this pteridine could be observed first in the pupal fat body and later during adult development in the wings, meconial sac, and eggs. These findings indicate that butterfly wings have separate but parallel capacities for pteridine synthesis and storage.

7. Conclusion

From the reported findings it appears that purines are generally utilized as biochemical precursors of the pteridine ring. A specific GTP-cyclohydrolase has been purified from a microorganism but even in this case there is uncertainty about the enzymatic reaction mechanism. The first tangible product of the purine-pteridine conversion in *Escherichia coli*[41] is D-*erythro*-7,8-dihydroneopterin triphosphate *(12)*; in *Comamonas* on the other hand it is a cyclic D-*erythro*-7,8-dihydroneopterin 2',3'-monophosphate[102]. However, the example of the indolyl derivative *(17)* shows that the Brown-Shiota scheme of purine-pteridine conversion is not universal, even for microorganisms.

Even greater reservations are held with regard to application of the scheme to higher organisms which appear able to synthesize the pteridine ring *de novo*. No enzyme of pteridine biosynthesis has been purified in such a case. However, one can predict that in view of the anabolic enzymes already described in Table 3, biosynthetic enzymes will be soon reported.

In contrast, pteridine catabolism is much clearer especially since the functions of xanthine oxidase and specific pterin deaminases are now known. Yet to be answered is the question whether the pteridine side chain is non-enzymatically split in an organism or whether there is a specific enzyme which performs this task and which thus can control the concentration of pteridine cofactors.

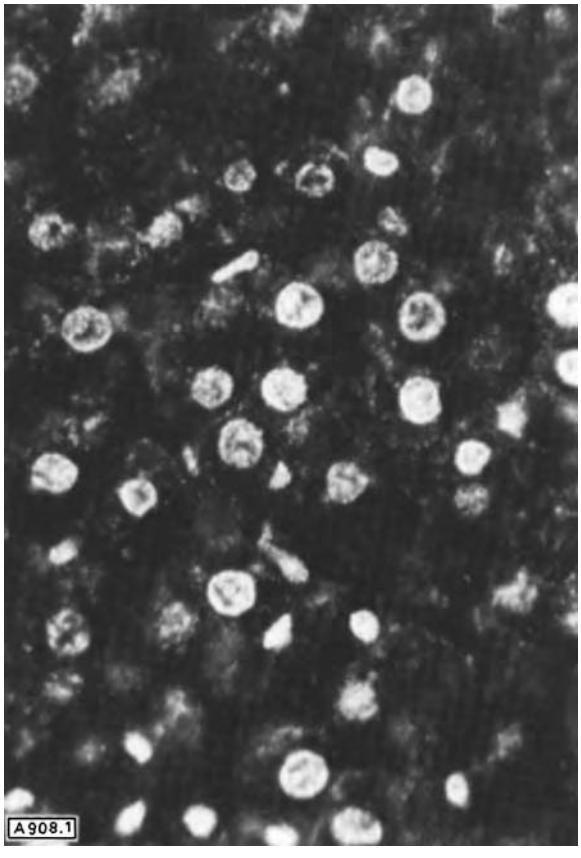


Fig. 1. Histoautoradiography of liver slices from a rat injected 24 hours earlier with [2-^{14}C]tetrahydrobiopterin. The bright shining spots which occur in the nucleus show the location of radioactivity in the cells. (Photograph by Dr. *G. Hanser*.)

Pteridines have not been found to be materials for the formation of high molecular weight substances, and their primary function appears to be much more that of redox catalysts which are coupled by specific reactions to the hydrogen potential of the pyridine nucleotides. In the case of the synthesis of the precursors of adrenaline (tyrosine, DOPA) and of serotonin (5-hydroxytryptophan) the cofactor importance of pteridines is already apparent and one can expect that this will apply to the other enzymes listed in Table 6.

The discovery that mitochondrial respiration is activated by tetrahydropterins in physiological concentrations throws up a number of questions concerning the importance of pteridines in cellular electron transport. Because of their very small concentration in the cell, pteridines must be limited to very special regulatory steps. On the other hand, it is remarkable how ubiquitous the 6-(polyhydroxyalkyl)-

pteridines are in nature. The autoradiographic data of Figure 1 show how pteridines are concentrated in the nucleus of rat cells.

Their physiological behavior shows also that pteridines do not generally play the role of metabolic end products as formerly thought. It is therefore necessary to further study the findings of protein-pteridine[97] and pteridine-flavin complexes[104] and of energy-dependent selective biopterin transport[105]. Pteridine binding to DNA[106] molecules may be the mechanism by which these substances can function as regulators. Also of regulatory importance may be the observations on the remarkable difference between the pteridine patterns in the ant *Formica polyctena*[107].

Received: July 21, 1971; revised: February 11, 1972 [A 908 IE]
German version: Angew. Chem. *84*, 1088 (1972)

[1] *F. G. Hopkins*, Nature *40*, 335 (1889).
[2] *H. Wieland* and *C. Schöpf*, Ber. Dtsch. Chem. Ges. *58*, 2178 (1925).
[3] *C. Schöpf* and *H. Wieland*, Ber. Dtsch. Chem. Ges. *59*, 2067 (1926).
[4] *R. Purrmann*, Liebigs Ann. Chem. *544*, 182 (1940); *546*, 98 (1940); *548*, 284 (1941).
[5] *W. Pfleiderer*, Angew. Chem. *75*, 993 (1963); Angew. Chem. internat. Edit. *3*, 114 (1964).
[6] *R. C. Elderfield* and *A. C. Mehta* in *R. C. Elderfield*: Heterocyclic Chemistry. Wiley, New York 1967, vol. 9, p. 1.
[7] *H. Rembold, H. Metzger, P. Sudershan*, and *W. Gutensohn*, Biochim. Biophys. Acta *184*, 386 (1969).
[8] *I. Ziegler* and *R. Harmsen*, Advan. Insect Physiol. *6*, 139 (1969).
[9] *H. S. Forrest* and *C. van Baalen*, Annu. Rev. Microbiol. *24*, 91 (1970).
[10] *T. Hama*, Ann. N.Y. Acad. Sci. *100*, 977 (1963).
[11] *L. Buschmann*, Dissertation, Universität München 1963.
[12] *H. Rembold* and *L. Buschmann*, Liebigs Ann. Chem. *662*, 72 (1963).
[13] *M. Tsujita* and *S. Sakurai*, Japan. J. Genet. *38*, 97 (1963).
[14] *J. M. Lagowski* and *H. S. Forrest*, Proc. Nat. Acad. Sci. USA *58*, 1541 (1967).
[15] *W. L. Gyure*, Dissertation, Tufts University 1970; University Microfilms, Ann. Arbor, Michigan No. 71—13, 749.
[16] *K. Buff*, Dissertation, Universität München 1971.
[17] *H. Rembold* and *L. Buschmann*, Hoppe-Seylers Z. Physiol. Chem. *330*, 132 (1960).
[18] *H. Rembold* and *H. Metzger*, Z. Naturforsch. *22b*, 827 (1967).
[19] *V. C. Dewey* and *G. W. Kidder*, J. Chromatogr. *31*, 326 (1968).
[20] *M. Viscontini* and *H. Stierlin*, Helv. Chim. Acta *45*, 2479 (1962).
[21] *E. Hadorn* and *H. K. Mitchell*, Proc. Nat. Acad. Sci. USA *37*, 650 (1951).
[22] *H. Descimon* and *M. Barial*, J. Chromatogr. *25*, 391 (1966).
[23] *M. Viscontini, E. Hadorn*, and *P. Karrer*, Helv. Chim. Acta *40*, 579 (1957).
[24] *J. D. Gerhart* and *R. J. MacIntyre*, Anal. Biochem. *37*, 2525 (1970).
[25] *C. H. Eugster, E. F. Frauenfelder*, and *H. Koch*, Helv. Chim. Acta *53*, 131 (1970).
[26] *V. C. Dewey* and *G. W. Kidder* in *D. B. McCormick* and *L. D. Wright* Medhods in Enzymology. Academic Press, New York 1971, vol. 18B, p. 618.
[27] *W. S. McNutt*, Anal. Chem. *36*, 912 (1964).
[28] *G. Guroff* in [26], p. 600.
[29] *P. Haug*, Anal. Biochem. *37*, 285 (1970).
[30] *T. Lloyd, S. Markey*, and *N. Weiner*, Anal. Biochem. *42*, 108 (1971).
[31] *H. Kraut, W. Pabst, H. Rembold*, and *L. Wildemann*, Hoppe-Seylers Z. Physiol. Chem. *332*, 101 (1963).
[32] *H. S. Forrest, M. McNater*, and *J. Alexander*, J. Insect Physiol. *12*, 1411 (1966).
[33] *T. Shiota* in *M. Florkin* and *E. H. Stotz*: Comprehensive Biochemistry. Elsevier, Amsterdam 1971, vol. 21, p. 111.
[34] *G. M. Brown* in *D. Greenberg*: Metabolic Pathways. Academic Press, New York 1970, vol. 4, p. 383; Advan. Enzymol. *35*, 35 (1971).
[35] *I. Takeda* in *K. Iwai, M. Goto, M. Akino*, and *Y. Iwanami*: Chemistry and Biology of Pteridines. Internat. Acad. Printing Co., Tokyo 1970. p. 183.
[36] *W. Pabst* and *H. Rembold*, Hoppe-Seylers Z. Physiol. Chem. *344*, 107 (1966).
[37] *H. Rembold*, unpublished
[38] *H. Rembold, V. Chandrashekar*, and *P. Sudershan*, Biochim. Biophys. Acta *237*, 365 (1971).
[39] *T. Fukushima*, Arch. Biochem. Biophys. *139*, 361 (1970).
[40] *T. H. D. Jones* and *G. M. Brown*, J. Biol. Chem. *242*, 3989 (1967).
[41] *A. W. Burg* and *G. M. Brown*, J. Biol. Chem. *243*, 2349 (1968).
[42] *H. Rembold* and *G. Heinz*, Hoppe-Seylers Z. Physiol. Chem. *352*, 1271 (1971).
[43] *G. M. Brown* in [35], p. 243.
[44] *H. Rembold* and *L. Buschmann*, Chem. Ber. *96*, 1406 (1963).
[45] *B. Green* and *H. Rembold*, Chem. Ber. *99*, 2162 (1966).
[46] *W. B. Watt*, J. Biol. Chem. *242*, 565 (1967).
[47] *H. Descimon*, Dissertation, Ecole Normale Superieure, Paris 1969.
[48] *T. Shiota, R. Jackson*, and *C. M. Baugh* in [35], p. 265.
[49] *J. B. Mahis* and *G. M. Brown*, J. Biol. Chem. *245*, 3015 (1970).
[50] *F. P. Richey* and *G. M. Brown*, J. Biol. Chem. *244*, 1582 (1969).
[51] *T. Shiota, C. M. Baugh, R. Jackson*, and *R. A. Dillard*, Biochemistry *8*, 5022 (1969).
[52] *K. Iwai, O. Okinaka, M. Ikeda*, and *N. Suzuki* in [35], p. 281.
[53] *M. Tsusue*, J. Biochem. (Tokyo) *69*, 781 (1971).
[54] *M. Matsubara*, Arch. Biochem. Biophys. *126*, 426 (1968).
[55] *H. Rembold* and *F. Simmersbach*, Biochim. Biophys. Acta *184*, 589 (1969).
[56] *H. Rembold, H. Metzger*, and *W. Gutensohn*, Biochim. Biophys. Acta *230*, 117 (1971).
[57] *H. Rembold* and *W. Gutensohn*, Biochem. Biophys. Res. Commun. *31*, 837 (1968).
[58] *C. Levy* and *W. S. McNutt*, Biochemistry *1*, 1161 (1962).
[59] *W. S. McNutt*, J. Biol. Chem. *238*, 1116 (1963).
[60] *F. Bergmann* and *H. Kwietny*, Biochim. Biophys. Acta *28*, 613 (1958).
[61] *F. Bergmann* and *H. Kwietny*, Biochim. Biophys. Acta *33*, 29 (1959).
[62] *H. S. Forrest, E. Glassman*, and *H. K. Mitchell*, Science *124*, 725 (1956).
[63] *S. H. Dustmann*, Hoppe-Seylers Z. Physiol. Chem. *352*, 1599 (1971).
[64] *H. Descimon*, C. R. Acad. Sci. *D. 268*, 416 (1969).
[65] *J. Harmsen*, J. Insect Physiol. *15*, 2239 (1969).
[66] *B. Levenberg* and *O. Hayashi*, J. Biol. Chem. *234*, 955 (1959).
[67] *M. Tsujita* and *S. Sakurai*, Proc. Jap. Acad. *43*, 991 (1967).
[68] *J. Eder* and *H. Rembold*, Z. Anal. Chem. *237*, 50 (1968).
[69] *J. Eder* and *H. Rembold*, Arzneimittel-Forsch. *21*, 562 (1971).
[70] *H. Rembold* and *H. Metzger*, Hoppe-Seylers Z. Physiol. Chem. *329*, 291 (1962).
[71] *S. Kaufman*, Proc. Nat. Acad. Sci. USA *50*, 1085 (1963).
[72] *S. Kaufman*, J. Biol. Chem. *239*, 332 (1964); Advan. Enzymol. *35*, 245 (1971).
[73] *S. Kaufman*, Trans. N.Y. Acad. Sci. *26*, 977 (1964).
[74] *M. Osanai* and *H. Rembold*, Hoppe-Seylers Z. Physiol. Chem. *352*, 1359 (1971).
[75] *G. Guroff and C. A. Rhoads*, J. Biol. Chem. *242*, 3641 (1967).
[76] *G. Guroff and C. A. Rhoads*, J. Biol. Chem. *244*, 142 (1969).
[77] *R. Shiman, M. Akino*, and *S. Kaufman*, J. Biol. Chem. *246*, 1330 (1971).
[78] *A. Tietz, M. Lindberg*, and *E. P. Kennedy*, J. Biol. Chem. *239*, 4081 (1964).
[79] *V. G. Zamoni, N. C. Brown*, and *B. N. LaDu*, Fed. Proc. *22*, 232 (1963).
[80] *W. F. Coulson, M. J. Powers*, and *J. B. Japson*, Biochim. Biophys. Acta *222*, 606 (1970).
[81] *M. Viscontini* and *T. Okada*, Helv. Chim. Acta *50*, 1845 (1967).
[82] *G. Hanser* and *H. Rembold*, Z. Naturforsch. *23b*, 666 (1968).
[83] *N. Kokolis* and *I. Ziegler*, Z. Naturforsch. *23b*, 860 (1968).
[84] *S. Hosoda* and *D. Glick*, J. Biol. Chem. *241*, 192 (1966).
[85] *P. M. Nair* and *L. C. Vinning*, Phytochemistry *4*, 161 (1965).
[86] *P. M. Nair* and *C. S. Vaidyanathan*, Phytochemistry *3*, 235 (1964).
[87] *D. D. Hagerman*, Fed. Proc. *23*, 480 (1964).
[88] *B. Peterkofsky* and *S. Udenfriend*, Proc. Nat. Acad. Sci. USA *53*, 335 (1965).
[89] *B. Samuelsson, E. Granstron*, and *M. Hamberg* in *S. Bergstrom* and *B. Samuelsson*: Prostaglandins. Nobel Symposium. Interscience, Stockholm 1967, vol. 2, p. 31.
[90] *C. Anthony* and *L. J. Zatman*, Biochem. J. *104*, 960 (1967).
[91] *H. Rembold* and *K. Buff* in *E. Quagliariello, S. Papa*, and *C. S. Rossi*: Energy Transduction in Respiration and Photosynthesis. Adriatica Editrice, Bari 1971, p. 467.
[92] *H. Rembold* and *H. Metzger*, Hoppe-Seylers Z. Physiol. Chem. *348*, 194 (1967).
[93] *M. C. Archer* and *K. G. Scrimgeour*, Can. J. Biochem. *48*, 526 (1970).
[94] *A. M. Bobst*, Proc. Nat. Acad. Sci. USA *68*, 541 (1971).
[95] *R. C. Fuller* and *N. A. Nugent*, Proc. Nat. Acad. Sci. USA *63*, 1311 (1969).
[96] *H. Rembold* and *K. Buff*, Eur. J. Biochem. *28*, 579, 586 (1972).
[97] *M. Tsujita* and *D. Sakurai*, Proc. Jap. Acad. *41*, 230 (1965).
[98] *S. Katoh*, Arch. Biochem. *146*, 202 (1971).
[99] *M. Obika* in [35], p. 413.
[100] *G. Hanser* and *H. Rembold*, Z. Naturforsch. *19b*, 938 (1964).
[101] *R. Harmsen*, J. Insect Physiol. *12*, 9 (1966).
[102] *J. Cone* and *G. Guroff*, J. Biol. Chem. *246*, 979 (1971).
[103] *S. Kaufman* and *D. B. Fisher*, J. Biol. Chem. *245*, 4745 (1970).
[104] *G. H. Schmidt* and *M. Viscontini*, Helv. Chim. Acta *47*, 2049 (1964).
[105] *H. Rembold* and *A. Vaubel*, Hoppe-Seylers Z. Physiol. Chem. *351*, 1277 (1970).

[106] *H. S. Forrest* in [35], p. 155.
[107] *G. H. Schmidt* in [35], p. 399.
[108] *S. Katoh, M. Nagai, Y. Nagai, T. Fukushima*, and *M. Akino* in [35], p. 225.
[109] *R. Lafont*, C. R. Acid. Sci. *D 273*, 1484 (1971).
[110] *T. Lloyd* and *N. Weiner*, Mol. Pharmacol. *7*, 569 (1971).
[111] *J. Dayman* and *G. Guroff*, Fed. Proc. *30*, 1141 (1971).
[112] *L. I. Woolf, A. Jakubovič*, and *E. Chan-Henry*, Biochem. J. *125*, 569 (1971).
[113] *A. Suzuki* and *M. Goto*, Bull. Chem. Soc. Jap. *44*, 1869 (1971).
[114] *K. Lind*, Eur. J. Biochem. *25*, 560 (1972).
[115] *P. A. Friedman, A. H. Kappelman*, and *S. Kaufman*, J. Biol Chem. *247*, 4165 (1972).

Thermally Reversible Photoisomerizations[**]

By Gerhard Quinkert[*]

Dedicated to Professor Vladimir Prelog

This article consists of a programmatic part and a pragmatic one. The programmatic aspects are the establishment of photochemistry, in the broadest definition of its scope, as a developing field directed toward the elucidation of photobiological phenomena, and an appeal for the wide development of the hitherto neglected dimension of electronically excited states. The pragmatic part is the detailed description of the photochemistry of linearly conjugated cyclohexadienones as an example of a thermally reversible photoisomerization system. The logical use of methods for obtaining information about the formal kinetics of light-induced reactions and for the identification of short-lived transients by low-temperature spectroscopy is of value to both parts.

1. The Developing Field of Photochemistry

As far as semantics are concerned all the processes participating in the formation and deactivation of electronically excited molecules are liberally treated as topics of photochemical interest. The purist's desire to speak generally of photoprocesses and to distinguish photophysical events from photochemical ones—intelligible at first sight—is opposed by the consequences of an obscure division of the field; such a subdivision is questionable from the standpoint of development of that part of science which, in the region of molecular dimensions, deals with interaction between light and matter and whose most challenging problems lie above all in the complex[***] systems of biology. With the broadest possible definition of its scope, photochemistry is a wide field aimed at the unravelling of photobiological phenomena selected through the processes of evolution[****].

Adaptation to and further development by existing terrestrial light conditions are characteristic of the various phases of evolution, which have been labeled chemical, biochemical, and biological[7] without regard for separative effects, in order to emphasize growing complexity. Photosynthesis, photomorphogenesis, and phototropism are the principal phenomena by which plant organisms have adapted themselves to the environmental condition of light, while the dominant comparable phenomenon in animal organisms is vision. The photoprocesses of the light-absorbing receptors are substantially unknown apart from the visual pigments[8]. Why is this so?

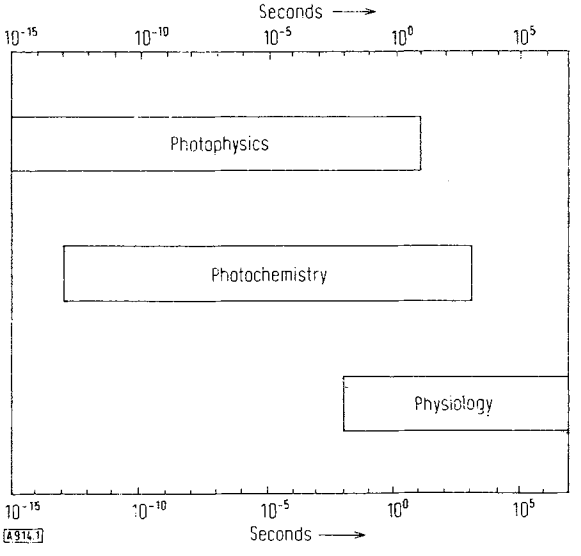


Fig. 1. Time ra[illegible]id schematized composition of the interdisciplinary complex of photobiology; cf. [9].

[*] Prof. Dr. G. Quinkert
Institut für Organische Chemie der Universität
6 Frankfurt/Main, Robert-Mayer-Strasse 7–9 (Germany)

[**] 5th essay on light-induced reactions; based on a lecture to the General Meeting of the Gesellschaft Deutscher Chemiker on September 14, 1971, in Karlsruhe. The 4th essay was ref. [35].

[***] From the largely indistinct clamour of voices expressing uneasiness over the present structure and role of chemistry there rises a clear call for a revision of the structure of chemistry and a turning towards complex problems; see [1–3].

[****] A guide to photobiological problems are *e.g.* the monographs of [4–6].

First there is the enormous span in the train of events that should belong to different regions according to a scheme that is still in use (see Fig. 1). The photophysical region in any case embraces the series of processes that are associated with light phenomena; for organic molecules of normal size the absorption occurs in approximately 10^{-15} seconds, and the decay time of the emission of phosphorescence is occasionally as long as a few seconds. The area of radiationless deactivation extends from almost 10^{-12} seconds for vibrational relaxations to a few seconds for slow intercombinations; it is normally regarded as a physical domain, but can also be advantageously included in the field of interest of chemical dynamics[*].

Where photoproducts are formed from electronically and vibrationally excited states, these have an average lifetime of about 10^{-13} second. In light-induced reactions kinetically unstable transients with a considerable diversity of half-lives, extending from the nanosecond range well into the minute range, frequently occur under normal conditions. The time span of the light-induced physiological processes also covers several orders of magnitude. Whereas the eyes of bees, for example, can detect up to 200 oscillations per second[12], flower formation is measured 10^6 to 10^7 seconds after photoperiodic induction[13]. The solution of photobiological problems thus requires the experimental treatment of processes that can extend over more than 20 orders of magnitude on the time scale! The "convoy principle", suitably applied, is valid for the disentanglement of interdisciplinary complexes. One can scarcely avoid the impression that chemists have not so far made the contribution that is necessary for the elucidation of photobiological phenomena.

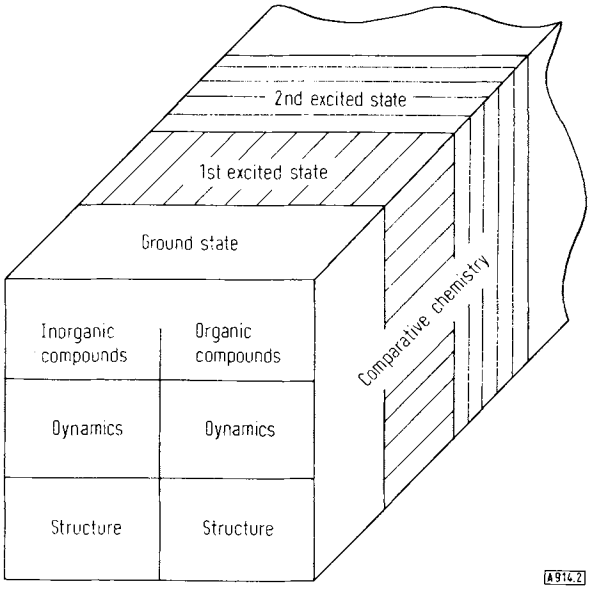


Fig. 2. Structure-oriented classification of chemistry, including electronically excited states.

[*] If conformational changes of molecules in their electronic ground state, such as occur *e.g.* by rotation about bonds and inversion at centers (including the accompanying changes in bond lengths) are the concern of chemical dynamics, this is also true of conformational changes in electronically excited molecules during radiationless deactivation. For a discussion of the geometry of electronically excited molecules see [10, 11].

This omission becomes understandable when one considers (see Fig. 2) that the structure-oriented part in the chemical education of scientists is still directed almost exclusively toward inorganic and organic compounds in their electronic ground state. Questions concerning the structure and chemical dynamics of compounds in their various electronically excited states are hardly considered in this connection. The reason for this is obvious: Electronically excited compounds are so short-lived that they have not been regarded consciously enough in the past as independent species with structures and reactivities of their own. Their study was a domain of spectroscopists, who did not use the conventional terminology of chemistry. Nowadays the need for development and cultivation of a "comparative chemistry"[14] (see Fig. 2) appears not only to exist but also to be largely feasible because of the disappearing linguistic differences.

With the growing familiarity at least with the qualitative principles of *Mulliken*'s molecular orbital method[15], which is largely due to the successes of the Hückel rule[16] and the Woodward-Hoffmann rules[17], there has also been an increase in the general ability to use intelligibly the terms of group theory. This has led to the removal of a barrier that formerly prevented a broad development of the neglected dimension of electronically excited states. Another impetus to that expansion has been provided by the dramatic development of experimental methods for the study of reactions not long ago considered to be immeasurably fast[18, 19], and hence for the reliable detection of short-lived transients. With the aid of information from flash spectroscopy[20, 21], electron emission spectroscopy[22–25], ESR spectroscopy[26], and NMR emission spectroscopy (CIDNP)[27], what were necessarily speculations of photochemistry in the past can now be turned into questions to be answered experimentally.

2. The Model of Thermally Reversible Photoisomerizations

The extremely numerous photobiological problems cannot be reduced to a common denominator as far as structure is concerned. They naturally all begin with the absorption of light by a chromophoric system. The photoprocesses of the electronically excited pigments, as was mentioned earlier, are inadequately known in almost all cases.

It may be useful at this stage to devise models for structure systems with similar reaction behavior. Their study not only furthers our knowledge of structure-photoreactivity relationships but also allows the continuous testing of promising experimental methods. A suitable model in our view is provided by thermally reversible photoisomerization systems[*].

[*] These include some of the photochromic systems. They have been suggested as systems for temporary storage of information ("memory models") [28], as systems for the temporary storage of energy [29], as subjects for practice in handling of transients [30], and for use in reproduction processes [31]; see [32] and further literature cited there.

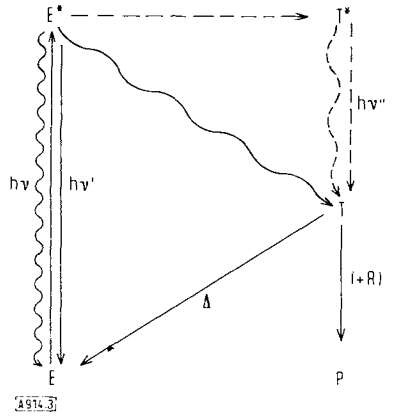


Fig. 3. Scheme of a thermally reversible photoisomerization system with transients that can be trapped (by R) (for the sake of completeness the broken lines show the adiabatic isomerization course).

A reactant E is converted *via* the electronically excited compound E* into an isomeric transient T, which is very short-lived (kinetically very unstable) under normal conditions since it is converted back into the original reactant E and/or reacts further to form the isolable product P. P is either isomeric with T, and hence also with E, or (*e.g.* after reaction of T with R) is not isomeric with T (see Fig. 3).

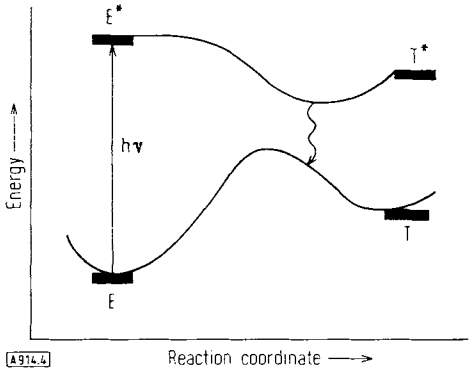


Fig. 4. Scheme of a diabatic photoisomerization.

Unlike in thermal isomerizations, which normally proceed exclusively on the lowest energy surface, *i.e.* adiabatically (see Fig. 4), it is possible in photoisomerizations, and is even the rule in condensed phase, for the electronically excited compound to pass from a higher energy surface to the lowest one even before the electronically excited transient T* has been reached; in other words, the photoisomerization can proceed diabatically from E *via* E* to T[33][*].

Whether isomer T accumulates under normal conditions and with suppression of formation of P or whether the intact reactant E is regenerated will depend on the height of the threshold on the lowest energy surface. In the latter case seemingly no chemical reaction will have occurred; one might lower the temperature in order to try to conserve transient T.

Quite apart from the fact that it may become possible in this way to prepare reactive compounds that are otherwise obtainable only with difficulty if at all, the manifestation of latent thermo-reversible photoisomerization systems is worth the effort for still another reason: The energy taken up by a compound E on absorption of light is used to synthesize the chemically different species E* (see Fig. 3) and thereupon partitions between radiationless and/or radiative deactivation paths leading either back to reactant E or on to product P. The quantum yield of photochemically produced P as well as the quantum yield of E regenerated with emission of light can be determined experimentally. The deficit by which this sum is smaller than the amount of energy originally taken up is accounted for by radiationless deactivation of E* leading back to E. This radiationless deactivation obtained by subtraction branches into one route from E* to E directly and another one from E* to E *via* T[*].

3. Structural and Kinetic Analysis in Real Model Cases

Understanding a thermally reversible photoisomerization requires a structure-oriented analysis of the product and transient involved as well as a kinetic analysis of the reaction course. Since the investigation of product P can be carried out in the usual manner, no explicit comment is needed. Special low-temperature techniques[14,39] have been developed for the analysis of the reactive transient T; details of these methods will be omitted here in favor of results obtained by these techniques. A brief discussion of the type of analysis of the reaction course, however, seems appropriate.

Light-induced reactions are generally so complex that the concept of reaction order becomes meaningless. According to *Mauser*[40], an extremely useful differentiation of photoreactions, which is admittedly based on formal kinetics, is possible by the following procedure: A diagram of extinction differences (ED diagram) is obtained by plotting differences in absorption intensity at specified wavelengths observed at various intervals during a light-induced reaction that can be followed electronic spectroscopically against each other in rectangular coordinates. This contains either a family of straight lines passing through the origin (see Fig. 5), in which case it is known as a linear ED diagram, or a family of curves arising from the origin, in which case the ED diagram is designated as nonlinear (see Fig. 6).

Linear ED diagrams belong to spectroscopically simple photoreactions. They are observed if *e.g.* the premise of

[*] Adiabatic types in which the chemical reaction occurs after the deactivation of the electronically excited reactant and those in which the chemical reaction occurs before the deactivation of the electronically excited product are discussed in [33, 34] and in [23, 33, 34] respectively.

[*] We referred earlier to the matter of differentiation for radiationless deactivations [35]. *Lamola, Hammond,* and *Mallory* [36] and *Phillips, Lemaire, Burton,* and *Noyes* [37] also regard isomerizations as a possibly widely occurring mechanism of radiationless transitions (see also [38]). The proposal to distinguish between "physical" and "chemical" deactivation may for a time provide a stimulus to experiment, but it readily gives the impression of two essentially different deactivation phenomena.

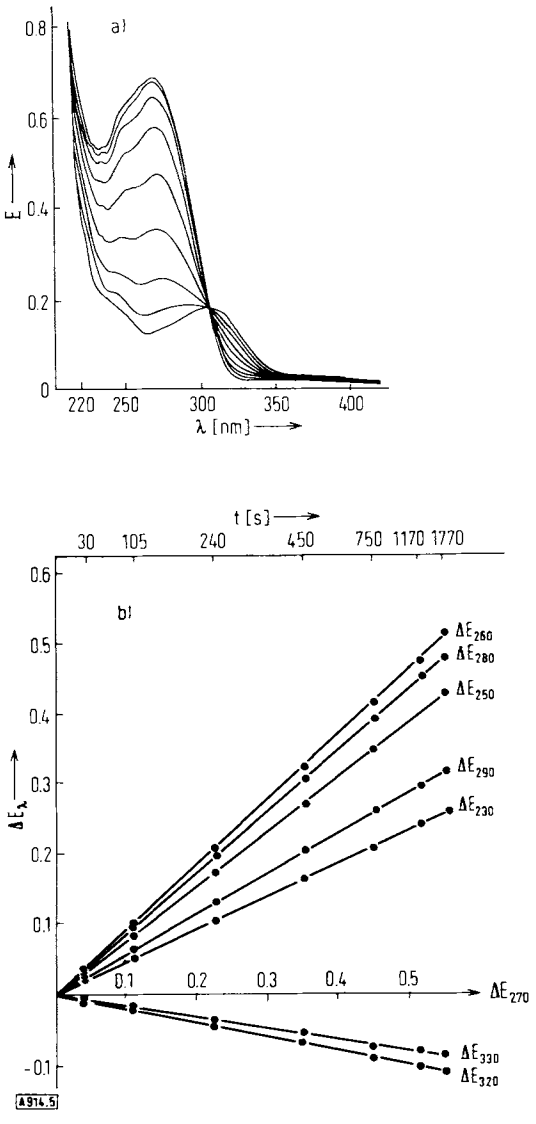


Fig. 5. The absorption spectra recorded at various times during a photochemical reaction (family of curves a) and the corresponding linear ED diagram (b).

the steady-state approximation[41] is fulfilled; *i.e.* if apart from reactant and product no further participant in its time-dependent change of concentration can be determined spectroscopically; if a reaction is accompanied by its reversed process or if parallel reactions of the same order occur.

Non-linear ED diagrams are due to spectroscopically complex photoreactions. The latter consequently are differentiated by the number of spectroscopically detectable partial reactions. Diagrams of quotients of extinction differences (EDQ diagrams) conveniently serve to distinguish between complex photoreactions[40]. In order to obtain these diagrams quotients $\Delta E_1/\Delta E_2$ and $\Delta E_3/\Delta E_2$ found after various reaction times are plotted against each other in rectangular coordinates. A resulting straight line signifies a linear EDQ diagram (see Fig. 6) which indicates the participation of two different partial reactions each of which can be recognized spectroscopically. If a curve arises, *i.e.* if one obtains a non-linear EDQ diagram, there are more than two spectroscopically detectable partial reactions.

Mention was made earlier of flash spectroscopy[20,21], which, with the aid of laser light, is preparing the way for an advance into the picosecond range and hence well into the range of molecular dynamics[42,43]. This technique can be used for the detection and identification of electronically excited species and of transients in their electronic ground state, as well as for the kinetic study of their decay processes[*].

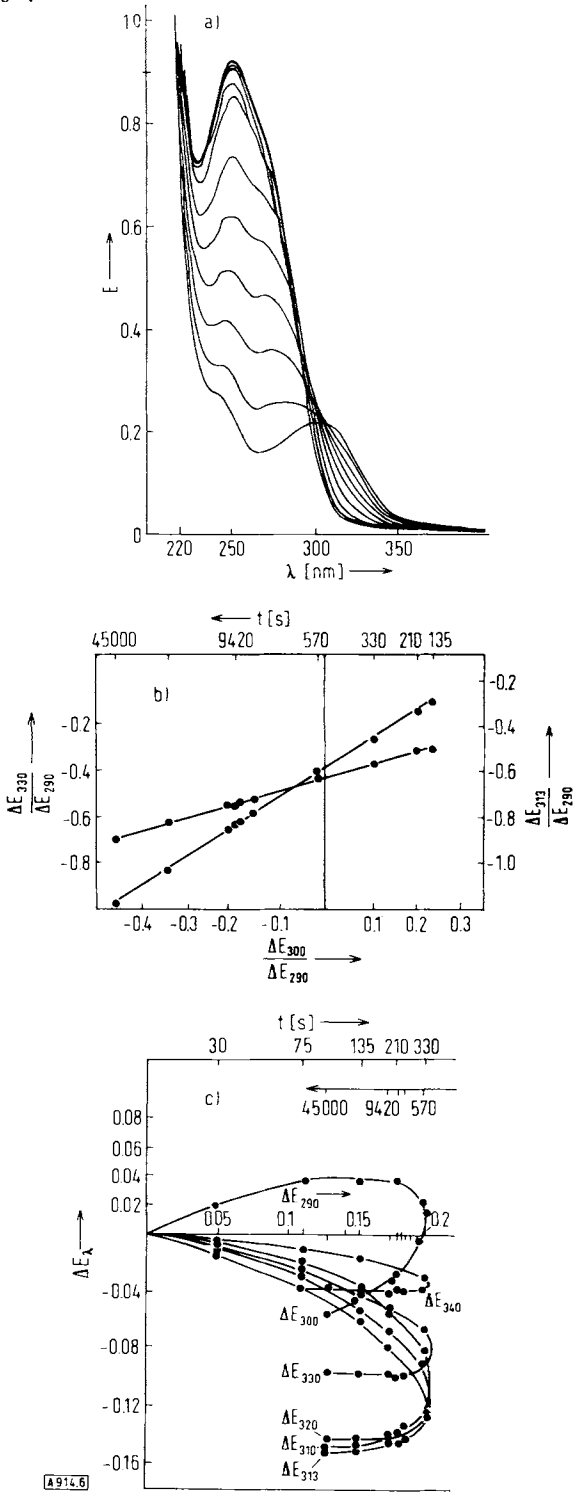


Fig. 6. The absorption spectra recorded at various times during a photochemical reaction (family of curves a), the corresponding non-linear ED diagram (c), and the corresponding linear EDQ diagram (b).

[*] In the following discussion of the chemistry of electronically excited cyclohexa-2,4-dienones, flash-spectroscopic studies, which have just begun, are not mentioned.

4. Thermally Reversible Light-Induced *cyclo/seco* Isomerization of Linearly Conjugated Cyclohexadienones to Dienylketenes

4.1. Introduction

When reference was made unspecifically in the past to cyclohexadienones on account of their photoreactivity, the compounds referred to were usually of the cross-conjugated type (C) (see Fig. 7). The careless manner in which these compounds were talked about arises from the extensive history of cyclohexa-2,5-dienones and is due to the role they have played in the renaissance of "organic photochemistry".



C L

A914.7

Fig. 7. The structurally isomeric cyclohexadienones: the cross-conjugated (C) cyclohexa-2,5-dienone and the linearly conjugated (L) cyclohexa-2,4-dienone.

Reports on the action of light on santonin date back to 1830[44]. The first investigations on the photoproducts of this sesquiterpene, which were completed toward the end of the 1950's[45-47], not only revealed their structure, but also considerably increased the confidence of chemists that with the aid of a sufficiently large number of cases of a reactant/product relationship it would be possible to find the underlying rules for light-induced reactions, just as had previously been accomplished in the investigation of reactions that do not require light.

The progress that has been achieved in the past 15 years can be seen in the growing use of photoreactions for specific structural transformations[*]. The photochemistry of linearly conjugated cyclohexadienones (L) (see Fig. 7), which was completely undeveloped at the beginning of this period, has caught up with the photochemistry of cross-conjugated cyclohexadienones as far as the variety of phenomena and the transparency of their interpretation are concerned.

4.2. Activation by Light Absorption, Deactivation by Competing Quenching Processes

The first question of general importance for an understanding of a light-induced reaction concerns the nature of the electronically excited reactant. For the sake of the discussion it may be assumed that the incident light has such a wavelength that the absorbing molecule passes—within about 10^{-15} seconds—from the ground state to the second excited singlet state. (see Fig. 8). Since only the relatively intense spin-allowed absorption (1) is considered here, the ground state of the molecule is, of course, also a singlet state (normal case for the compounds encountered in organic chemistry).

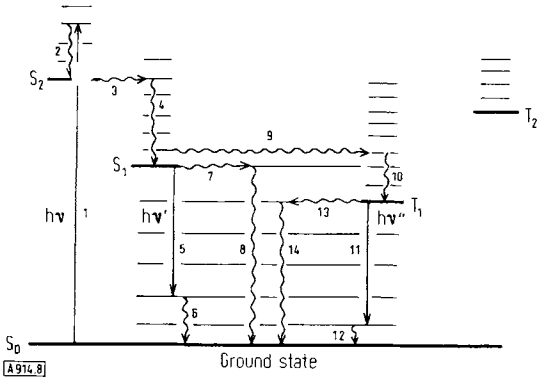


Fig. 8. Extended Jablonski diagram with radiationless transitions (wavy arrows) and transitions associated with radiation (straight arrows) between singlet (S) and triplet (T) states, such as is typical of organic compounds; for explanation of numbers see text.

Since the nuclear coordinates of a molecule, of course, do not change in the time interval mentioned (Franck-Condon principle), and since the various electronic states generally have different equilibrium conformations[10, 11], it is plausible that a higher vibrational level of the corresponding electronically excited state is reached in the general case. A chemical reaction can occur from this vibronic state if it is fast enough. Otherwise, or additionally, a Boltzmann energy distribution occurs over the vibrational levels (and the rotational levels, which are not considered here) of the first excited singlet state. This takes place by vibrational relaxation (Fig. 8, 2 and 4) and by an isoenergetic transition between two electronic states having the same multiplicity (3), which is known as an internal conversion[*].

The ground state and/or the triplet state can be reached from the zeroth vibrational level of the lowest excited singlet state. The initial state is restored by a combination of fluorescence emission (5) and vibrational relaxation (6) or of internal conversion (7) and vibrational relaxation (8). The triplet state is reached by a sequence of vibrational relaxation (10) and intersystem crossing (9), an isoenergetic transition between two electronic states with different multiplicities. If the molecule whose energy has been enriched by light absorption fails to enter into a chemical reaction from the singlet ladder, it often has a further opportunity to do so from the triplet sequence. If at this stage it does not use the routes of phosphorescence emission (11) and vibrational relaxation (12) or of radiationless deactivation (to be regarded in this case as a sequence of intersystem crossing (13) and vibrational relaxation (14)) leading back to the ground state, the triplet state can be quenched by a chemical reaction.

[*] The most outstanding example is the light-induced cycloisomerization of a *seco*-corrinoid metal complex to the *trans*-corrin complex in *Eschenmoser*'s corrin synthesis [48], which involves a hydrogen shift and proceeds extremely stereoselectively.

[*] The nature of the resulting photoproduct and the quantum yield in which it is formed may depend on the stage of the sequence of singlet or of triplet electronic or vibrational levels from which the reaction takes place [34, 49].

By analogy with the scheme of an extended Jablonski diagram (see Fig. 8)[*], therefore, for every compound undergoing a photochemical reaction there arises the fundamental question whether the decisive structural change takes place from an excited singlet state or from the relevant triplet state. Molecules in the two excited states differ in structure and reactivity from one another and from molecules in the ground state. It is therefore necessary, but by no means sufficient, to know the multiplicity.

4.3. π^*,π and π^*,n Excited States of Linearly Conjugated Cyclohexadienones

With the aid of the formal partial MO scheme (see Fig. 9) one attains a deeper understanding of the properties of an electronically excited linearly conjugated cyclohexa-2,4-dienone.

Figure 9 shows the π_3 and π_4^* MOs of the conjugated six-center system, which are occupied by electrons or unoccupied, respectively, in the ground state, as well as the orthogonal p orbital of the carbonyl oxygen atom, with the so-called nonbonding n electrons, which are in reality delocalized to a considerable degree[**].

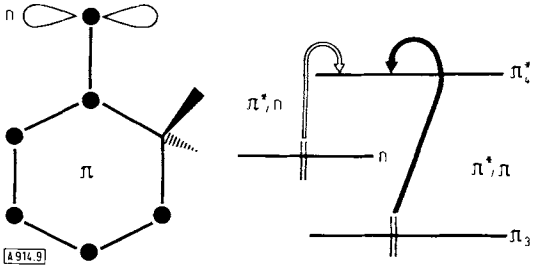


Fig. 9. Partial formal MO scheme of linearly conjugated cyclohexadienones with the two highest occupied MOs and the lowest unoccupied MO in the electronic ground state.

Electronic transitions not requiring much energy take place from the relatively high n and π_3 MOs to the lowest antibonding π_4^* MO. The π^*,n absorption[***] takes place in the gas phase at relatively long wavelengths; it is symmetry forbidden, and is consequently not very strong. On the other hand, the π^*,π absorption[***] which requires more energy under these conditions, is symmetry allowed, and is more intense by about two orders of magnitude. How do the absorption spectra appear in a concrete case?

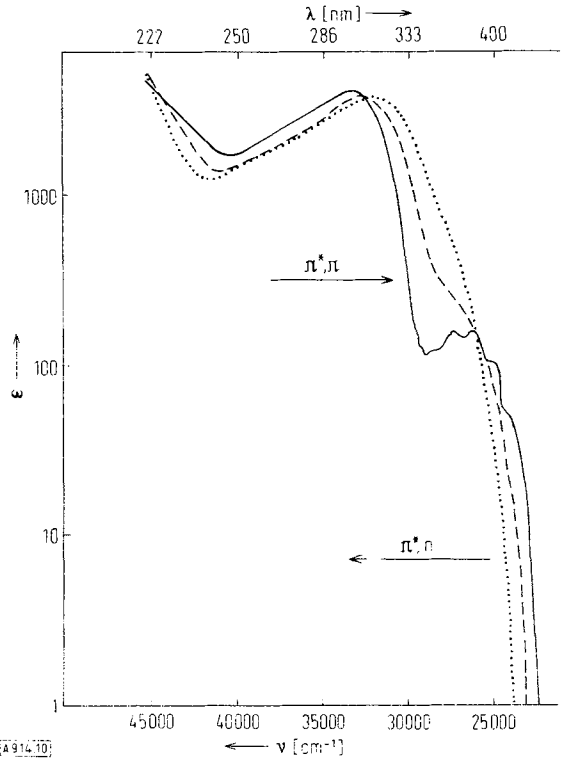


Fig. 10. Electronic absorption spectra of 6-phenyl-6-methylcyclohexa-2,4-dienone at room temperature in methylcyclohexane (———), ethanol (- - - -), and trifluoroethanol (·····).

Figure 10 shows the electronic spectra of 6-phenyl-6-methyl-cyclohexa-2,4-dienone in several solvents at room temperature. In the curve recorded in methylcyclohexane, two relatively long-wave absorption regions can clearly be distinguished. That at higher wavelengths is due to the π^*,n transition, as is shown not only by its energy but also by its low intensity and the characteristic vibrational fine structure. The relatively intense absorption region at lower wavelengths corresponds to the π^*,π transition.

This assignment is supported by the direction of the band shift observed when alcoholic solvents are used. On replacement of the weakly polar hydrocarbon by a strongly polar alcohol, which also acts as a proton donor in systems allowing hydrogen bonding, one observes the disappearance of the fine structure and a red shift of the π^*,π absorption region, as well as a blue shift of the π^*,n absorption region; these shifts may be sufficiently large to cause the two regions to coincide. A glance at a state diagram[*] (see Fig. 11) may help in the understanding of this solvent effect and in the consideration of its consequences.

If these opposing effects are so strong that they lead to leveling of the excited states, or possibly even to a reversal of their hierarchic order, the following question arises. Does the chemical reaction take place from the lowest

[*] The diagram contains no details concerning the various routes to or from electronically excited molecules [50]. In particular, "chemical quenching processes", which do not lead back to the reactant, are entirely absent. Similarly, biphotonic processes [51] and the direct interaction with other molecules (of the same or of a different kind) in spectral transitions [52], in the formation of electronically excited complexes [51, 53, 54], and in the transfer of electronic energy [55] have not been taken into account.

[**] The highest σMO of a ketone that is occupied by electrons in the electronic ground state corresponds to a mixture in which the main contribution is from the p orbital of the oxygen, with contributions from skeletal σ orbitals that are by no means negligible [56]. This delocalization is shown both by *ab initio* calculations [57] and by experimentally determined ionization potentials [58], and has already been taken into account in the interpretation of the photochemistry of formaldehyde [59, 60]; see also [61].

[***] For the discussion of the electronic spectra of organic compounds see [62, 63].

[*] Concerning the dependence of electronic spectra on the nature of the solvent used, see [52].

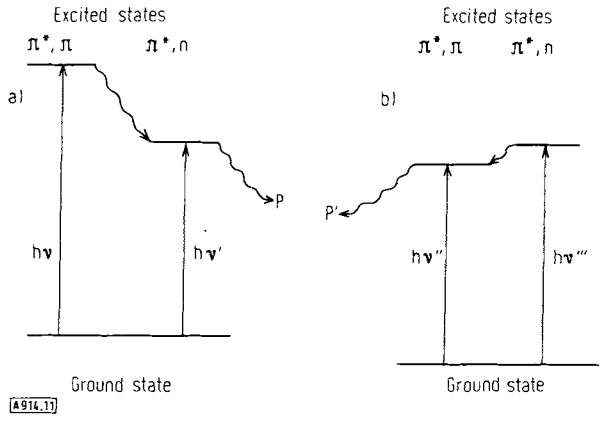


Fig. 11. State diagrams illustrating a medium-induced perturbation of the hierarchy of electronically excited states: a) unperturbed in the gas phase and in weakly polar saturated hydrocarbons; b) strongly perturbed, in alcoholic solvents.

excited state[*], irrespective of which excited state was initially reached on absorption of light, or do the nature and/or quantum yield of the photoproduct depend on the electronically and possibly on the vibrationally excited state that is reached directly on excitation by light? In the latter case irradiation conditions and medium effects would be product-determining variables, while in the former case the wavelength of the light that interacts with the dienone chromophore has no product-determining effect. In addition to knowing the multiplicity (singlet or triplet), therefore, one has to know the electronic configuration (π^*,n or π^*,π) of the initial spectroscopic state and of the photoreactive excited state, which are usually different.

4.4. Photoisomerization of Linearly Conjugated Cyclohexadienones to Dienylketenes

Under conditions favoring the π^*,n state as the lowest excited state, a linearly conjugated cyclohexa-2,4-dienone is converted into the derivative of a hexadienoic acid in the presence of a protonic nucleophile HX[64-66]. As indicated in our model (see Fig. 3), the reaction may be regarded as a primary photoisomerization of the *cyclo*-isomeric reactant to the *seco*-isomeric dienylketene. The transient undergoes

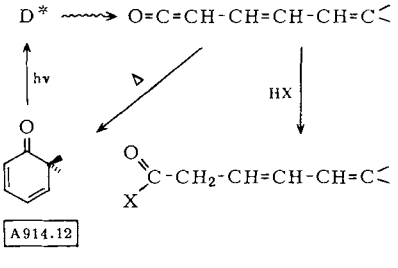


Fig. 12. Thermally reversible photoisomerization of a linearly conjugated cyclohexadienone to a dienylketene, which can in principle be trapped. Concrete example of the abstract scheme in Fig. 3.

[*] When we refer here to the lowest excited state, we are concerned, for the moment, only with the electronic configuration and not with the multiplicity.

secondary reaction with HX and/or recyclizes to form the original dienone (see Fig. 12).

Checking this proposed reaction course requires answering the following questions. What precisely is the isolable reaction product? Its constitution is in doubt, since 1,4 and/or 1,6 additions may occur alongside or instead of the 1,2 addition of a protonic nucleophile to a hypothetical dienylketene as outlined in the scheme (Fig. 12). Even if the constitution indicated proved to be correct, the stereochemistry and ultimately the conformation[*] would still remain to be determined. Stereoisomers are possible with respect to the disubstituted CC double bond, and also with respect to the trisubstituted CC double bond if the substituents at the terminal C atom are different.

Does the postulated transient actually occur? If so, it is necessary to determine its complexity, the stereochemistry of the individual components, and their thermal and/or light-induced recyclization to the original reactant. If these details were known, the uncertainty surrounding the stereoselectivity of the postulated *cyclo/seco* isomerization would disappear[**]. Finally, the multiplicity (singlet or triplet) and the postulated π^*,n electronic configuration of the photoreactive excited state must be determined.

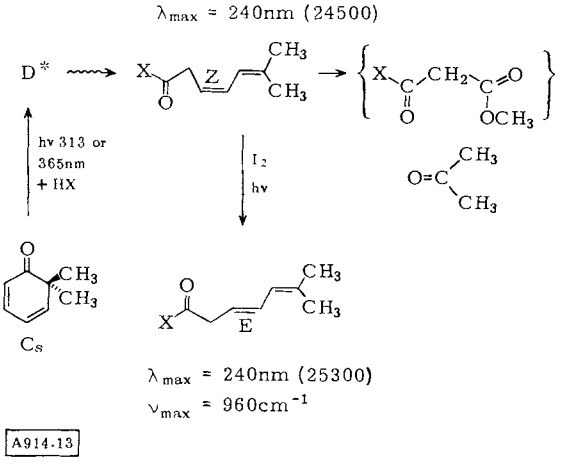


Fig. 13. Information on the constitution and stereochemistry of the irradiation product obtained from 6,6-dimethylcyclohexa-2,4-dienone at room temperature and in the presence of a protonic nucleophile HX.

The first subject to be investigated was 6,6-dimethylcyclohexa-2,4-dienone, which belongs to the symmetry point group C_s. This compound was irradiated in ether solution and in the presence of cyclohexylamine as a protonic nucleophile. Irrespective of whether 365 nm or 313 nm light is used one and the same product is obtained in practically quantitative yield. The ozonolysis products confirm the constitution indicated (see Fig. 13). The 3*Z*

[*] Stereochemical usage is so diverse (see [67]) that it is always necessary to define the term "conformation". In this article the conformation of a molecule denotes the arrangement of its atoms in space in terms of bond lengths, bond angles, and dihedral angles. Stereoisomerism with respect to a CC double bond is specified according to IUPAC Rule E 2.21 [67].

[**] As far as we know, only three articles have expressed an opinion on this point. The findings were interpreted in two cases [68, 69] as indicating extreme stereoselectivity, and in the third case [70] as indicating partial selectivity.

arrangement is deduced from the absence of the IR band at 960 cm^{-1} that is characteristic of 1,2-disubstituted ethylene derivatives having the *E* orientation, and which is observed on the other hand for the iodine isomerization product. UV data given for both stereoisomers indicate that these are of no value for a reliable stereochemical assignment. If one of the two methyl groups is replaced by a different substituent one obtains a more promising source of information.

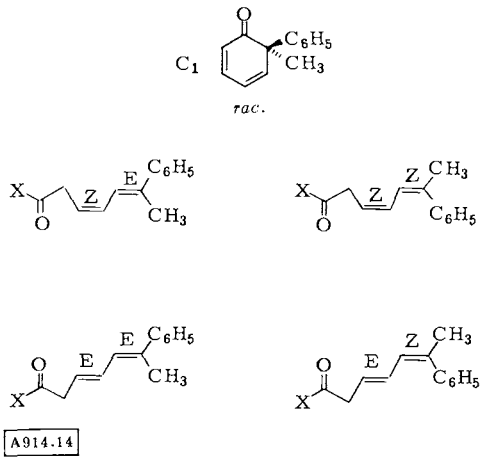


Fig. 14. 6-Phenyl-6-methylcyclohexa-2,4-dienone and the complete set of possible stereoisomers of derivatives of 6-phenylhepta-3,5-dienoic acid; $X = C_6H_{11}NH$.

6-Phenyl-6-methylcyclohexa-2,4-dienone is chiral; consequently, the stereochemistry of potential ring cleavage products with respect to both the CC double bonds is uncertain *a priori*. The complete set of stereoisomers of the constitution to be expected by analogy is shown in Figure 14. To ensure an unequivocal reaction and product

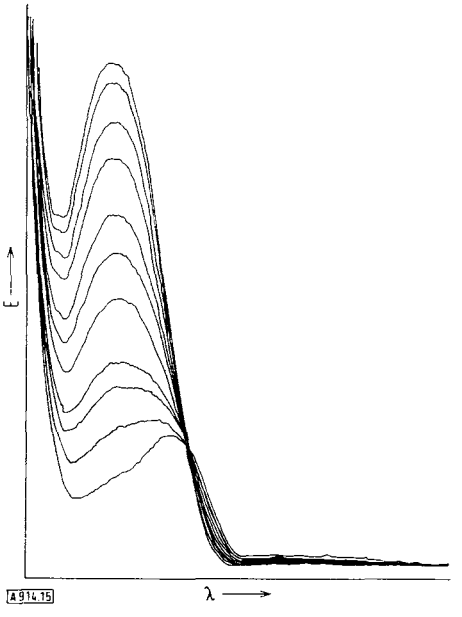


Fig. 15. The electronic absorption spectra recorded at various times for the UV irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone with 365 nm light at room temperature in the presence of cyclohexylamine in ether (isosbestic point at 306.5 nm, $\varepsilon = 3700$).

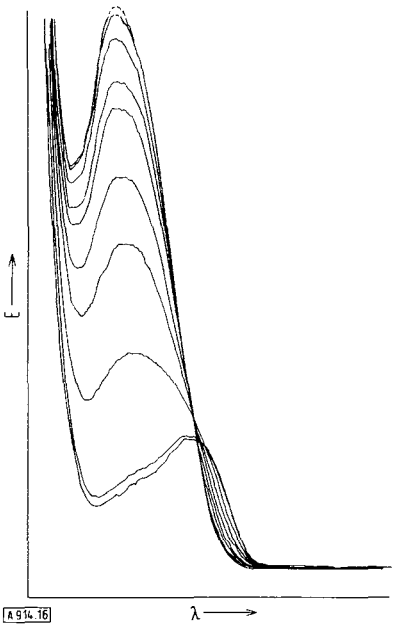


Fig. 16. The electronic absorption spectra recorded at various times for the UV irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone with 313 nm light at room temperature in the presence of cyclohexylamine in ether.

analysis for the UV irradiation in the presence of cyclohexylamine, all the stereoisomeric cyclohexylamides ($X = C_6H_{11}NH$ in Fig. 14) were synthesized by conventional methods and their stereochemistry was determined[71, 72]. Before considering the identity of the photo-

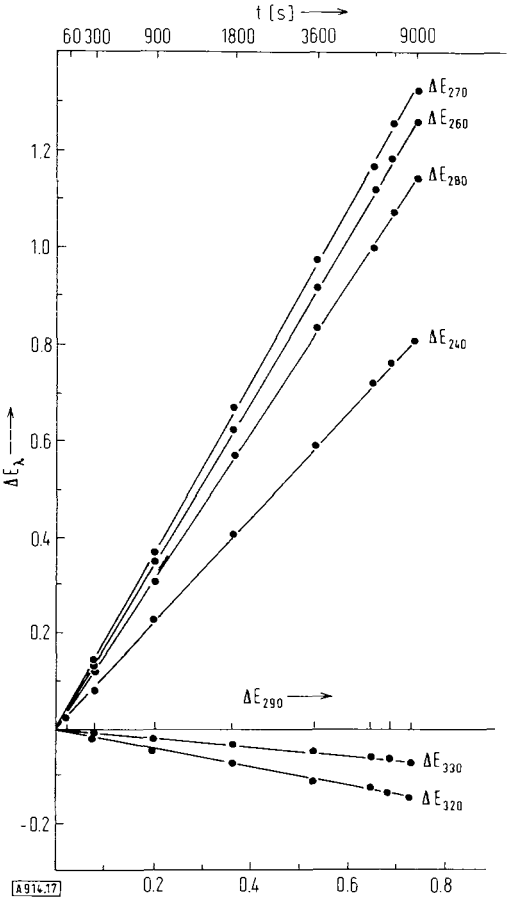


Fig 17. Linear ED diagram for the family of curves in Fig 15.

product from 6-phenyl-6-methylcyclohexa-2,4-dienone, we shall first discuss spectroscopic information on the kinetics of the light-induced ring cleavage.

When a solution of 6-phenyl-6-methylcyclohexa-2,4-dienone in methylcyclohexane/isopentane to which cyclohexylamine has been added[70] is irradiated with 365 nm light, one obtains a family of curves (Fig. 15) that intersect at an isosbestic point having the indicated characteristics. The picture changes when 313 nm light is used instead; no isosbestic point is now found (Fig. 16). The difference between the two figures may not be very impressive; it becomes more distinct and instructive when one makes use of the ED and EDQ diagrams mentioned earlier (see Figs. 5 and 6).

The family of curves having an isosbestic point (Fig. 15) is associated with the linear ED diagram of Figure 17. Irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone with 365 nm light in the presence of cyclohexylamine thus leads to a spectroscopically simple photoreaction. The conditions of the steady state are satisfied; apart from reactant and product, no other reaction participant can be detected spectroscopically.

The nonlinear ED diagram of Figure 18 was found for the irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone with 313 nm light in the presence of cyclohexylamine, and corresponds to the family of curves with no isosbestic point (Fig. 16). Since this is a spectroscopically complex photoreaction, the number of spectroscopically detectable

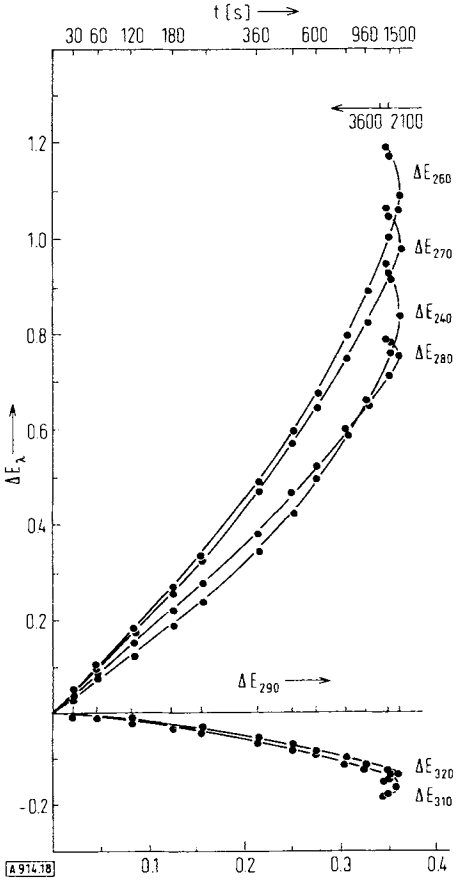


Fig. 18. Nonlinear ED diagram for the family of curves in Fig. 16.

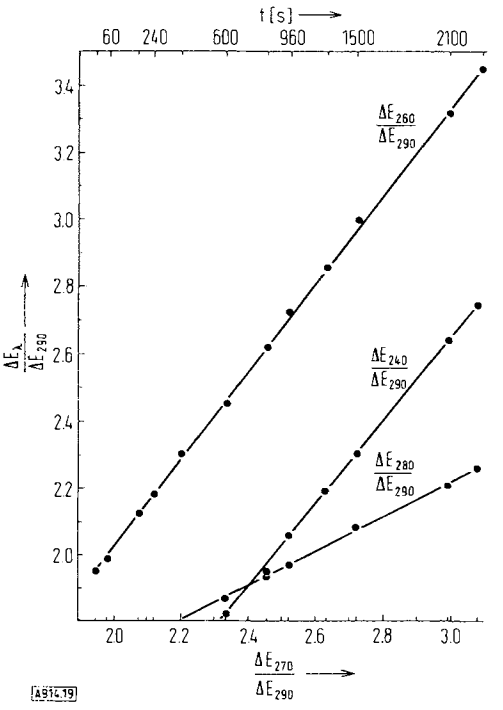


Fig. 19. Linear EDQ diagram for the family of curves in Fig. 16.

reaction steps remains to be established. The linear EDQ diagram in Figure 19 shows that two different reaction steps can now be detected spectroscopically. The result of the reaction analysis is supplemented by that of the product analysis.

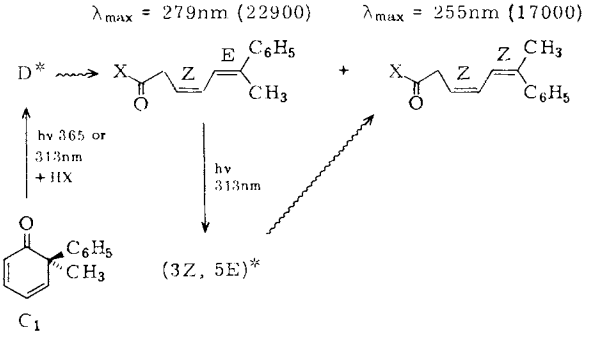


Fig. 20. Information on the constitution, stereochemistry, and wavelength dependence of the irradiation product obtained from 6-phenyl-6-methylcyclohexa-2,4-dienone at room temperature and in the presence of protonic nucleophiles.

Irradiation of the 2,4-dienone in question with 365 nm light[70] leads, by a reaction that has been shown to be spectroscopically simple, to a mixed product; among its components, the stereoisomers with *Z* orientation of the 3,4 double bond occur in a ratio of 1:1.8 (see Fig. 20). Irradiation with 313 nm light, on the other hand, leads in a spectroscopically complex reaction to a single product with 3*Z*, 5*Z* arrangement of the CC double bonds. It seems reasonable to assume that in the product, which is primarily binary in both cases, the component that absorbs at longer wavelengths is converted by secondary photoiso-

merization into the component that absorbs at shorter wavelengths by 313 nm light, but not by 365 nm light. This assumption can be confirmed by separate investigations on the two stereoisomers.

What do we know about the dienylketene transient? Under normal conditions it cannot be detected by UV, IR, or NMR spectroscopy in any of the cases investigated, even in the absence of protonic nucleophiles. However, this negative result simply means that the dienylketene is not present in measurable concentrations, a fact that could well be explained by the assumed ability to recyclize (see Fig. 12). If the ring opening of linearly conjugated cyclohexadienones still takes place at low temperatures, low-temperature photolysis offers prospects for the conservation of the potential transient, and low-temperature spectroscopy for its detection and identification.

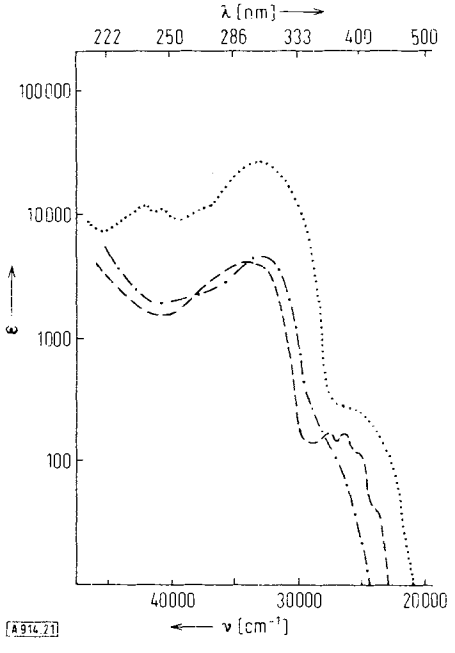


Fig. 21. Detection of the formation of a photoproduct from 6-phenyl-6-methylcyclohexa-2,4-dienone at −189 °C in methylcyclohexane/isopentane (1 : 4) with 365 nm light by low-temperature electronic spectroscopy. (– – –) spectrum of the reactant at room temperature; (–·–·–) spectrum of the reactant at −189 °C; (·····) spectrum of the photoproduct at −189 °C.

Figure 21 shows the electronic absorption spectrum of 6-phenyl-6-methylcyclohexa-2,4-dienone in methylcyclohexane/isopentane at −189 °C, as well as the room-temperature spectrum. A comparison of the spectra shows that lowering the temperature in the low-polarity medium is equivalent in its effect to the use of ethanol instead of saturated hydrocarbons at room temperature (see Fig. 10)[*].

Exposure of the glass specimen to 365 nm light[74] causes a spectroscopically detectable reaction, at the end of which the third absorption curve in Figure 21 is found.

[*] It is know [73] that lowering the temperature leads to an increase in the density and in the dispersion forces of the system (red shift) and to a decrease in the Boltzmann distribution of higher vibrational levels (blue shift).

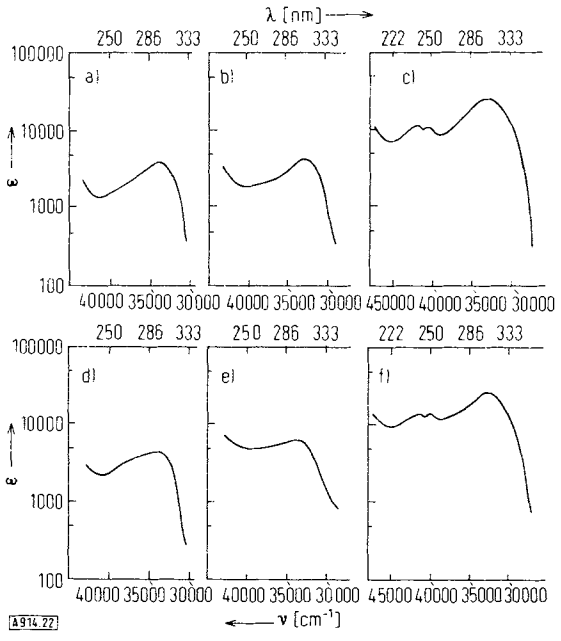


Fig 22. Detection of the thermally induced regeneration of 6-phenyl-6-methylcyclohexa-2,4-dienone from the corresponding photoproduct (which is kinetically stable at −189 °C) in methylcyclohexane/isopentane (1 : 4) by electronic spectroscopy; for explanation of the partial spectra see text.

Figure 22 shows parts of the spectra (a) at room temperature, (b) at −189 °C, and (c) after irradiation at −189 °C. If the irradiation product is then warmed to room temperature one obtains d, and subsequent recooling to −189 °C leads to curve e, which changes into curve f on renewed irradiation of the sample. This indicates formation of a photoproduct that is kinetically stable at low temperature, but reverts almost quantitatively[*] into the original reactant at room temperature.

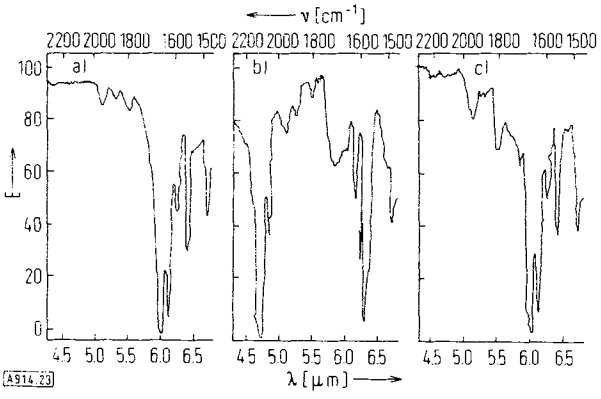


Fig. 23. Detection of the ketenic nature and of the thermally reversible formation of the photoproduct by low-temperature IR spectroscopy; for explanation of the partial spectra see text.

Following the reaction by low-temperature IR spectroscopy[74] indicates that the photoproduct is a ketene. The partial room-temperature IR spectrum of 6-phenyl-6-methylcyclohexa-2,4-dienone in chloroform shows the

[*] Comparison of extinctions shows 92% reversion to the original reactant.

absorption of the conjugated unsaturated carbonyl system (Fig. 23a). After cooling to −63 °C and exposure to light from which wavelengths below 340 nm have been filtered one obtains the partial spectrum b. The carbonyl band has at least largely disappeared, and a new absorption characteristic of the ketene group appears at 2120 cm^{-1}. The initial situation is substantially restored (c) if the irradiated sample is warmed to room temperature.

After the observation that a *seco*-isomeric dienylketene is related to the *cyclo*-isomeric cyclohexa-2,4-dienone by thermally reversible photoisomerization[*], it should be remembered that two ring cleavage products are formed together on irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone with 365 nm light in the presence of a protonic nucleophile (see Fig. 20). The simplest interpretation would of course be that these two components of the product have two stereoisomeric dienylketenes as precursors. The spectra discussed so far give no information on this point; however, such information is provided by the NMR spectra recorded at about −60 °C in deuteriochloroform[74].

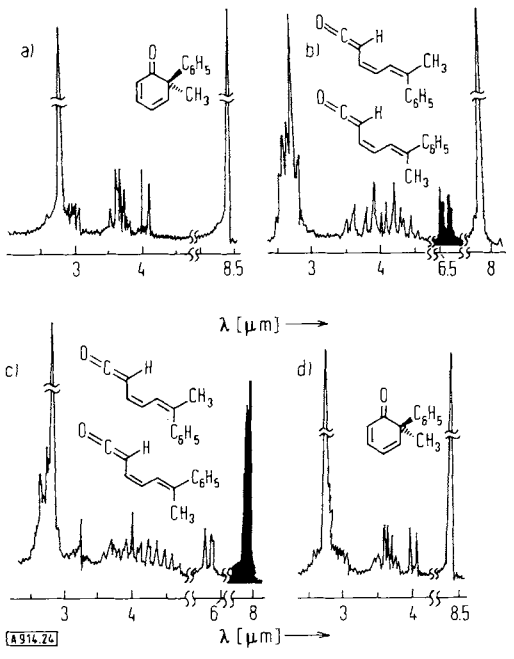


Fig. 24. Detection of the existence and of the thermally induced *seco/cyclo* isomerization of two stereoisomeric dienylketenes as photoproducts from 6-phenyl-6-methylcyclohexa-2,4-dienone by low-temperature NMR spectroscopy; for explanation of the partial spectra see text.

In addition to the proton resonance signals of the reactant at room temperature (a), Figure 24 shows the absorption of the photoproduct obtained at a low temperature (b). The two overlapping doublets[**] observed in the aldoketene proton region constitute evidence in favor of a mixture of two stereoisomers. On the other hand, the presence of only one methyl proton singlet contradicts the above conclusion, unless this singlet occurs by accidental coincidence of two signals. Justification of the latter assumption is provided by the spectrum obtained in the presence of 25% of deuteriobenzene (c). While the two doublets of the aldoketene protons have now moved closer together, the methyl proton signal is clearly split. In this case too, the initial spectrum is restored when the irradiated solution is warmed to room temperature (d).

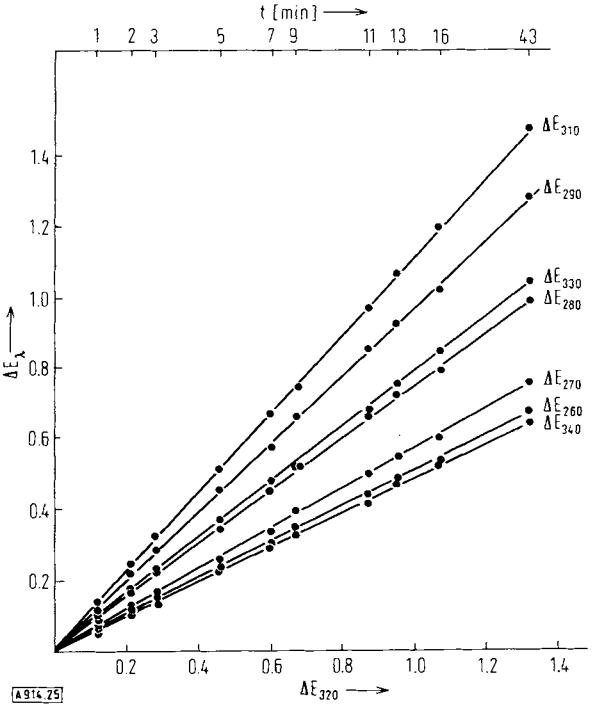


Fig. 25. Linear ED diagram corresponding to the conditions of the low-temperature NMR spectroscopic measurements (see Fig. 24).

The linear ED diagram (see Fig. 25) corresponding to the conditions of the low-temperature NMR measurements rules out the possibility that the binary transient was formed by subsequent photoisomerization of a single original dienylketene.

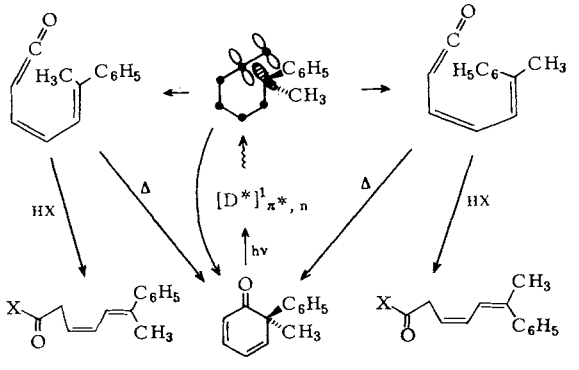


Fig. 26. Interpretation of the results of the structure-oriented product and transient analysis and of the formal kinetic analysis of the reaction course for the UV irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone.

[*] Following our report that we had detected the thermally reversible photoisomerization of linearly conjugated cyclohexadienones to dienylketenes by low-temperature UV and IR spectroscopy [75], similar investigations were reported from other laboratories: for UV spectroscopic studies see [69, 76], and for IR studies see [76—79].

[**] One doublet is shown *e.g.* by the stereochemically less complex dienylketene from 6,6-dimethylcyclohexa-2,4-dienone. A report on NMR spectra of aldoketenes at −80 °C was recently published [80]. For a discussion of the NMR spectra of cyclohexa-2,4-dienones see [81].

The pieces of information obtained fit together to give the model case of a thermally reversible photoisomerization system (see Fig. 26). In the presence of cyclohexylamine, 6-phenyl-6-methylcyclohexa-2,4-dienone is converted by 365 nm light in a partly stereoselective reaction into a mixture of two stereoisomeric amides. These are derived from the two corresponding dienylketenes, which are formed side by side during ring cleavage.

Since the components of the transient undergo unimolecular recyclization to the reactant[*] and/or bimolecular reaction to form the acid derivatives, the product composition is expected to be influenced by the nucleophilic strength and by the concentration of the addend HX[83]. Complete suppression of thermal recyclization of the two dienylketenes requires adequate nucleophilicity and corresponding minimum concentration of HX.

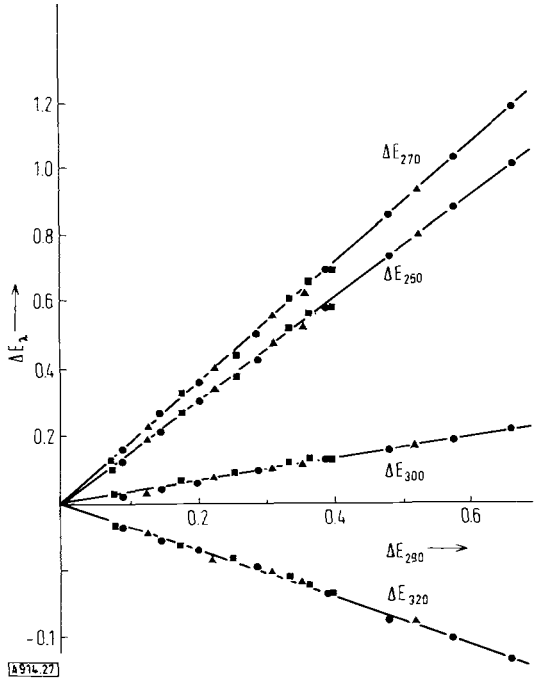


Fig. 27. Linear ED diagram with concentration-invariant lines for the irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone in ether/isopentane (1:1) containing cyclohexylamine at 25 °C with 365 nm light. Cyclohexylamine content: 0.0730 mol/l; • 0.135 mol/l; 0.173 mol/l.

The linear ED diagram of the light-induced amide formation in ether/isopentane at 25 °C (see Fig. 27) shows that the experimental points obtained at various concentrations and for a given wavelength lie on the same straight line in the concentration range indicated. Since the components of the reaction product differ in their absorption at the various wavelengths (see Fig. 20), failure of the straight lines to vary with concentration of HX means that the product composition is independent of this concentration. In the present case, therefore, the concentration exceeds the critical limit, which is specific for each nucleophile, and above which every dienylketene molecule is converted into the amide.

With the much weaker nucleophile ethanol, the slope of the straight lines varies with the nucleophile concentration in the same concentration range as in the previous case (see Fig. 28). The gas-chromatographic study confirms that the relative weights of the ester components in the reaction product are partly determined by the ethanol concentration.

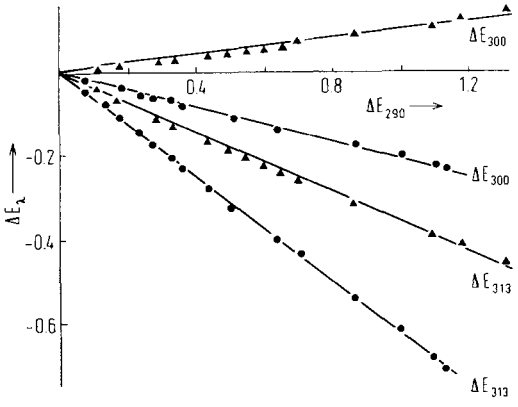


Fig. 28. Linear ED diagram with concentration-dependent lines for the irradiation of 6-phenyl-6-methylcyclohexa-2,4-dienone in ether/isopentane (1:1) containing ethanol at 25 °C with 365 nm light. Ethanol content: ▲ 0.0805 mol/l; • 0.171 mol/l.

Under conditions ensuring conversion of every transient molecule into the acid derivative, the quantum yield, both for 365 nm and for 313 nm light (!), reaches a maximum value of 0.55[83]. This value is reached at relatively low concentrations with cyclohexylamine, but only at very high concentrations with ethanol. What happens to the other 45% of the energy absorbed, which is not available for ring cleavage in any circumstances?

Since the electronically excited dienone does not emit either at room temperature or at the boiling point of nitrogen[84], the only possible explanation for the deficit is radiationless deactivation. This might, in part, be accounted for in a structurally reasonable manner, the electronically excited ketone undergoing a so-called α-cleavage[*] and the resulting bifunctional species being converted partly into the dienylketenes and partly back into the dienone. An optically active reactant, the racemization of which could provide the answer, was hitherto unavailable. The existence of the bifunctional species would in any case be consistent with the fact that the two stereoisomeric dienylketenes occur together.

What are the electronic configuration and the multiplicity of the photoreactive state of the light-induced *cyclo/seco* isomerization? Does it possess π*,n character, as assumed, and is it singlet and/or triplet in nature? The absence of any emission[84] rules out a source of information that

[*] The half-life for the dienylketene corresponding to 6-phenyl-6-methylcyclohexa-2,4-dienone is 95 min at −15.4 °C; for further data see [74]. Alkyl substituents of the dienone chromophore decrease the half-life of the corresponding dienylketenes while substituents with n or π electrons at C-6 increase it [82] (see also [76]).

[*] π*,n-Excited ketones in which at least one of the two C atoms adjacent to the carbonyl chromophore carries four ligands generally undergo homolysis of the bond between the C atom specified and that of the carbonyl group; see also "Norrish type I cleavage" *e.g.* in [85]. Concerning the problem of "biradicals" see [86—89].

would otherwise be important. The photochemical formation of the acid derivative cannot be sensitized by triplet-excited benzophenone (or by derivatives of benzophenone)[90][*], and piperylene, a common ketone triplet quencher[94–96], has practically no effect on the quantum yield[83]; the former observation provides no clear-cut answer to the questions raised, but the second definitely rules out the participation of relatively long-lived dienone triplets.

Finally, the fact that the molecular environment affects not only the shape of the electronic absorption spectra of the cyclohexa-2,4-dienones (see Section 4.3), but also the nature of the resulting photoproduct (see Section 5), can be used as a pointer to the electronic configuration of the photoreactive state involved. In a medium favoring the spectroscopic π^*,n excited state energetically over the π^*,π excited state, the light-induced *cyclo/seco* isomerization discussed leads, irrespective of the wavelength of the incident light (365 or 313 nm), to the dienylketene transient. On the other hand, under conditions that decrease the difference between the spectroscopic excited states, or even reverse their order, a reaction type that has not yet been mentioned occurs. This is the photoisomerization of linearly conjugated cyclohexadienones to bicyclo[3.1.0]hexenones (see Fig. 29)[79, 97–104][**].

Though a correlation of spectroscopic properties of the reactant with the nature of the photoproduct is problematic, since the spectroscopic excited states reached on absorption are not necessarily the same as the product-determining photoreactive excited states, the characteristics of the reactions occurring indicate a specific electronic configuration of the photoreactive state in question. As was mentioned earlier, α cleavage is characteristic of π^*,n excited ketones with at least one α-C atom having a coordination number of 4; the intramolecular cycloaddition to form bicyclo[3.1.0]hexenones is typical of π^*,π excited linearly conjugated cyclohexadienones[***].

5. Photoisomerization of Linearly Conjugated Cyclohexadienones to Bicyclo[3.1.0]hexenones

Hart et al.[97–104] gave a powerful boost to the chemistry of electronically excited cyclohexa-2,4-dienones with their observation that, under certain conditions, bicyclo[3.1.0]-hexenones are photoproducts of linearly conjugated cyclohexadienones. The explanation[107] that the direct photoisomerization takes place from the π^*,π excited reactant (see Fig. 29) raises the question of the conditions under which the photoreactive π^*,π excited state can be reached. The solvent dependence of the absorption spectra (see Section 4.3) suggests the use of an alcoholic solvent; experience shows that trifluoroethanol should be particularly suitable as a polar solvent, while silica gel should prove useful as a polar adsorbent[*][107].

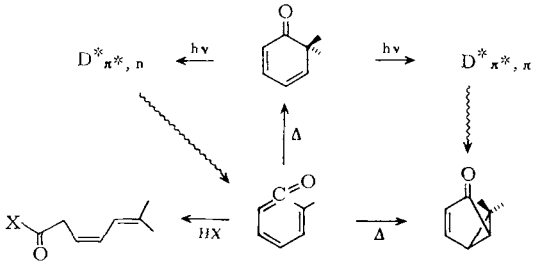


Fig. 29. The different paths of the photoisomerization of linearly conjugated cyclohexadienones. Elaboration of the scheme in Fig. 12.

The effectiveness of these perturbing factors on the relative positions of the π^*,π and π^*,n excited states (see Fig. 11) requires that in the unperturbed case (in the gas phase or in weakly polar hydrocarbons) the two excited states are not so far apart as to rule out the necessary regrouping. The difference between the π^*,π and π^*,n absorption regions depends on the substitution of the dienone chromophore. Figure 30 shows the electronic spectra of three linearly conjugated cyclohexadienones, measured in *n*-heptane at room temperature. The bathochromic shift

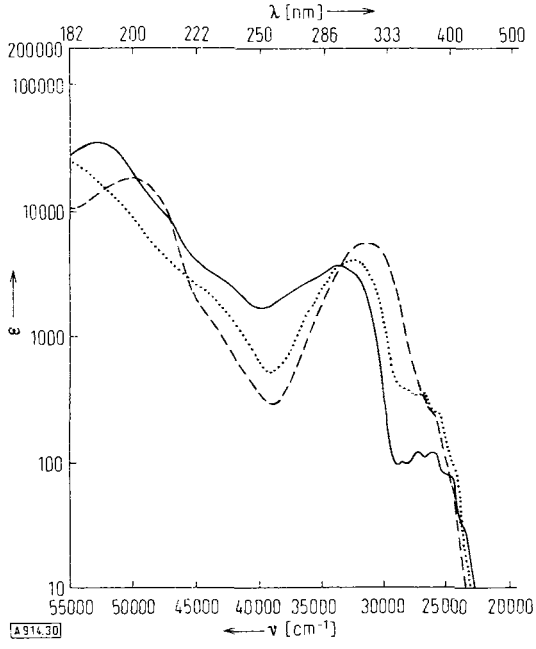


Fig. 30. Electronic absorption spectra of several cyclohexa-2,4-dienones at room temperature in *n*-heptane; 6-phenyl-6-methylcyclohexa-2,4-dienone (———); 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dienone (·····), 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dienone (– – –).

[*] For a discussion of sensitized photoreactions see [91–93].

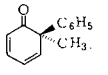
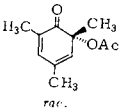
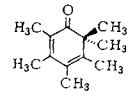
[**] Detailed investigations (see Section 5) show that bicyclo[3.1.0]-hexenones are formed directly from π^*,π-excited cyclohexa-2,4-dienones, and under certain conditions they are also formed from dienylketenes by intramolecular cycloaddition. Both isomerizations of the *seco* isomer, *i.e.* the recyclization to the linearly conjugated cyclohexadienone are symmetry allowed as one-step reactions in the electronic ground state.

[***] This is shown by linearly conjugated methylenecyclohexadienes, where π^*,n excitation is of course impossible; these compounds photoisomerize stereospecifically to form conjugated methylenebicyclo[3.1.0]hexene derivatives [105, 106].

[*] Concerning the spectroscopy and photochemistry of adsorbed organic compounds see [108].

Table 1. Summary of conditions and products of the photoreactions of cyclohexa-2,4-dienones.
Reaction conditions:
1. Irradiation at room temperature without (additional) protonic nucleophile
2. Irradiation at room temperature with (additional) protonic nucleophile
3. Low-temperature spectroscopic information on the transient obtained at low temperatures
4. Spectroscopic or gas-chromatographic information on the photoproduct obtained by irradiation at low temperatures followed by warming to room temperature.

Photoproducts:
A: Cyclohexa-2,4-dienone
B: Bicyclo[3.1.0]hexenone
C: Cyclohexa-2,5-dienone
D: Dienylketene
E: Ester of carboxylic acid
F: *N*-Cyclohexylamide of carboxylic acid.

Cyclohexa-2,4-dienone	Photoproduct obtained under particular reaction conditions Φ = quantum yield	Medium
 *rac.*	1. A; Φ = 0.014 [a] 2. (Cyclohexylamine): two F [70], Φ = 0.58 (365 nm, 25 °C) [b] 3. Two D [74] 4. A (92%); see Figs. 22–24	MCl [c] or EI [d]
	1. Two E; Φ = 0.58 (ethanol, 365 nm, 25 °C) [e]; Φ = 0.55 (ethanol, 313 nm, 25 °C) [e] 3. Two D [39] 4. Two E [39]	CH_3OH, C_2H_5OH or EPA [f]
	1. Two E [109]	CF_3CH_2OH
 *rac.*	1. A; Φ = 0.018 [a, g] 2. (Cyclohexylamine): two F [109] 3. Two D [35, 109] 4. A [35]	MCl [c] or EI [d]
	1. Three E; Φ = 0.21 (methanol; 313 nm; 25 °C) [109] 2. (Cyclohexylamine) = two F [h]; Φ = 0.53 (365 nm; 20 °C) [109] 3. Two D [109] 4. A + three E [109]	CH_3OH, C_2H_5OH or EPA [f]
	1. A + B + C [109]; Φ = 0.32 (313 nm; 20 °C); Φ = 0.32 (365 nm; 20 °C) [109] 2. (Cyclohexylamine): A + B + two F + C [109]; Φ = 0.42 (313 nm; 20 °C); Φ = 0.40 (365 nm; 20 °C) [109] 3. Two D + B + C [109] 4. A + B + C [109]	CF_3CH_2OH
	1. A [109], Φ = 0.007 (EI [d]; 365 nm; 25 °C) [a] 2. (Cyclohexylamine): F [79] 3. D [79, 82] 4. A + E [79, 82]	MCl [c] or EI [d]
	1. A + B [79, 109]; Φ = 0.41 (ethanol; 313 nm; 25 °C) [109]	CH_3OH or C_2H_5OH

[a] Slow, irreversible degradation of the reactant.
[b] 0.77 mol/l of cyclohexylamine.
[c] Methylcyclohexane/isopentane = 4:1.
[d] Ether/isopentane = 1:1.
[e] The quantum yield, which is described as independent of the wavelength [34], is slightly influenced by the energy of the incident light.
[f] Ether/isopentane/ethanol = 5:5:2.
[g] On prolonged exposure to light in the absence of protonic nucleophiles, or in the presence of protonic nucleophiles whose concentration and/or nucleophilic strength are too low to allow complete trapping of the dienylketene transients, phenols are formed [64]. Another possible reaction of electronically excited cyclohexa-2,4-dienones, which was observed *e.g.* for 1,1-disubstituted 2(1*H*)-naphthalenones, is cycloaddition to give dimeric cyclobutane derivatives [66].
[h] The two stereoisomeric *N*-cyclohexylamides are formed with an extremely unequal weight distribution [109].

of the π^*,π absorption region due to methyl substituents and the resulting shift of the π^*,π excited state toward the π^*,n state are clearly to be seen. Table 1 shows the effect of varying conditions on the photoproducts from these three cyclohexa-2,4-dienones[109, 110].

6-Phenyl-6-methylcyclohexa-2,4-dienone does not give the corresponding stereoisomeric bicyclo[3.1.0]hexenones under any of these conditions. 6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dienone photoisomerizes either to dienylketenes (for detection by low-temperature spectroscopy see[35]) and their further reaction products (original reactant or acid derivative; see footnote [g] in the Table) or directly to the corresponding bicyclo[3.1.0]hexenone derivatives. Under nearly all the conditions indicated, 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dienone gives the bicyclo[3.1.0]hexenone, irrespective of whether the dienylketene occurs as an intermediate or not (for detection of the transient by low-temperature spectroscopy see Figs. 31 and 32, and[79]).

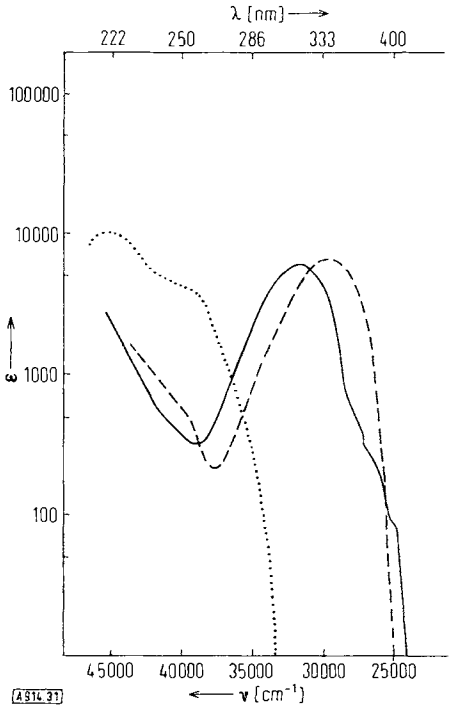


Fig. 31. Detection of the formation of a photoproduct from 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dienone at −189 °C in methylcyclohexane/isopentane (1:4) with 365 nm light by low-temperature electronic spectroscopy. (———) spectrum of the reactant at room temperature, (– – –) spectrum of the reactant at −189 °C, (·····) spectrum of the photoproduct.

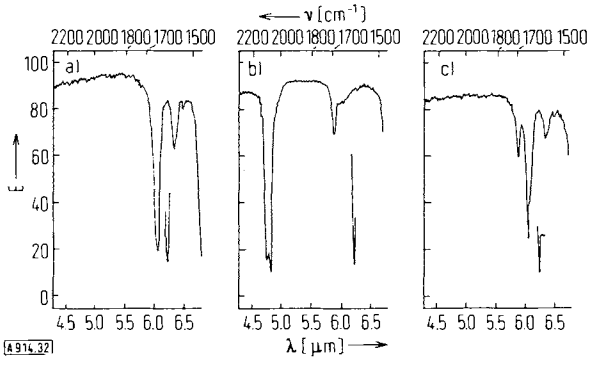


Fig. 32. Detection of the ketenic nature of the photoproduct from 2,3,4,5,6,6-hexamethylcyclohexa-2,4-dienone (which is kinetically unstable at room temperature) by low-temperature IR spectroscopy. a) Partial spectrum of the reactant at room temperature in paraffin; b) after irradiation with light of wavelengths >340 nm at −155 °C; c) after subsequent warming to room temperature.

Since bicyclo[3.1.0]hexenones can be formed directly from π^*,π excited cyclohexa-2,4-dienones and/or from π^*,n excited cyclohexa-2,4-dienones *via* intermediate dienylketenes (see Fig. 29), the nature of the product isolated is not a reliable guide to its mode of formation. However, a definite answer to the question whether dienylketenes occur as short-lived transients in the photoisomerization of linearly conjugated cyclohexadienones can be obtained by low-temperature spectroscopy.

I am indebted to Prof. Dr. H. H. Perkampus, Dr. B. Bronstert, P. Michaelis, Dr. G. Prescher, Dr. D. Egert, Dr. M. Hintzmann, Dr. P. Jürges, A. Syldatk, K. Schmieder, Dr. U. Krüger, and H. Appelt for suggestions and active assistance. The investigations were generously supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie and assisted by research grants from the State of Lower Saxony. B. B., D. E., P. J., and K. Sch. were temporarily stipendiaries of Schering AG. I am very grateful to the institutions mentioned.

Received: December 23, 1971 [A 914 IE]
German version: Angew. Chem. *83*, 1157 (1972)
Translated by Express Translation Service, London

[1] *G. S. Hammond*, Pure Appl. Chem. *22*, 3 (1970).

[2] *G. S. Hammond* and *R. Nyholm*, J. Chem. Educ. *48*, 6 (1971).

[3] *G. S. Hammond*, J. Chem. Educ. *48*, 362 (1971).

[4] *M. Florkin* and *E. M. Stotz*: Comprehensive Biochemistry. Vol. 27, Elsevier, Amsterdam 1967.

[5] *J. B. Thomas*: Einführung in die Photobiologie. Thieme, Stuttgart 1968.

[6] *C. P. Swanson*: An Introduction to Photobiology. Prentice-Hall, Englewood Cliffs, New Jersey 1969.

[7] *J. D. Bernal* and *H. Gaffron* in *M. Kasha* and *B. Pullman*: Horizons in Biochemistry. Academic Press, New York 1962, pp. 11 and 59, resp.

[8] *G. Wald*, Angew. Chem. *80*, 857 (1968).

[9] *M. D. Kamen*: Primary Processes in Photosynthesis. Academic Press, New York 1963.

[10] *J. C. D. Brand* and *D. G. Williamson*, Advan. Phys. Org. Chem. *1*, 365 (1963).

[11] *R. Hoffmann*, Pure Appl. Chem. *24*, 567 (1970).

[12] *R. P. Feynman, R. B. Leighton*, and *M. Sands*: The Feynman Lectures on Physics. Vol. 1. Addison-Wesley Publ. Comp., Reading, Mass. 1970.

[13] *Th. Butterfass*: Wachstums- und Entwicklungsphysiologie der Pflanze. Quelle & Meyer, Heidelberg 1970.

[14] *G. Quinkert, M. Finke, J. Palmowski*, and *W.-W. Wiersdorff*, Mol. Photochem. *1*, 433 (1969).

[15] *R. S. Mulliken*, Angew. Chem. *79*, 541 (1967).

[16] *E. Hückel*, Z. Physik *70*, 204 (1931); *72*, 310 (1931); *76*, 628 (1932).

[17] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[18] *M. Eigen* in *S. L. Friess, E. S. Lewis*, and *A. Weissberger*: Very Rapid Reactions in Solution, Investigation of Rates and Mechanisms of Reactions. Interscience, New York 1963.

[19] *M. Eigen*, Angew. Chem. *80*, 892 (1968).

[20] *G. Porter* in *S. L. Friess, E. S. Lewis*, and *A. Weissberger*: Flash Photolysis, Investigation of Rates and Mechanisms of Reactions. Interscience, New York 1963, p. 1055.

[21] *G. Porter*, Angew. Chem. *80*, 882 (1968).

[22] *Th. Förster*: Fluoreszenz Organischer Verbindungen. Vandenhoeck & Ruprecht, Göttingen 1951.

[23] *A. Weller*, Progr. React. Kinet. *1*, 187 (1961).

[24] *D. M. Hercules*: Fluorescence and Phosphorescence Analysis. Interscience, New York 1966.

[25] *C. A. Parker*: Photoluminescence of Solutions. Elsevier, Amsterdam 1968.

[26] *M. Bersohn* and *J. C. Baird*: An Introduction to Electron Paramagnetic Resonance. Benjamin, New York 1966.

[27] *R. Kaptain*, Proefschrift Rijksuniversiteit Leiden 1971; see further literature cited therein.

[28] *Y. Hirshberg* and *E. Fischer*, J. Amer. Chem. Soc. *78*, 2309 (1956).

[29] *M. Kasha* in *M. Kasha* and *B. Pullman*: Horizons in Biochemistry. Academic Press. New York 1962, p. 583.

[30] *P. Douzou* in *B. Pullman* and *M. Weissbluth*: The Study of Transient Molecular Configuration in Some Biophysical Problems, Molecular Biophysics. Academic Press, New York 1965, p. 239.

[31] *R. C. Bertelson* in *G. H. Brown*: Photochromism. Wiley Interscience, New York 1971, p. 733.

[32] *T. Bercovici, R. Korenstein, K. A. Muszkat*, and *E. Fischer*, Pure Appl. Chem. *24*, 531 (1970).

[33] *Th. Förster*, Pure Appl. Chem. *24*, 443 (1970).

[34] *E. F. Ullman*, Accounts Chem. Res. *1*, 353 (1968).

[35] *G. Quinkert*, Photochem. Photobiol. *7*, 783 (1968).

[36] *A. A. Lamola, G. S. Hammond*, and *F. B. Mallory*, Photochem. Photobiol. *4*, 259 (1965).

[37] *D. Phillips, J. Lemaire, C. S. Burton*, and *A. W. Noyes, jr.*, Advan. Photochem. *5*, 329 (1968).

[38] *J. Jortner, S. A. Rice*, and *R. M. Hochstrasser*, Advan. Photochem. *7*, 149 (1969).

[39] *G. Quinkert, B. Bronstert, P. Michaelis, G. Prescher, D. Egert, P. Jürges*, and *A. Syldatk*, to be published.

[40] *H. Mauser*, Z. Naturforsch. *23b*, 1025 (1968).

[41] *A. A. Frost* and *R. G. Pearson*: Kinetics and Mechanism. Wiley, New York 1962.

[42] *J. R. Novak* and *M. C. Windsor*, Proc. Roy. Soc. (London) *A 308*, 95 (1968).

[43] *M. M. Malley* and *P. M. Rentzepis*, Chem. Phys. Lett. *3*, 534 (1969).

[44] *J. Simonsen* and *D. H. R. Barton*: The Terpenes. Vol. 3. The University Press. Cambridge 1952.

[45] *K. Schaffner*, Fortschr. Chem. *22*, 1 (1964).

[46] *K. Schaffner*, Advan. Photochem. *4*, 81 (1966).

[47] *P. J. Kropp* in *O. L. Chapman*: Photochemical Transformations of Cyclohexadienones and Related Compounds. Organic Photochemistry. Vol. 1. Marcel Dekker, New York 1967, p. 1.

[48] *Y. Yamada, D. Miljkovic, P. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller*, and *A. Eschenmoser*, Angew. Chem. *81*, 301 (1969); Angew. Chem. internat. Edit. *8*, 343 (1969).

[49] *R. S. Becker, E. Dolan*, and *D. E. Balke*, J. Chem. Phys. *50*, 239 (1969).

[50] *L. M. Stephenson* and *G. S. Hammond*, Angew. Chem. *81*, 279 (1969); Angew. Chem. internat. Edit. *8*, 261 (1969).

[51] *J. B. Birks*: Photophysics of Aromatic Molecules. Wiley Interscience, London 1970.

[52] *R. S. Becker*: Theory and Interpretation of Fluorescence and Phosphorescence. Wiley Interscience, New York 1969.

[53] *Th. Förster*, Angew. Chem. *81*, 364 (1969); Angew. Chem. internat. Edit. *8*, 333 (1969).

[54] *B. Stevens*, Advan. Photochem. *8*, 161 (1971).

[55] *J. E. Leonhard* and *G. S. Hammond*, Annu. Surv. Photochem. *3*, 215 (1971).

[56] *J. R. Swenson* and *R. Hoffmann*, Helv. Chim. Acta *53*, 2331 (1970).

[57] *J. M. Foster* and *S. F. Boys*, Rev. Mod. Phys. *32*, 303 (1960).

[58] *M. S. J. Dewar* and *S. D. Worley*, J. Chem. Phys. *50*, 654 (1969).

[59] *A. D. Peters*, Trans. Faraday Soc. *59*, 1121 (1963).

[60] *E. W. Abrahamson, J. G. Littler*, and *K.-P. Vo*, J. Chem. Phys. *44*, 4082 (1966).

[61] *L. Goodman* and *R. Zwarich*, J. Amer. Chem. Soc. *93*, 2068 (1971).

[62] *J. N. Murell*: The Theory of the Electronic Spectra of Organic Molecules. Methuen, London 1963.

[63] *H. H. Jaffé* and *M. Orchin*: Theory and Application of Ultraviolet Spectroscopy. Wiley, New York 1962.

[64] *D. H. R. Barton* and *G. Quinkert*, Proc. Chem. Soc. *1958*, 197; J. Chem. Soc. *1960*, 1.

[65] *D. H. R. Barton*, Helv. Chim. Acta *42*, 2605 (1959).

[66] *G. Quinkert*, Angew. Chem. *77*, 229 (1965); Angew. Chem. internat. Edit. *4*, 211 (1965).

[67] IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Fundamental Stereochemistry. J. Org. Chem. *35*, 2849 (1970).

[68] *J. E. Baldwin* and *M. C. McDaniel*, J. Amer. Chem. Soc. *90*, 6118 (1968).

[69] *M. R. Morris* and *A. J. Waring*, Chem. Commun. *1969*, 526.

[70] *G. Quinkert, M. Hintzmann, P. Michaelis*, and *P. Jürges*, Angew. Chem. *82*, 219 (1970); Angew. Chem. internat. Edit. *9*, 238 (1970).

[71] *G. Quinkert, M. Hintzmann, P. Michaelis, P. Jürges*, and *U. Krüger*, Angew. Chem. *82*, 220 (1970); Angew. Chem. internat. Edit. *9*, 239 (1970).

[72] *G. Quinkert, M. Hintzmann, P. Michaelis, P. Jürges, H. Appelt*, and *U. Krüger*, Liebigs Ann. Chem. *748*, 38 (1971).

[73] *W. W. Robertson*, J. Chem. Phys. *33*, 362 (1960).

[74] *G. Quinkert, B. Bronstert, P. Michaelis*, and *U. Krüger*, Angew. Chem. *82*, 221 (1970); Angew. Chem. internat. Edit. *9*, 240 (1970).

[75] *G. Quinkert*, Lectures: Gordon Research Conference on Organic Photochemistry, Tilton 1967: Summer Congress of the Koninklijke Nederlandse Chemische Vereniging, Groningen 1967; International Symposium on Basic Mechanisms in Photochemistry and Photobiology, Caracas 1967; see [35].

[76] *J. D. Hobson, M. M. Al Holly*, and *J. R. Malpass*. Chem. Commun. *1068*, 764.

[77] *D. Lemmer* and *H. Perst*, Tetrahedron Lett. *1972*, 2735.

[78] *O. L. Chapman* and *J. D. Lassila*, J. Amer. Chem. Soc. *90*, 2449 (1968).

[79] *J. Griffiths* and *H. Hart*, J. Amer. Chem. Soc. *90*, 3297 (1968).

[80] *O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen*, and *H. E. Wright*, J. Amer. Chem. Soc. *91*, 6856 (1969).

[81] *W. Regel* and *W. von Philipsborn*, Helv. Chim. Acta *51*, 867 (1968).

[82] *B. Bronstert*, Dissertation, Technische Universität Braunschweig 1970.

[83] *H. H. Perkampus, G. Prescher, B. Bronstert*, and *G. Quinkert*, Angew. Chem. *82*, 222 (1970); Angew. Chem. internat. Edit. *9*, 241 (1970).

[84] *A. Syldatk*, unpublished.

[85] *J. G. Calvert* and *J. N. Pitts, jr.*: Photochemistry. Wiley, New York 1966, Chapter V.

[86] *P. J. Wagner* and *G. S. Hammond*, Advan. Photochem. *5*, 21 (1968).

[87] *R. Hoffmann*, J. Amer. Chem. Soc. *90*, 1475 (1968).

[88] *R. Hoffmann, A. Imamura*, and *W. J. Hehre*, J. Amer. Chem. Soc. *90*, 1499 (1968).

[89] *L. Salem* and *C. Rowland*, Angew. Chem. *84*, 86 (1972); Angew. Chem. internat. Edit. *11*, 92 (1972).

[90] *H. Appelt*, unpublished.

[91] *G. S. Hammond*: Energy Transfer in Organic Photochemistry, Reactivity of the Photoexcited Organic Molecule. Interscience, London 1967.

[92] *A. A. Lamola* in *P. A. Leermakers* and *A. Weissberger*: Electronic Energy Transfer in Solution, Energy Transfer and Organic Photochemistry. Interscience, New York 1969.

[93] *P. S. Engel* and *B. M. Nonroe*, Advan. Photochem. *8*, 245 (1971).

[94] *G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt*, and *C. Dalton*, J. Amer. Chem. Soc. *86*, 3197 (1964).

[95] *G. S. Hammond, N. J. Turro*, and *P. A. Leermakers*, J. Amer. Chem. Soc. *83*, 2396 (1961).

[96] *G. S. Hammond, N. J. Turro*, and *P. A. Leermakers*, J. Phys. Chem. *66*, 1144 (1962).

[97] *A. J. Waring* and *H. Hart*, J. Amer. Chem. Soc. *86*, 1454 (1964).

[98] *H. Hart* and *A. J. Waring*, Tetrahedron Lett. *1965*, 325.

[99] *H. Hart, P. M. Collins*, and *A. J. Waring*, J. Amer. Chem. Soc. *88*, 1005 (1966).

[100] *P. M. Collins* and *H. Hart*, J. Chem. Soc. *C 1967*, 895.

[101] *P. M. Collins* and *H. Hart*, J. Chem. Soc. *C 1967*, 1197.

[102] *H. Hart* and *D. W. Swatton*, J. Amer. Chem. Soc. *89*, 1874 (1967).

[103] *R. J. Bastiani, D. J. Hart*, and *H. Hart*, Tetrahedron Lett. *1969*, 4841.

[104] *H. Hart* and *R. K. Murray, jr.*, J. Org. Chem. *35*, 1535 (1970).

[105] *D. H. R. Barton* and *A. S. Kende*, J. Chem. Soc. *1958*, 688.

[106] *D. H. R. Barton, R. Bernasconi*, and *J. Klein*, J. Chem. Soc. *1960*, 511.

[107] *J. Griffiths* and *H. Hart*, J. Amer. Chem. Soc. *90*, 5296 (1968).

[108] *C. H. Nicholls* and *P. A. Leermakers*, Advan. Photochem. *8*, (1971).

[109] *G. Prescher, B. Bronstert*, and *K. R. Schmieder*, unpublished.

[110] *G. Quinkert, B. Bronstert*, and *K. R. Schmieder*, Angew. Chem. *84*, 638 (1972); Angew. Chem. internat. Edit. *11*, 637 (1972).

[(η-Phenyl)phenylethylphosphane](η-2,3-dimethylbutadiene)iron(0), A Phosphane Complex without Coordinated Phosphorus

By *Ernst Koerner von Gustorf, Ingrid Fischler, Johannes Leitich,* and *Herbert Dreeskamp*[*]

In our systematic studies of the photochemistry of transition metal π-complexes[1,2] we have now turned our attention to complexes of molecular nitrogen. We have turned to an observation by *Sacco et al.*, who report that solid $[(C_6H_5)_2PC_2H_5]_3FeH_2N_2$ *(1)*[3] loses H_2 reversibly in sunlight and is converted[4] into

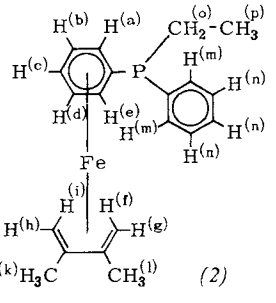
$HFe[C_6H_4P(C_6H_5)C_2H_5][N_2][C_2H_5P(C_6H_5)_2]_2$

Solid *(1)* exhibits strong photochromism: In daylight it changes color from yellow-orange to brown within a few minutes. After a few days in the dark, it shows its original color again. According to remission measurements this process is about six times faster under 60 at of N_2 than under argon. Therefore, it can be assumed to involve primary loss of N_2 rather than that of H_2. If this is so then the coordinatively unsaturated intermediate ought, as a derivative of iron hydride, to be capable of hydrogenating unsaturated hydrocarbons[5]. We have therefore irradiated solutions of *(1)* in benzene in the presence of methyl acrylate or 2,3-dimethylbutadiene. In the former case 60 to 65% propionate, 40 to 35% H_2, and the theoretical amount of N_2 are formed, in the latter 40 to 50% 2,3-dimethyl-2-butene, 60—50% H_2, and, once again, a quantitative amount of N_2. We consider these findings as evidence that electronic excitation of *(1)* in the region of the absorption maximum at 24600 cm^{-1} leads, with primary loss of N_2, to formation of $[(C_6H_5)_2PC_2H_5]_3FeH_2$, which acts as hydrogenating agent.

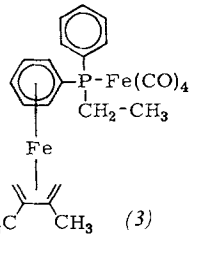
On working up the products of the photoreaction of *(1)* with 2,3-dimethylbutadiene we were able to isolate an orange colored substance *(2)*, m.p. 43—46 °C, in yields of about 50%. According to elemental analysis and molecular weight determination the composition of *(2)* is $C_6H_{10}Fe[(C_6H_5)_2PC_2H_5]$. The mass spectrum shows the molecular ion (M) and fragment ions corresponding to $(M-C_6H_{10})$, $(M-C_6H_{10}-C_2H_4)$, and $(C_6H_5)_2PC_2H_5$. The ^{1}H-NMR spectrum[6] shows an intact, coordinated[2] 2,3-dimethylbutadiene system in an asymmetric environment: τ = 7.94 ppm (CH_3^k), 7.97 (CH_3^l), 8.63 (H^g), 8.71 (H^h), 10.63 (H^f), 10.68 (H^i); $J_{i,h}$ = 1.1 Hz; $J_{f,g}$ = 0.9 Hz; J_{allyl} can be estimated to be about 0.3 Hz. Of the aromatic protons of the coordinated $(C_6H_5)_2PC_2H_5$ only five are to be found (as two multiplets) in the same region as in the free phosphane[7]: τ = 2.32 ppm (H^m) and 2.85 (H^n). The remaining aromatic protons appear much further upfield: τ = 4.52 ppm (H^a), 4.87 (H^e), 5.33 (H^c), 5.68 (H^b), 5.84 (H^d)[8]. The protons of the ethyl group in *(2)* appear at τ = 7.85 ppm (H^o) and 8.77 (H^p) [$J_{o,p}$ = 7.6 Hz; $J_{o,P}$ = 0; $J_{p,P}$ = 17 Hz]. The chemical shifts show that a phenyl group of the phosphane is coordinated to the iron; according to the coupling constants this ring functions as a 6-electron donor. A stable 1,3-diene-arene-iron(0) complex must therefore be present for which there are several analogs, *e.g.* 1,3-cyclohexadiene-benzene-iron(0)[9] and butadiene-toluene-iron(0)[10], in which the aromatic protons appear at τ = 5.13 ppm (in C_6D_6) and τ = 4.8 ppm (in CD_3COCD_3). Our observation that a phenyl ring and not the phosphorus participates in the coordination of an aryl substituted phosphane must be ascribed to the high tendency of formation of diene-arene-Fe(0) complexes.

Further evidence that the phosphorus in *(2)* is not coordinated is provided by the following facts: The chemical shift[11] of ^{31}P in *(2)* with δ = 12.5 ppm is very similar to that in $(C_6H_5)_2PC_2H_5$ (12.0 ppm). As expected[12], on the other hand, we have found that δ = −66.3 ppm for $[(C_6H_5)_2PC_2H_5]Fe(CO)_4$ prepared photochemically from $Fe(CO)_5$. The values $J_{o,P} \approx 0$ and $J_{p,P}$ = 17 Hz for *(2)* are in complete agreement with those found for $(C_6H_5)_2PC_2H_5$[7], whereas the values for $[(C_6H_5)_2PC_2H_5]Fe(CO)_4$ are 9.5 and 19 Hz.

We have also been able to coordinate $Fe(CO)_4$ to the phosphorus of *(2)* to give the complex *(3)* by photochemical reaction with $Fe(CO)_5$; *(3)* [m.p. ≈ 60 °C (decomp.); ν_{CO} (in KBr): 2055, 1978, and 1940 cm^{-1}] was characterized by elemental analysis and its mass spectrum [*m/e* = 520 (M); 492 (M − CO); 436 (M − 3CO); 352 (M − $Fe(CO)_4$)]. ^{31}P in *(3)* is observed at δ = −69.3 ppm.



(2)



(3)

Coordination at an aromatic ring in bis(diphenylarsino)-methane and tri(*o*-tolyl)phosphane can also be achieved with Cr, Mo, and W[13].

Procedure for preparation of (2):

A solution of *(1)* (5.6 mmol) in benzene (100 ml) and 2,3-dimethylbutadiene (10 ml) was irradiated under argon in an immersion apparatus (filter, λ > 370 nm) at 20 °C with a high-pressure mercury-vapor lamp (Philips HPK 125 W) until evolution of gas was complete (*ca.* 90 min). After evaporation of the solvent from the reaction mixture, the liberated phosphane was removed by molecular

[*] Dr. E. Koerner von Gustorf, Dipl.-Chem. I. Fischler, Dr. J. Leitich, and Priv.-Doz. Dr. H. Dreeskamp
Max-Planck-Institut für Kohlenforschung, Abteilung Strahlenchemie
433 Mülheim/Ruhr, Stiftstrasse 34—36 (Germany)

distillation under high vacuum at room temperature (time required *ca.* 48 h). Double recrystallization of the residue from pentane afforded *(2)* in 50 to 55% yield (based on *(1)*).

For conversion of *(2)* into *(3)* a solution of *(2)* (2.3 mmol) and $Fe(CO)_5$ (3 ml) in ether (50 ml) was irradiated at −40 °C until evolution of 1 mol CO/mol *(2)*. After evaporation of the ether and addition of pentane (10 ml) *(3)* precipitates almost quantitatively.

Received: September 4, 1972 [Z 715 IE]
German version: Angew. Chem. *84*, 1143 (1972)

[1] *E. Koerner von Gustorf* and *F.-W. Grevels*, Fortschr. Chem. Forsch. *13*, 366 (1969).

[2] *E. Koerner von Gustorf, J. Buchkremer, Z. Pfaifer*, and *F.-W. Grevels*, Angew. Chem. *83*, 249 (1971); Angew. Chem. internat. Edit. *10*, 260 (1971); *E. Koerner von Gustorf, F.-W. Grevels, C. Krüger, G. Olbrich, F. Mark, D. Schulz*, and *R. Wagner*, Z. Naturforsch. *27b*, 392 (1972).

[3] *M. Aresta, P. Giannoccaro, M. Rossi*, and *A. Sacco*, Inorg. Chim. Acta *5*, 115, 203 (1971). We thank Prof. *Sacco* for details of an experimental procedure prior to its publication.

[4] *A. Sacco* and *M. Aresta*, Chem. Commun. *1968*, 1223.

[5] *W. Strohmeier*, Fortschr. Chem. Forsch. *25*, 71 (1972). Note added in proof: *V. D. Bianco, S. Doronzo*, and *M. Aresta*, J. Organometal. Chem. *42*, C 63 (1972) observed ethane in the reaction of *(1)* with ethylene.

[6] Recorded with a Varian HA 100 in C_6D_6; assignment of the resonances by ^1H and ^{31}P double resonance experiments.

[7] $\tau = 2.51$ ppm (H^m), 2.88 (H^n), 8.11 (H^o), 9.01 (H_p); $J_{o,p} = 7.6$ Hz; $J_{o,P} \approx 0$; $J_{p,P} = 17$ Hz.

[8] $J_{a,b} = J_{b,c} = J_{c,d} = J_{d,e} = J_{e,P} = 5.8$ Hz; $J_{a,P} = 3.8$ Hz; $J_{b,P} = J_{d,P} = 0$; $J_{c,P} = 2.2$ Hz; $J_{a,e} = J_{a,c} = J_{e,c} = 1.1$ Hz; $J_{d,b} = 0.9$ Hz.

[9] *E. O. Fischer* and *J. Müller*, Z. Naturforsch. *17b*, 776 (1962).

[10] *D. L. Williams-Smith, L. R. Wolf*, and *P. S. Skell*, J. Amer. Chem. Soc. *94*, 4042 (1972).

[11] Relative to 85% H_3PO_4, accuracy ±0.3 ppm.

[12] *J. F. Nixon* and *A. Pidcock*, Ann. Rep. NMR Spectr. *2*, 346 (1969).

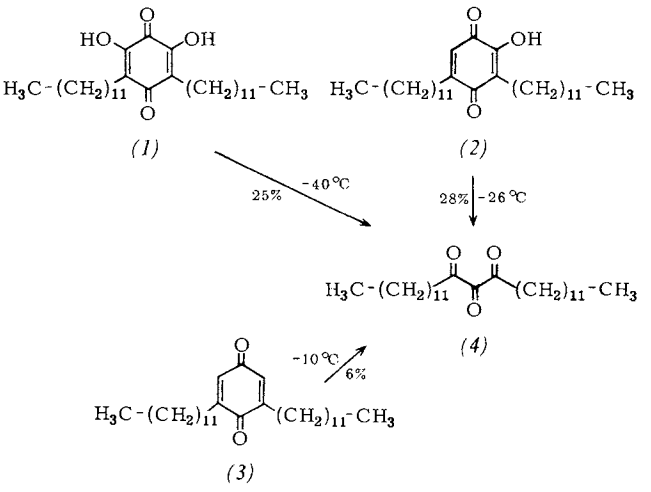
[13] *R. Colton* and *C. J. Rix*, Aust. J. Chem. *24*, 2461 (1971); *J. A. Bowden* and *R. Colton*, *ibid. 24*, 2471 (1971).

Aliphatic 1,2,3-Triketones by Ozonolysis of Dialkyl-1,4-benzoquinones[**]

By *Gottfried Schill, Enno Logemann*, and *Clemens Zürcher*[*]

The ozonolysis of 1,4-benzoquinone and its derivatives is not uniform[1–4]. 1,2,3-Tricarbonyl compounds, which ought to be formed by ozonolytic cleavage of the two double bonds of the quinonoid nucleus have been isolated in only one case: *Bernatek*[3] obtained small yields of mesoxaldialdehyde by ozonolysis of unsubstituted 1,4-benzoquinone.

We have found that ozonolysis of 3,5-didodecyl-2,6-dihydroxy-1,4-benzoquinone *(1)*, 3,5-didodecyl-2-hydroxy-1,4-benzoquinone *(2)*, and 2,6-didodecyl-1,4-benzoquinone *(3)*, in ethyl acetate/methanol (10:1) below 0 °C followed by reduction of the ozonide with dimethyl sulfide[5] leads to heptacosa-13,14,15-trione *(4)*. Repeated recrystallization of the crude product from petroleum ether



(60—70 °C) or CCl_4, or chromatography on silica gel with benzene/glacial acetic acid (8:2) afforded yellow crystals of *(4)* (m. p. 71.5 to 73 °C). The structure of *(4)* was confirmed by elemental analysis, IR and NMR spectra. The molecular ion occurs at $m/e = 422$. The base peak at $m/e = 197$ is assigned to the fragment $C_{12}H_{25}$—CO. Addition of water[6] to a solution of *(4)* in acetone afforded the colorless hydrate.

The triketone *(4)* could be reduced to the triol by treatment with sodium borohydride and converted *via* the bromides into *n*-heptacosane (m. p. 58.5 to 60.0 °C; Ref. [8]: 59.5 °C). Aliphatic 1,2,3-triketones were previously prepared from 1,3-diketones[6, 7].

Received: September 8, 1972 [Z 716a IE]
German version: Angew. Chem. *84*, 1144 (1972)

[1] *F. Fichter, M. Jetzer*, and *R. Leepin*, Liebigs Ann. Chem. *395*, 1 (1913).

[2] *E. Bernatek*, Acta Chem. Scand. *8*, 1943 (1954).

[3] *E. Bernatek* and *K. A. Straumsgard*, Acta Chem. Scand. *13*, 178 (1959).

[4] *E. Bernatek* and *K. Valen*, Acta Chem. Scand. *14*, 224 (1960).

[5] *J. J. Pappas, W. P. Keaveney, E. Gancher*, and *M. Berger*, Tetrahedron Lett. *1966*, 4273; Brit. Pat. 1092615 (Nov. 29, 1967) Interchemical Corp.; Chem. Abstr. *69*, 2516 (1968).

[6] *L. Horner* and *F. Maurer*, Liebigs Ann. Chem. *736*, 145 (1970); References cited therein.

[7] *E. H. Rodd*: Chemistry of Carbon Compounds. 1. Edit. Elsevier, Amsterdam 1952, Vol. IB, p. 1045.

[8] *A. Müller* and *W. B. Saville*, J. Chem. Soc. *127*, 599 (1925).

Ozonolytic Degradation of a Catenane[**]

By *Gottfried Schill, Enno Logemann*, and *Walter Vetter*[*]

We have found that the catenane *(2)*[1], which is accessible from the triansa compound *(1)*, can be subjected to a

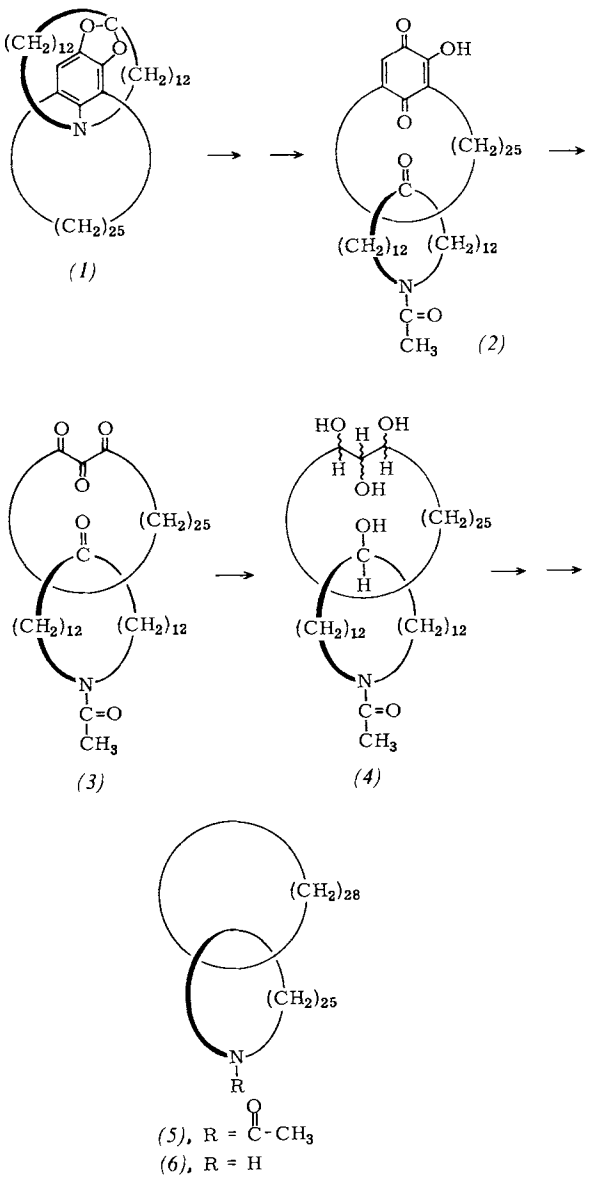
[*] Prof. Dr. G. Schill, Dipl.-Chem. E. Logemann, and Dipl.-Chem. C. Zürcher
Chemisches Laboratorium der Universität
78 Freiburg, Albertstrasse 21 (Germany)

[**] We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for supporting these investigations and Dr. *W. Vetter*, Physikalische Abteilung der Hoffmann-La Roche & Co. AG, Basel, for recording the mass spectra.

[*] Prof. Dr. G. Schill and Dipl.-Chem. E. Logemann
Chemisches Laboratorium der Universität
78 Freiburg, Albertstr. 21 (Germany)
Dr. W. Vetter
Physikalische Abteilung der Hoffmann-La Roche & Co. AG
Basel (Switzerland)

[**] G. S. and E. L. thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support of these investigations, as well as Badische Anilin- und Sodafabrik AG, Farbenfabriken Bayer AG, and Chemische Werke Hüls AG for the supply of chemicals.

degradation reaction with retention of the catenane structure to give the compounds *(5)* and *(6)*.



3,5-Dialkyl-2-hydroxy-1,4-benzoquinones can be converted by ozonolysis into 1,2,3-triketones[2]. In a similar fashion we have ozonized the catenane *(2)* in ethyl acetate at −40 °C in the presence of tetracyanoethylene[3]. Without isolation the tetraketone *(3)* was reduced with sodium borohydride to the tetraol *(4)*. The crude product *(4)* was treated at room temperature with hydrogen bromide in glacial acetic acid to give a mixture of the bromides and acetates. After hydrogenation of the mixture over Raney nickel the *O*-acetyl groups were saponified. The above treatment of *(4)*, *i.e.* reaction with hydrogen bromide, catalytic reduction, and hydrolysis, was carried out four times in order to ensure complete replacement of the hydroxyl groups by hydrogen. The catenane *(5)* was isolated in pure form [yield 24% based on *(1)*; m. p. 149.5 to 150.5 °C (one recrystallization from ethanol/methanol)] from the reaction mixture by chromatography on a silical-gel column with *n*-butyl acetate; its composition and structure were confirmed by elemental analysis, and NMR, IR, and mass spectra.

Hydrolysis of the *N*-acetyl group with hydrochloric acid in dioxane or with sulfuric acid in acetic acid afforded the catenane *(6)*, which was separated from small amounts of unreacted *(5)* by preparative thin-layer chromatography on silica gel with *n*-butyl acetate. One recrystallization from benzene/ethanol or *n*-butyl acetate provided colorless plates, having m. p. 191 to 194 °C (after previous sintering).

Compounds *(5)* and *(6)* are the first catenanes to be obtained in crystalline form from solution.

The mass spectrum of *(6)* shows the peak for the molecular ion at $m/e = 757$ (intensity 53%). The region from $m/e = 755$ to $m/e = 395$ is practically free of peaks (no peak with intensity greater than 0.2% of that of the base peak). A signal appears at $m/e = 392.4372$ (calc. 392.4382; intensity 1.6%) which originates from the 28-membered polymethylene ring of the catenane. The base peak at $m/e = 366.4085$ (calc. 366.4100) corresponds to the (M + 1)-ion of the aza-macrocycle of the catenane *(6)*. We explain its occurrence as resulting from hydrogen transfer within the catenane[4].

Received: September 8, 1972 [Z 716 b IE]
German version: Angew. Chem. *84*, 1144 (1972)

[1] *G. Schill* and *A. Lüttringhaus*, Angew. Chem. *76*, 567 (1964); Angew. Chem. internat. Edit. *3*, 546 (1964); *G. Schill*, Chem. Ber. *100*, 2021 (1967).

[2] *G. Schill*, *E. Logemann*, and *C. Zürcher*, Angew. Chem. *84*, 1144 (1972); Angew. Chem. internat. Edit. *11*, 1089 (1972).

[3] *R. Criegee* and *P. Günther*, Chem. Ber. *96*, 1564 (1963).

[4] *W. Vetter* and *G. Schill*, Tetrahedron *23*, 3079 (1967).

1,1-Dihalo-λ^5-phosphorins

By *Hartmut Kanter* and *Karl Dimroth*[*]

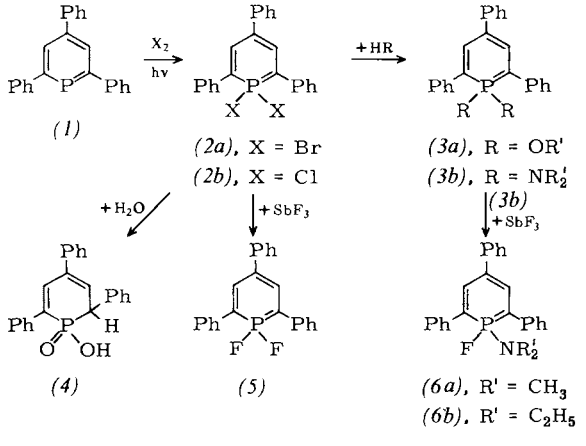
λ^3-Phosphorins bearing substituents in positions 2, 4, and 6 are readily oxidized to the radical cation[1]. Nucleophiles and radicals add to the phosphorus atom to give 1,1-disubstituted λ^5-phosphorins *(3)*[2]. According to *Mach*, prolonged action of an excess of bromine or chlorine on 2,4,6-tri-*tert*-butyl-λ^3-phosphorin leads to higher oxidation products[3].

We have now found that the dibromides and dichlorides, *(2a)* and *(2b)* respectively, can be synthesized by reaction of 2,4,6-triphenyl-λ^3-phosphorin with 1 mol. equiv. of bromine or chlorine in the presence of light. Whereas the dibromide *(2a)*, which is very readily soluble in all common inert solvents, has been obtained as a solid but not in crystalline form, the dichloride *(2b)* could be isolated as a yellow crystalline, analytically pure substance. Both compounds were characterized by their ^{1}H-NMR spectra (see below). They can also be prepared without the aid of light, *(2a)* from *(1)* with pyridinium perbromide, and *(2b)* from *(1)* with phosphorus pentachloride.

The high reactivities of the dihalides *(2a)* and *(2b)* open up numerous synthetic possibilities. Reaction of *(2a)* with alcohols or amines affords 1,1-dialkoxy- or bis(dialkyl-

[*] Dipl.-Chem. H. Kanter and Prof. Dr. K. Dimroth
Organische Chemie im Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

amino)-2,4,6-triphenyl-λ^5-phosphorins, which have already been obtained by another route[2]; reaction with water yields the likewise known cyclic phosphinic acids *(4)*[4]. Treatment with antimony trifluoride furnishes the 1,1-difluoro compound *(5)* as a yellow crystalline, chemically highly stable compound. Particular interest attaches to its ^{1}H-, ^{19}F-, and ^{31}P-NMR data (see below) on account of the bonding in the λ^5-phosphorin series.



We prepared the 1-dialkylamino-1-fluoro compounds *(6a)* and *(6b)* by nucleophilic displacement[5] from the bis(dialkylamino)-λ^5-phosphorins of type *(3b)* with antimony trifluoride.

1,1-Dibromo-2,4,6-triphenyl-λ^5-phosphorin (2a)

A solution of Br_2 (1 mmol) in CCl_4 (20 ml) is added dropwise over one hour to an irradiated (mercury arc lamp) solution of *(1)* (1 mmol) in anhydrous CCl_4 (25 ml) under a nitrogen atmosphere; irradiation is continued for another hour and the solvent then removed *in vacuo*, leaving a brown powder as residue (crude yield quantitative). ^{1}H-NMR in C_6D_6 (TMS internal standard): δ = 7.0–7.8 ppm (m/15 H); 7.47 ppm (d/2 H, J_{P-H} = 48 Hz). Treatment with alcohols immediately affords the strongly fluorescent 1,1-dialkoxy-2,4,6-triphenyl-λ^5-phosphorins *(3a)* (R' = = CH_3 or C_2H_5) in more than 50% yield.

1,1-Dichloro-2,4,6-triphenyl-λ^5-phosphorin (2b)

A stirred mixture of compound *(1)* (6 mmol) and PCl_5 (8 mmol) in CCl_4 (125 ml) is irradiated for 25 min with a mercury arc lamp. The residue left on evaporation of solvent gives analytically pure *(2b)* on recrystallization from a small volume of acetonitrile. Yield at least 55%, m.p. 100–103 °C. ^{1}H-NMR in C_6D_6 (TMS internal standard): δ = 7.1–7.8 ppm (m/15H); 7.6 ppm (d/2H; J_{P-H} = 50 Hz); ^{31}P-NMR in C_6D_6 (H_3PO_4 external reference): $\delta = -17.00$ ppm (t, $J_{P-H} = 50$ Hz).

1,1-Difluoro-2,4,6-triphenyl-λ^5-phosphorin (5)

Compound *(5)* results from *(2a)* or *(2b)* on 12 hours' stirring with an excess of SbF_3 in CCl_4 and evaporation of solvent. The residue is taken up in light petroleum (60 to 70 °C)/acetone (3 : 1), filtered over a silica gel column (activity 4), and concentrated; yellow crystals, m.p. 129—131 °C, analytically pure, 50—60% yield. ^{1}H-NMR in C_6D_6 (TMS internal standard): δ = 7.0—7.6 ppm (m/15H); 7.68 ppm (2t/2H, J_{P-H} = 46 Hz; J_{F-H} = 8 Hz); ^{19}F-NMR in C_6D_6 ($CFCl_3$ internal standard): $\delta = +47.02$ ppm (2t, J_{F-H}=8Hz; J_{P-F}=1040Hz); ^{31}P-NMR in C_6D_6 (H_3PO_4 external reference): $\delta = -73.0$ ppm (3t, J_{P-F}=1040Hz; J_{P-H}=46Hz).

1-Diethylamino-1-fluoro-2,4,6-triphenyl-λ^5-phosphorin (6b)

(6b) is obtained by 3 hours' refluxing of 1,1-bis(diethylamino)-2,4,6-triphenyl-λ^5-phosphorin (1 mmol) in anhydrous acetonitrile (40 ml) with SbF_3 (1.5 mmol) and trifluoroacetic acid (1.2 mmol) under N_2; yield 74%, m.p. 158—159 °C. The compound is also formed with BF_3-ether in the presence of nucleophiles. ^{1}H-NMR in C_6D_6 (TMS internal standard): δ=7.9 ppm (2d/2H; J_{P-H}= 37Hz; J_{F-H}=6Hz); 7.0—7.5 ppm (m/15H); 2.64 ppm (2q/4H, J_{H-H}=7Hz; J_{P-H}=11Hz) 0.47 ppm (t/6H; J_{H-H}= 7 Hz); ^{19}F-NMR in C_6D_6 ($CFCl_3$ internal standard): $\delta = +29.3$ ppm (J_{P-F} = 1020 Hz).

Received: September 11, 1972 [Z 717a IE]
German version: Angew. Chem. *84*, 1145 (1972)

[1] *K. Dimroth, N. Greif, H. Perst*, and *F. W. Steuber*, Angew. Chem. *79*, 58 (1967); Angew. Chem. internat. Edit. *6*, 85 (1967); *K. Dimroth, N. Greif, W. Städe*, and *F. W. Steuber*, Angew. Chem. *79*, 725 (1967); Angew. Chem. internat. Edit. *6*, 711 (1967).

[2] *K. Dimroth* and *W. Städe*, Angew. Chem. *80*, 966 (1968); Angew. Chem. internat. Edit. *7*, 881 (1968); *A. Hettche* and *K. Dimroth*, Tetrahedron Lett. *1972*, 829.

[3] *W. Mach*, Dissertation, Universität Marburg 1968.

[4] *A. Hettche* and *K. Dimroth*, unpublished; see also *K. Dimroth, K. Vogel, W. Mach*, and *U. Schoeler*, Angew. Chem. *80*, 359 (1968); Angew. Chem. internat. Edit. *7*, 371 (1968).

[5] *K. Dimroth, A. Hettche, H. Kanter*, and *W. Städe*, Tetrahedron Lett. *1972*, 835; *Note added in proof* (October 17, 1972): *(2b)* also reacts with organolithium and organomagnesium compounds to give 1-alkyl and 1-aryl substituted λ^5-phosphorins.

Reactions of λ^3-Phosphorins with Arenediazonium Salts to Give λ^5-Phosphorins

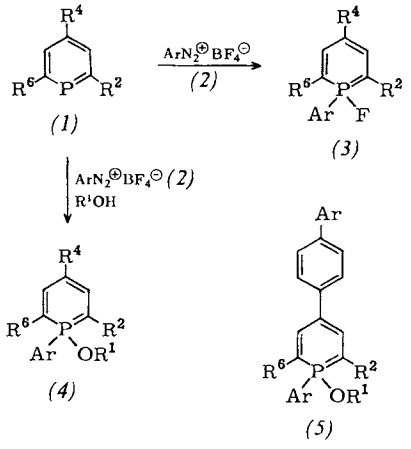
By *Ortwin Schaffer* and *Karl Dimroth*[*]

The ease of oxidation of 2,4,6-trisubstituted λ^3-phosphorins *(1)* to the radical cation[1] and the product's ability to add nucleophiles[2] and radicals[3] at the phosphorus prompted us to study their behavior towards arenediazonium tetrafluoroborates *(2)* in nonaqueous solution. Reaction proceeds surprisingly smoothly in dimethoxyethane with liberation of N_2 to give 1-aryl-1-fluoro-2,4,6-trisubstituted λ^5-phosphorins *(3)*. If the reaction is carried out in the presence of alcohols then 1-alkoxy-1-aryl-2,4,6-trisubstituted λ^5-phosphorins *(4)* result (see Table 1). The radical cation of λ^3-phosphorin can readily be detected by ESR spectroscopy. It is probably the first intermediate, formed by oxidation of λ^3-phosphorin by the arenediazonium ion and then giving 1,1-addition products with the aryl radical and the nucleophile (alcohol or $F^\ominus$ ion from the $BF_4^\ominus$ ion). The new synthesis is highly adaptable.

In the presence of an excess of 2-methyl-4-nitrobenzenediazonium tetrafluoroborate, λ^3-phosphorins bearing a phenyl group in position 4 also give small amounts (yields up to 5%) of doubly arylated λ^5-phosphorins *(5)*; they were also formed with evolution of nitrogen from *(4)* and the diazonium salt *(2)*, thus establishing the intermediacy of *(4)*. The course of the reaction resembles the

[*] Dipl.-Chem. O. Schaffer and Prof. Dr. K. Dimroth
Organische Chemie im Fachbereich Chemie der Universität
355 Marburg, Lahnberge (Germany)

formation of iodobenzene from arenediazonium salts and iodide ions, with the λ^3- and λ^5-phosphorin respectively



1-Alkoxy-1-aryl-2,4,6-trisubstituted λ^5-phosphorins (4)

(1) (1 mmol) is dissolved in a mixture of dry benzene (15 ml) and the desired alcohol (10 ml). Reaction and work-up of the likewise strongly colored 1-alkoxy-λ^5-phosphorins *(4)* were as above.

Received: September 11, 1972 [Z 717b IE]
German version: Angew. Chem. *84*, 1146 (1972)

[1] *K. Dimroth, N. Greif, H. Perst*, and *F. W. Stauber*, Angew. Chem. *79*, 58 (1967); Angew. Chem. internat. Edit. *6*, 85 (1967).

[2] *K. Dimroth* and *W. Städe*, Angew. Chem. *80*, 966 (1968); Angew. Chem. internat. Edit. *7*, 881 (1968).

[3] *K. Dimroth, A. Hettche, W. Städe*, and *F. W. Steuber*, Angew. Chem. *81*, 784 (1969); Angew. Chem. internat. Edit. *8*, 770 (1969).

[4] *G. Märkl, A. Merz*, and *H. Rausch*, Tetrahedron Lett. *1971*, 2989.

[5] *H. Kanter*, Diplomarbeit, Universität Marburg 1972; *H. Kanter* and *K. Dimroth*, Angew. Chem. *84*, 1145 (1972); Angew. Chem. internat. Edit. *11*, 1090 (1972).

Table 1. Compounds prepared *(3a)*, *(3b)*, and *(4a)*—*(4n)*.

	OR^1	Ar	R^2	R^4	R^6	Yield [%] [a]	M.p. [°C]
(3a)	F(OR^1 = F)	*p*-$C_6H_4CH_3$	C_6H_5	C_6H_5	C_6H_5	43	130—132
(3b)	F(OR^1 = F)	[c]	C_6H_5	C_6H_5	C_6H_5	41	221—223
(4a)	OCH_3	C_6H_5	C_6H_5	C_6H_5	C_6H_5	47	135—136
(4b)	OC_3H_7(*n*)	C_6H_5	C_6H_5	C_6H_5	C_6H_5	53	123—124
(4c)	OCH_3	C_6H_5	$C(CH_3)_3$	C_6H_5	$C(CH_3)_3$	21	137—139
(4d)	OCH_3	*p*-$C_6H_4CH_3$	C_6H_5	C_6H_5	C_6H_5	33	121—123
(4e)	OCH_3	*p*-$C_6H_4CH_3$	C_6H_5	CH_3	C_6H_5	8	134—136
(4f)	OCH_3	*p*-$C_6H_4OCH_3$	C_6H_5	C_6H_5	C_6H_5	59	147—149
(4g)	OC_6H_{11} [b]	*p*-$C_6H_4OCH_3$	C_6H_5	C_6H_5	C_6H_5	24	171—172
(4h)	OC_2H_5	*p*-C_6H_4Cl	C_6H_5	C_6H_5	C_6H_5	64	149—151
(4i)	OCH_3	[c]	C_6H_5	C_6H_5	C_6H_5	23	203—205
(4j)	OC_2H_5	[c]	C_6H_5	C_6H_5	C_6H_5	45	198—200
(4k)	OC_2H_5	[c]	$C(CH_3)_3$	C_6H_5	$C(CH_3)_3$	35	217—219
(4l)	OCH_3	[c]	C_6H_5	[d]	C_6H_5	12	249—251
(4m)	OC_2H_5	[c]	$C(CH_3)_3$	[d]	$C(CH_3)_3$	3.5	237—239
(4n)	OC_3H_7(*i*)	C_6H_5	C_6H_5	C_6H_5	C_6H_5	33	158—160

[a] Analytically pure substance, yield not optimized.
[b] Cyclohexyloxy.
[c] 2-Methyl-4-nitrophenyl.
[d] 2'-Methyl-4'-nitro-4-biphenylyl.

in place of the readily polarizable and oxidizable iodide. The composition of the new compounds was confirmed by elemental analyses and spectroscopic data. 1-Methoxy-1,2,4,6-tetraphenyl-λ^5-phosphorin has already been prepared by *Märkl et al.*[4] from 2,4,6-triphenylpyrylium tetrafluoroborate with phenylphosphane and methanol.

Compounds *(3a)* and *(3b)* appear to be of special interest since they number among the first 1-fluoro-λ^5-phosphorins[5]. For instance, *(3a)* gave the following NMR data in C_6D_6: ^{1}H-NMR (TMS internal standard): besides the multiplet of aromatic protons a quartet at $\delta = 8.01$ ppm (2H, $J_{H-P}=33$ Hz; $J_{F-H}=6$ Hz). ^{19}F-NMR ($CFCl_3$ internal standard): $\delta=25.6$ ppm (sextet, $J_{F-P}=1115$ Hz; $J_{F-H}=5.5$ Hz); ^{31}P-NMR (85% H_3PO_4 external reference): $\delta=48.98$ ppm (2m, $J_{F-P}=1113$ Hz).

1-Aryl-1-fluoro-2,4,6-trisubstituted λ^5-phosphorins (3)

Compound *(1)* (1 mmol) is dissolved in dry dimethoxyethane (20 ml). *(2)* (1 mmol) is then added portionwise to the stirred and cooled reaction mixture. The deeply colored fluoro-λ^5-phosphorins *(3)* formed with evolution of N_2 can be isolated by preparative layer chromatography with benzene/light petroleum (1 : 1) on silica gel, and recrystallized from methanol or ethanol.

Tetranitrosylchromium $[Cr(NO)_4]$[**]

By *Max Herberhold* and *Abbas Razavi*[*]

Attempts to prepare the binary nitrosylmetal compound, $Cr(NO)_4$, have so far failed[1]. This mononuclear complex is the last missing member in the isoelectronic series of uncharged, tetracoordinated carbonyl-nitrosyl complexes, the so-called pseudo-carbonylnickel series:

$$Ni(CO)_4 \quad Co(CO)_3NO \quad Fe(CO)_2(NO)_2 \quad Mn(CO)(NO)_3 \quad Cr(NO)_4$$

We have found that $Cr(NO)_4$ is formed when a slow stream of NO is drawn through an irradiated solution of $Cr(CO)_6$ in a hydrocarbon solvent (*n*-pentane, *n*-hexadecane, benzene). The reaction can be followed by IR spectroscopic measurement of the decrease in intensity of the C≡O stretching vibration of $Cr(CO)_6$ (mode F_{1u}, 1986 cm^{-1} in *n*-pentane). According to the IR spectra, the unknown

[*] Doz. Dr. M. Herberhold and Dipl.-Chem. A. Razavi
Anorganisch-chemisches Laboratorium der
Technischen Universität
8 München 2, Arcisstrasse 21 (Germany)

[**] These investigations were supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

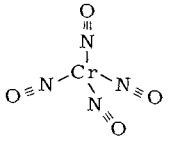
compound $Cr(CO)_3(NO)_2$, which could conceivably occur as an intermediate of the photoinduced nitrosylation, is *not* formed in noticeable amounts; furthermore, recarbonylation of the dissolved $Cr(NO)_4$ by CO gas cannot be achieved under the reaction conditions.

$Cr(NO)_4$ dissolves in hydrocarbons to give intense reddish brown solutions, which absorb over the whole range of the visible spectrum. In *n*-hexane solution, absorption maxima were recorded at $\approx$750 nm ($\log\varepsilon\approx1.85$), $\approx$555 ($\approx$2.80), 458 (3.29), and $\approx$290 (3.61); a further maximum occurs below 220 nm ($\log\varepsilon>4.7$).

Formulation of the new complex as "$Cr(NO)_4$" is supported by the following facts:

1. Satisfactory elemental analyses (Cr, N) have been obtained, even though the air-sensitivity and high volatility of the compound present considerable problems.—2. The complex is diamagnetic (^{1}H-NMR).—3. The highest peak in the mass spectrum corresponds to $m/e=172$, as would be expected for $Cr(NO)_4^+$; in addition, the mass spectrum contains peaks for all the fragments expected to occur by successive loss of NO ligands: $Cr(NO_3)^+$ (142), $Cr(NO)_2^+$ (112), $Cr(NO)^+$ (82), Cr^+ (52). All these fragment ions show the characteristic isotopic pattern of chromium.—4. The IR spectrum in the range 4000 to 800 cm^{-1} contains only one strong absorption (1721 cm^{-1} in *n*-pentane), which can be assigned to the asymmetric N≡O stretching vibration (mode F_2) in a tetrahedral complex[2]. Two additional bands appear at 650 and 496 cm^{-1} (in Nujol)[3].

We assume, on the basis of these finding, that the reddish brown complex of the composition $Cr(NO)_4$ is isoelectronic and isostructural with the colorless complex $Ni(CO)_4$. A tetrahedral molecule of this type possesses only four IR-active fundamentals, which belong to the triply degenerate representation F_2[2]; three bands ($\nu(N\equiv O)_{as}$, $\nu(Cr—NO)_{as}$, and $\delta(Cr—N—O)_{as}$) appear in our IR spectra, the fourth ($\delta(ON—Cr—NO)_{as}$) should lie below 100 cm^{-1}. The two vibrations $\nu(Cr—NO)_{as}$ and $\delta(Cr—N—O)_{as}$ are presumably strongly coupled, and the corresponding bands at 650 and 496 cm^{-1} ought to be considered as absorptions of mixed character. The comparatively high frequencies of these absorptions indicate a strong Cr→NO back bonding; similar IR frequencies (646 and 556 cm^{-1})[4] have been reported for the tetrahedral ion $[Fe(CO)_4]^{2-}$ (cf. Ref. [5]), which is again isoelectronic with the pseudocarbonylnickel series.



It is tempting to extrapolate the valence force constants $k(N\equiv O)$ of the carbonyl-nitrosyl complexes[6] $Co(CO)_3NO$ (14.6 mdyn/Å), $Fe(CO)_2(NO)_2$ (14.1), and $Mn(CO)(NO)_3$ (13.7) and to predict a $k(N\equiv O)$ value of *ca.* 13.2 mdyn/Å for $Cr(NO)_4$. However, just how problematic such an extrapolation can be is indicated by a comparison of the valence force constants $k(C\equiv O)$ of the same compounds: extrapolation of the $k(C\equiv O)$ values from the series $Mn(CO)(NO)_3$ (17.6 mdyn/Å), $Fe(CO)_2(NO)_2$ (17.1) and $Co(CO)_3NO$ (16.5) yields for the end member $Ni(CO)_4$ a value of *ca.* 15.9 mdyn/Å, which deviates considerably from the value of 17.4 mdyn/Å found experimentally[6].

From purely formalistic considerations the central metal in $Cr(NO)_4$ can be assigned an oxidation state of −IV if—as is usual—the nitrosyl ligand is considered as a NO^+ cation. Actually, the effective charge on the chromium should deviate very little from zero because of strong backbonding. In any case, $Cr(NO)_4$ is an interesting counterpart to the paramagnetic, tetracoordinated Cr^{+IV} complexes (such as *e.g.* $Cr[CH_2C(CH_3)_3]_4$[7], Cr[1-norbornyl]$_4$[8], $Cr[CH_2Si(CH_3)_3]_4$[9], $Cr(OR)_4$ (R = *tert*-alkyl[10,11] or $Si(C_2H_5)_3$[11]), and $Cr(NR_2)_4$ (NR_2 = dialkylamido)[12], to which a tetrahedral or pseudotetrahedral structure has also been ascribed. It can be assumed that a whole series of complexes of the general type $Cr(NO)_nL_{(4-n)}$ exists ($n=0$—4; L = univalent, anionic ligand without β hydrogen atoms, *e.g.* neopentyl, *tert*-alkyl, trialkylsilylmethyl, *tert*-alkoxy or dialkylamido). Of this series, both the end members ($Cr(NO)_4$ and CrL_4) and the mononitrosylchromium(III) complexes $Cr(NO)L_3$ (L = *e.g.* $N[CH(CH_3)_2]_2$, $N[Si(CH_3)_3]_2$, $OCH(CH_3)_2$, $OC(CH_3)_3$) are already known[13]; according to an X-ray structure analysis $Cr(NO)[N(Si(CH_3)_3)_2]_3$ has a pseudotetrahedral structure with a linear CrNO group[14].

The synthesis of transition metal-nitrosyl complexes by photoinduced nitrosylation of carbonylmetal compounds can be applied to other systems. Thus $Mn_2(CO)_{10}$ is converted stepwise into red $Mn(CO)_4NO$, green $Mn(CO)(NO)_3$, and finally into a new nitrosylmangenese complex, which is green and very volatile ($\nu(N\equiv O)$ 1666 cm^{-1} in tetrahydrofuran). Similarly, the know complexes $Fe(CO)_2(NO)_2$ and $(\pi\text{-}C_5H_5)V(CO)(NO)_2$[15] are formed when solutions of $Fe(CO)_5$ and $(\pi\text{-}C_5H_5)V(CO)_4$, respectively, are irradiated in solution and simultaneously treated with gaseous NO.

Experimental:

A stream of purified NO is passed through a solution of $Cr(CO)_6$ (220 mg; 1 mmol) in *n*-pentane (300 ml) which is irradiated with a high-pressure mercury arc (Hanovia L-450 W) until the strong IR absorption of $Cr(CO)_6$ has completely disappeared (*ca.* 2 hours). The intense reddish brown solution is filtered in a nitrogen atmosphere and evaporated at normal pressure to about 30 ml; the remaining solvent is removed in a high vacuum at −78 °C. The extremely volatile complex, $Cr(NO)_4$, can be isolated as a brownish black solid (m. p. 38—39 °C in a nitrogen-filled capillary) and purified by multiple sublimation at low temperature: final yield *ca.* 50% (80—90 mg).

Received: October 3, 1972 [Z 720 IE]
German version: Angew. Chem. *84*, 1150 (1972)

[1] Cf.: *B. F. G. Johnson* and *J. A. McCleverty*, Progr. Inorg. Chem. *7*, 277 (1966); *W. P. Griffith*, Advan. Organometal. Chem. *7*, 211 (1968).

[2] *D. M. Adams*: Metal-Ligand and Related Vibrations. Edward Arnold, London 1967, Chapt. 3, p. 84, 120.

[3] Raman investigations are rendered difficult because of the intense color of the complex.

[4] *W. F. Edgell, J. Huff, J. Thomas, H. Lehman, C. Angell*, and *G. Asato*, J. Amer. Chem. Soc. *82*, 1254 (1960).

[5] *H. Stammreich, K. Kawai, Y. Tavarés, P. Krumholz, J. Behmoiras*, and *S. Bril*, J. Chem. Phys. *32*, 1482 (1960).

[6] *C. G. Barraclough* and *J. Lewis*, J. Chem. Soc. *1960*, 4842.

[7] *W. Mowat* and *G. Wilkinson*, J. Organometal. Chem. *38*, C35 (1972).

[8] *B. K. Bower* and *H. G. Tennent*, J. Amer. Chem. Soc. *94*, 2512 (1972).

[9] *G. Yagupsky, W. Mowat, A. Shortland*, and *G. Wilkinson*, Chem. Commun. *1970*, 1369; *W. Mowat, A. Shortland, G. Yagupsky, N. J. Hill, M. Yagupsky*, and *G. Wilkinson*, J. C. S. Dalton *1972*, 533.

[10] *N. Hagihara* and *H. Yamazaki*, J. Amer. Chem. Soc. *81*, 3160 (1959); *H. Yamazaki* and *N. Hagihara*, Nippon Kagaku Zasshi *81*, 821 (1960); Chem. Abstr. *56*, 1589 (1962).

[11] *E. C. Alyea, J. S. Basi, D. C. Bradley*, and *M. H. Chisholm*, J. Chem. Soc. *A 1971*, 772.

[12] *J. S. Basi* and *D. C. Bradley*, Proc. Chem. Soc. (London) *1963*, 305; *J. S. Basi, D. C. Bradley*, and *M. H. Chisholm*, J. Chem. Soc. *A 1971*, 1433.

[13] *D. C. Bradley* and *C. W. Newing*, Chem. Commun. *1970*, 219.

[14] *D. C. Bradley, M. B. Hursthouse, C. W. Newing*, and *A. J. Welch*, J. C. S. Chem. Commun. *1972*, 567.

[15] *E. O. Fischer, R. J. J. Schneider*, and *J. Müller*, J. Organometal. Chem. *14*, P4 (1968); *E. O. Fischer* and *R. J. J. Schneider*, Chem. Ber. *103*, 3684 (1970).

Reaction of ClF_5 with OF_2: Preparation and Properties of Chlorine Oxide Trifluoride and the Existence of Chlorine Oxide Pentafluoride[1]

By *Klaus Züchner* and *Oskar Glemser*[*]

Irradiation of a gaseous mixture of ClF_5 and OF_2 in a quartz flask leads to formation of white crystalline $[ClOF_2]_2^+[SiF_6]^{2-}$, which melts under its own vapor pressure at 50.5 °C and dissociates into $ClOF_3$ and SiF_4, both of which can be detected in the gaseous phase by IR and mass spectrometry. Subsequent cooling leads to reformation of $[ClOF_2]_2^+[SiF_6]^{2-}$, which is also formed from $ClOF_3$ and SiF_4 at room temperature.

Chlorine oxide trifluoride $ClOF_3$ *(1)*, which was recently prepared *via* another route[2][**], was characterized by elemental analysis, mass, IR, Raman, and ^{19}F-NMR spectra[**]. Mass spectrum (rel. intensity in %): $^{37}ClOF_2^+$ (30), $^{35}ClOF_2^+$ (100); $^{37}ClF_2^+$ (0.8), $^{35}ClF_2^+$ (2.8); $^{37}ClOF^+$ (25.6), $^{35}ClOF^+$ (78.9); $^{37}ClO_2^+$ (1.1), $^{35}ClO_2^+$ (2.2); $^{37}ClF^+$ (2.6), $^{35}ClF^+$ (7.8); $^{37}ClO^+$ (11.1), $^{35}ClO^+$ (32.8); $H^{37}Cl^+$ (0.6), $^{37}Cl^+$ (2.8), $H^{35}Cl^+$ (2.4), $^{35}Cl^+$ (8.9); HF^+ (2.8), F^+ (2.2); O^+ (1.5).—^{19}F-NMR ($CFCl_3$ as external standard): $\delta_{ClF} - 253$ ppm. The vibration spectra are given in Table 1 along with a tentative assignment of the bands assuming C_s symmetry for the molecule. We are of the opinion that our assignment of the bands is more probable than that by *Bougon et al.* assuming C_{3v} symmetry.

We have studied the reactions of *(1)* both with Lewis acids and with Lewis bases. Reaction with AsF_5, SbF_5, and SiF_4 affords the white salts $[ClOF_2]^+[AsF_6]^-$, $[ClOF_2]^+[Sb_2F_{11}]^-$, and $[ClOF_2]_2^+[SiF_6]^{2-}$, the first two of which can also be prepared from $[ClOF_2]_2^+[SiF_6]^{2-}$ by reaction with AsF_5 and SbF_5 respectively at room temperature with removal of SiF_4. The Raman spectra of the salts containing the $[ClOF_2]^+$ ion are in complete agreement with those given in the literature[3]. The hexafluoroarsenate and the new hexafluorosilicate may be quoted as examples. Raman spectrum [cm^{-1}] of $[ClOF_2]^+$: $[ClOF_2]^+[AsF_6]^-$ (values in brackets: cf. Ref. [3]): ν_1 1335 (1332), ν_1 1325 (1321); ν_2 763 (760); ν_3 513 (511); ν_4 410 (408); ν_5 747 (725); ν_6 not observed. $[ClOF_2]_2^+[SiF_6]^{2-}$: ν_1 1333, ν_1 1324; ν_2 728; ν_3 521; ν_4 428; ν_5 not observed; ν_6 383.

Reaction of *(1)* with fluoride ion as Lewis base leads to formation of the hitherto unknown oxotetrafluorochlorate ion $[ClOF_4]^-$:

$$ClOF_3 + CsF \xrightarrow{20\,^\circ C} Cs^+[ClOF_4]^-$$

The bands in the Raman spectrum [cm^{-1}] of the $[ClOF_4]^-$ ion were assigned, by analogy with the assignment of the bands in the Raman spectrum of $XeOF_4$[4], as follows: ν_1 1202 (w); ν_2 455 (vs); ν_3 410 (s); ν_4 349 (vs); ν_5 – ; ν_6 285 (m); ν_7 – ; ν_8 – ; ν_9 204 (w).

If the photochemical reaction of ClF_5 and OF_2 is carried out in a nickel vessel fitted with sapphire window the principal product is $ClOF_3$ *(1)*; small amounts of $ClOF_5$ *(2)* are also formed, but this could not be isolated in pure form. The mass spectrum (negative ions!) of the reaction product contains the fragments $^{37}ClOF_4^-$, $^{35}ClOF_4^-$, $^{37}ClOF_3^-$, and $^{35}ClOF_3^-$, which can originate only from *(2)*, since the spectrum of pure *(1)* does not contain

Table 1. Vibration spectra of $ClOF_3$ *(1)*.

Raman (liquid) [cm^{-1}]			IR (gaseous) [cm^{-1}]		Assignment		
			1370	w	$\nu_2+\nu_7$	A″	
1233	m	p	1226	s	ν_1	A′	$\nu(^{35}Cl—O)$
			1216	m	ν_1	A′	$\nu(^{37}Cl—O)$
			1165	w	$\nu_5+\nu_3$	A″	
			1155	w	$\nu_5+\nu_7$	A″	
			980	w	$\nu_4+\nu_5$	A′	
			900	w	$\nu_4+\nu_6$	A′	
			730	Sh, w	$\nu_4+\nu_9$	A″	
695	s	p	697	Sh, m	ν_2	A′	$\nu_{sym.}$ (Cl—F)
—			(684) [a]		ν_3	A′	ν (Cl—F)
668	Sh, m	dp?	676	vs	ν_7	A″	$\nu_{asym.}$ (Cl—F)
498	Sh, w	p	500	m	ν_4	A′	δ (Cl—O)
467	vs	p	478	m	ν_5	A′	δ (Cl—F)
406	w	p?	400	w	ν_6	A′	$\delta_{wag.}$ (ClF_2)
320	w	dp	325	m	ν_8	A″	$\delta_{twist.}$ (ClF_2)
230	m	dp	230	w	ν_9	A″	$\delta_{rock.}$ (ClF_2)

[a] Determined from combination vibration.

[*] Prof. Dr. O. Glemser and Dipl.-Phys. K. Züchner
Anorganisch-chemisches Institut der Universität
34 Göttingen, Hospitalstrasse 8—9 (Germany)

[**] Note added in proof (26. Oct. 72): In the meantime a series of reports on $ClOF_3$ have been published: *D. Pilipovich, C. B. Lindahl, C. J. Schack, R. D. Wilson*, and *K. O. Christe*, Inorg. Chem. *11*, 2189 (1972); *D. Pilipovich, H. H. Rogers*, and *R. D. Wilson*, *ibid. 11*, 2192 (1972); *K. O. Christe* and *E. C. Curtis*, *ibid. 11*, 2196 (1972); *C. J. Schack, C. B. Lindahl, D. Pilipovich*, and *K. O. Christe*, *ibid. 11*, 2201 (1972); *K. O. Christe, C. J. Schack*, and *D. Pilipovich*, *ibid. 11*, 2205 (1972); *K. O. Christe* and *E. C. Curtis*, *ibid. 11*, 2209 (1972); *K. O. Christe, E. C. Curtis*, and *C. J. Schack*, *ibid. 11*, 2212 (1972).

these ions. Mass spectrum (rel. intensity in %): $^{37}ClOF_4^-$ (0.6), $^{35}ClOF_4^-$ (1.8); $^{37}ClF_4^-$ (1.0), $^{35}ClF_4^-$ (2.9); $^{37}ClOF_3^-$ (1.1), $^{35}ClOF_3^-$ (3.3); $^{37}ClF_3^-$ (8.7), $^{35}ClF_3^-$ (28.3); $^{37}ClOF_2^-$ (32.6), $^{35}ClOF_2^-$ (100.0); $^{37}ClO_3^-$ (15.2), $^{35}ClO_3^-$ (50.0); $^{37}ClF_2^-$ (28.3), $^{35}ClF_2^-$ (95.7); $^{37}ClOF^-$ (8.7), $^{35}ClOF^-$ (23.9); $^{37}ClF^-$ (3.3), $^{35}ClF^-$ (11.9); $^{37}ClO^-$ (0.7), $^{35}ClO^-$ (2.2); F_2^- (52.2); $^{37}Cl^-$ (56.5); $^{35}Cl^-$ (193.5); F^- (>100); O^- (>100).

The recording of the ^{19}F-NMR spectrum was difficult, since inexplicable exchange effects led to extensive line broadening that could not be resolved in the spectrometer. The best spectrum at room temperature showed a broad signal at −146 ppm ($CFCl_3$, external; halfwidth 180 Hz), which broadened with decreasing temperature and had almost disappeared at −30 °C (Fig. 1). At −76 °C a new

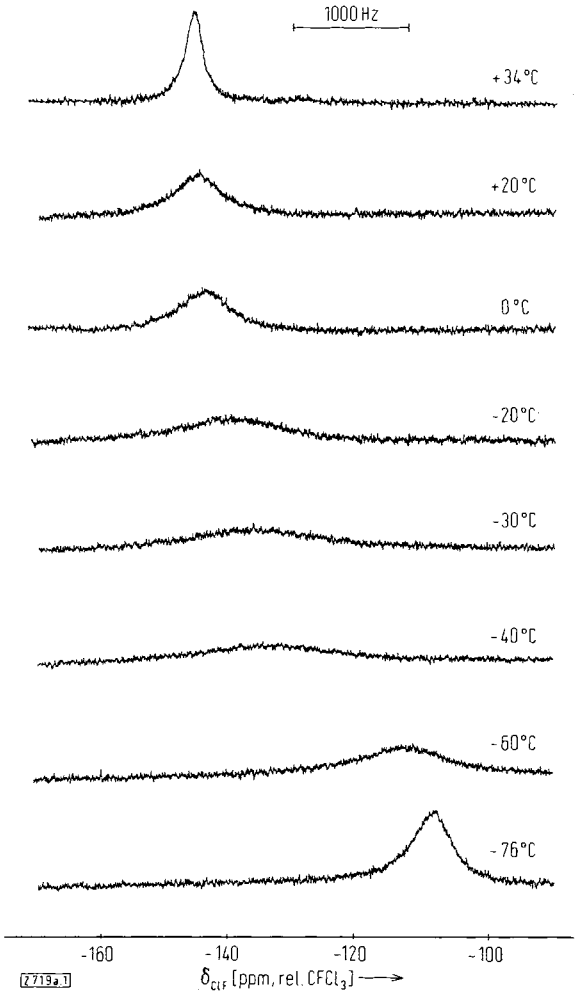


Fig. 1. ^{19}F-NMR spectrum of $ClOF_5$ *(2)* at various temperatures.

signal appeared at −103 ppm (halfwidth 480 Hz). The sample still contained ClF_5, which was identified by a sharp doublet at −256 ppm[5]. We assume that the ligand exchange processes in $ClOF_5$ at −76 °C are so slow that the variously bound F atoms can be differentiated. If the molecule is assumed to have a tetragonal bipyramidal structure, then the signal at −103 ppm can be ascribed to the four equivalent equatorially disposed F atoms. The signal of the axial F atoms could not be observed since the very broad lines due to nuclear quadrupole interactions are spread over a fourfold greater base line with only 1/4 of the area. At room temperature reorientation of structure takes place rapidly, all F atoms becoming equivalent and giving rise to just one signal at −146 ppm.

Experimental:

A 1:1 mixture of ClF_5[6] and OF_2[6] (500 torr) is irradiated in a 3 l quartz flask for 48 hours with a high-pressure mercury vapor lamp. The reaction product is condensed in a quartz trap and purified by evaporation in a high vacuum at −78 °C to free it from unused ClF_5 and OF_2 and other volatile reaction products. In the trap there remained white crystalline $[ClOF_2]_2^+[SiF_6]^{2-}$

The same procedure is adopted when using a nickel flask (3 l), the products, in this case, being condensed in a KEL-F trap.

Received: January 18, 1971 [Z 719a IE]
revised: September 18, 1972
German version: Angew. Chem. *84*, 1147 (1972)

[1] From a lecture by *K. Züchner* at the IV. European Fluorine Symposium in Ljubljana, Yugoslavia, on August 28, 1972.

[2] *R. Bougon, J. Isabey*, and *P. Plurien*, C. R. Acad. Sci. Paris *271*, 1366 (1970).

[3] *R. Bougon, J. Isabey*, and *P. Plurien*, C. R. Acad. Sci. Paris *273*, 415 (1971).

[4] *G. M. Begun, W. H. Fletscher*, and *D. F. Smith*, J. Chem. Phys. *42*, 2236 (1965).

[5] *D. Pilipovich, W. Maya, E. A. Lawton, H. F. Bauer, D. F. Sheehan, N. N. Ogimachi, R. D. Wilson, F. C. Gunderloy jr*, and *V. E. Bedwell*, Inorg. Chem. *6*, 1918 (1967).
Our high-resolution spectrum of pure ClF_5 shows the chemical shift for the chlorine isotopes. $\delta^{35}ClF_4 = -260.35$ ppm ($CFCl_3$, external); $\delta^{37}ClF_4 - \delta^{35}ClF_4 = 0.076$ ppm; $^2J_{FF}(^{37}ClF_4-F) = {}^2J_{FF}(^{35}ClF-F) = 134.2 \pm 0.2$ Hz.

[6] We thank Dr. *Massone*, Kalichemie AG Hannover, for supplying the ClF_5 and OF_2.

Oxohalocyclothiazenes[1]

By *Teh-Pei Lin, Uwe Klingebiel*, and *Oskar Glemser*[*]

Thermal cleavage of $ClSO_2—N{=}PCl_3$ in a vacuum leads to formation of 1,3,5-trioxo-1,3,5-trichloro-1λ⁶,3λ⁶,-5λ⁶,2,4,6-trithiatriazene (trioxotrichlorocyclotrithiazene, "trimeric sulfanuric chloride") $[—N{=}S(O)Cl—]_3$[2]. In the mass spectrum of the products of this reaction there occur also fragments such as $N_5S_5O_5Cl_4^+$ (450), $N_5S_5O_5Cl_3^+$ (415), and $N_4S_4O_3Cl_4^+$ along with corresponding Cl isotope distribution. They cannot, however, be unequivocally ascribed to the larger rings $[NSOCl]_5$ and $[NSOCl]_4$. The completely fluorinated eight-membered ring $[NSOF]_4$ was prepared by thermolysis of $Hg(NSOF_2)_2$. The mass spectrum shows a fragmentation analogous to that of $[NSOF]_3$.

Fluorination of $[NSOCl]_3$ with SbF_3 (1:1.2) at 110 °C and 200 torr for 24 hours affords $[NSOF]_3$ in about 80% yield, whereas the yields obtained previously with other fluorinating agents[3] were much lower. Partially fluorinated products are also formed, usually in yields of about 10%.

$$[NSOCl]_3 + SbF_3 \xrightarrow[-SbCl_3]{110\,°C/200\,torr} [(NSOCl)_2(NSOF)]$$
$$[(NSOCl)(NSOF)_2], [NSOF]_3$$

The fluorinated products are first evaporated in a vacuum (oil-pump) and the $[NSOF]_3$ is subsequently separated

[*] Prof. Dr. O. Glemser, Dipl.-Chem. T.-P. Lin, and Dr. U. Klingebiel
Anorganisch-chemisches Institut der Universität
34 Göttingen, Hospitalstrasse 8—9 (Germany)

from partially fluorinated compounds by distillation at 12 torr. $[(NSOCl)_2(NSOF)]$ and $[(NSOCl)(NSOF)_2]$ are isolated by further distillation in a spinning band column. The *cis-trans* isomers of $[NSOF]_3$ were separated gas-chromatographically and their physical properties were determined. These were in complete agreement with those reported in the literature[3].

The colorless compounds $[(NSOCl)_2(NSOF)]$, b. p. 105 to 110 °C/20 torr, and $[(NSOCl)(NSOF)_2]$, b. p. 168 to 175 °C/760 torr, each occur in three isomeric forms, which are completely separable by analytical gas-chromatography and which can be characterized by the ^{19}F-NMR spectrum.

Trioxodichlorofluorocyclotrithiazene $[(NSOCl)_2(NSOF)]$: Mass spectrum (rel. intensity in %): $N_3S_3O_3FCl_2^+$ (1), $N_3S_3O_3FCl^+$ (7), $N_3S_3O_3F^+$ (21), $NS_2O_2^+$ (1), $NSOCl^+$ (2), $SOCl^+$ (37), SOF^+ (100), NSO^+ (9), SO^+ (43). IR [cm^{-1}]: 1350 (vs), 1205 (w), 1133 (vs), 837 (s), 768 (vs), 691 (m), 557 (vs), and 512 (vs). ^{19}F-NMR ($CFCl_3$, external): δ_{SF} *(cis-cis)* −59 ppm; δ_{SF} *(cis-trans)* −64.8 ppm; δ_{SF} *(trans-cis)* −67.2 ppm[5].

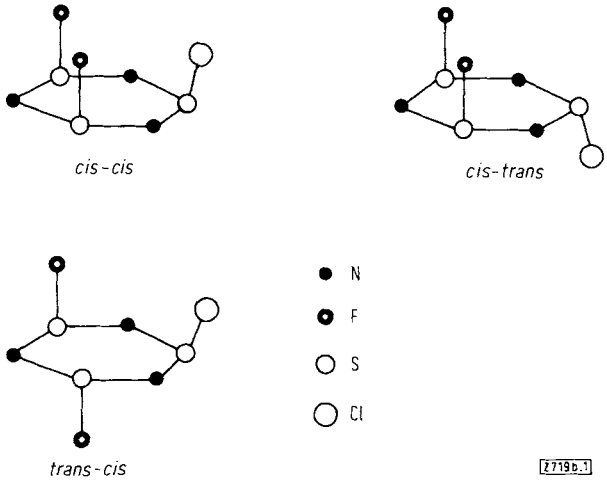


Fig. 1. Isomers of $[(NSOCl)(NSOF)_2]$: simplified models assuming a planar ring, cf. the structure of $[NSOCl]_3$ [4].

Trioxochlorodifluorocyclotrithiazene $[(NSOCl)(NSOF)_2]$ (Fig. 1): Mass spectrum (rel. intensity in %): $N_3S_3O_3F_2Cl^+$ (1), $N_3S_3O_3FCl^+$ (4), $N_3S_3O_3F_2^+$ (100), $SOCl^+$ (4), SOF^+ (98), NSF^+ (1), SF^+ (1), SO^+ (20). IR [cm^{-1}]: 1358 (vs), 1215 (s), 1140 (vs), 840 (s), 775 (vs), 695 (s), 565 (vs), 515 (vs). ^{19}F-NMR ($CFCl_3$, external): δ_{SF} *(cis-cis)* −56.4 ppm; δ_{SF} *(cis-trans)* −66.3 ppm; δ_{SF} *(trans-cis)* [AB spectrum]: δ_{SF_A} −64.0, δ_{SF_B} −71.7 ppm: $J_{F_AF_B}$ 22.0 Hz.

Preparative separation of the isomers is in progress.

Received: September 18, 1972 [Z 719b IE]
German version: Angew. Chem. *84*, 1149 (1972)

[1] Based on a lecture by *T.-P. Lin* at the IV. European Fluorine Symposium in Ljubljana, Yugoslavia, on September 1, 1972.

[2] *A. V. Kirsanov*, Zh. Obshch. Khim. *22*, 81 (1952); Chem. Abstr. *46*, 6984b (1952).

[3] *F. Seel* and *G. Simon*, Z. Naturforsch. *19b*, 354 (1964).

[4] *G. A. Wiegers* and *A. Vos*, Proc. Roy. Soc. (London) *1962*, 387.

[5] Isomerism with respect to fluorine.

Relation between Structure and Proton Donor Strength of Octahedrally Coordinated Tris(3,5-di-isopropylsalicylato)-aluminum(III), -gallium(III), and -indium(III)

By *H. F. Eicke*, *V. Arnold*, and *F. L'Eplattenier*[*]

The surprisingly high proton donor strength of tris(3,5-di-isopropylsalicylato)aluminum(III) $[Al(dips)_3]$[1] in apolar media of very low dielectric constant made it desirable to investigate the structure of this compound. We have found it to have the structure shown in Figure 1.

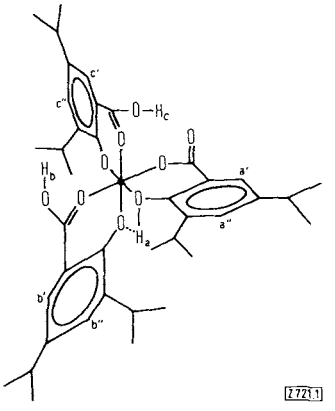


Fig. 1. Structure postulated for tris(3,5-diisopropylsalicylato)aluminum(III).

The 100 MHz NMR spectrum of the CCl_4 solution showed three separate proton signals in the 10—11 ppm region (Table 1 and Fig. 2). Exchange measurements with D_2O showed the protons to exchange at differing rates.

Table 1. Positions of the NMR signals (10—11 ppm) of 3,5-diisopropylsalicylic acid (Hdips) and some of its chelates (100 MHz, CCl_4, δ values).

Cpd.	H_a	H_b	H_c
Hdips	10.42	—	—
$Al(dips)_3$	10.83	10.44	10.25
$Ga(dips)_3$	10.62	10.5	10.05
$In(dips)_3$	—	10.4	—

The signals in the 10—11 ppm region can arise in this case only from hydrogen atoms of COOH and/or OH groups; phenolic protons, however, can be found in this region only if they occur in a hydrogen bridge. Signals of carboxylic protons always lie above 9 ppm.

In principle these conditions can be fulfilled by four types of structures, namely chelate structures with (i) three carboxylic protons, (ii) three phenolic protons contained in H-bridges, (iii) one carboxylic and two bridged phenolic protons, and (iv) two carboxylic and one bridged phenolic proton.

To decide between these four possibilities $Al(dips)_3$ was methylated stepwise by diazomethane. Only two groups

[*] Dr. H. F. Eicke and V. Arnold
Institut für Physikalische Chemie der Universität
CH-4056 Basel, Klingelbergstrasse 80 (Switzerland)
Dr. F. L'Eplattenier
Ciba-Geigy AG, Basel (Switzerland)

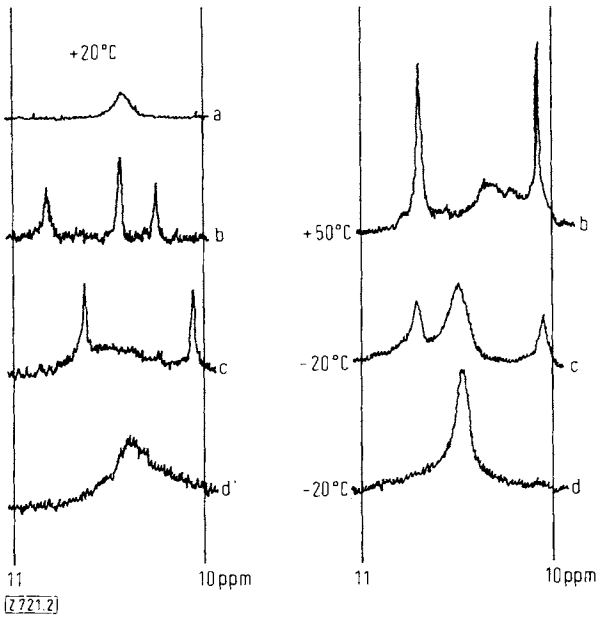


Fig. 2. Temperature-dependence of the 100 MHz NMR spectrum of (a) 3,5-diisopropylsalicylic acid (Hdips), (b) tris(3,5-diisopropylsalicylato)aluminum(III) [Al(dips)$_3$], (c) tris(3,5-diisopropylsalicylato)-gallium(III) [Ga(dips)$_3$], and (d) tris(3,5-diisopropylsalicylato)indium(III) [In(dips)$_3$].

could be methylated in this way. The relative rates of methylation corresponded to those of H/D exchange. IR spectroscopic study of Al(dips)$_3$ showed the C=O stretching vibration of free diisopropylsalicylic acid at 1662 cm^{-1} (see, *e.g.*, Refs. [2 and 3]); this band is shifted to 1683 cm^{-1} by methylation, as is typical of methyl ester formation[4].

On the basis of these NMR and IR results the existence of limiting structure iv appears the most probable (see Fig. 1). This structure explains very simply the chemical shift of the protons of the aromatic ring [indicated by ′ and ″] in the region 7—8 ppm for the two-fold methylated chelates (Table 2).

Table 2. Positions of the NMR signals (7—8 ppm) of 3,5-diisopropylsalicylic acid (Hdips) and some of its dimethylated chelates (100 MHz, CCl_4, δ values).

Cpd.	$H_{a'}$	$H_{a''}$	$H_{b'}$	$H_{b''}$	$H_{c'}$	$H_{c''}$
Hdips	7.59	7.26	—	—	—	—
Dimethylated Al(dips)$_3$	7.82	7.45	7.58	7.25	7.25	7.00
Dimethylated Ga(dips)$_3$	7.87	7.46	7.53	7.19	7.22	7.00
Dimethylated In(dips)$_3$	7.76	7.55	7.55	7.18	7.18	7.03

The difficulty in methylating the phenolic group engaged in intramolecular hydrogen bridging also indicates stability of that bridge, as is to be expected from structure iv. These facts are also in line with the relative rates of H/D exchange, since the intramolecularly bridged proton was completely exchanged only after 48 hours. Activation of the carboxylic proton (H_b) by this hydrogen bridge confers the character of free 3,5-diisopropylsalicylic acid (Hdips)) on ligand (b), as can be seen from the NMR spectrum. This proton should thus have the greatest reactivity (and thus the greatest rate of H/D exchange).

Analogous studies of other elements of group 3B appeared interesting for comparison with the above results. The NMR spectrum of the gallium compound at 20 °C (Fig. 2) in the 10—11 ppm region, unlike that of the aluminum compound, shows marked broadening of the middle proton signal (H_b, Table 1); with Ga(dips)$_3$, cooling to −20 °C results in a considerable decrease in the half-width of the middle band. It is interesting that this spectral region for the aluminum compound at +50 °C is similar to that of the gallium compound at +20 °C. The sign of the chemical shift of the ring protons in tris(3,5-diisopropylsalicylato)-gallium(III) corresponds to that of the δ_H values for the aluminum compound.

In(dips)$_3$ at room temperature gives a broad band between 10 and 11 ppm which becomes appreciably narrower at −20 °C (center of gravity of the band: 10.46 ppm). The slight resolution of the ring proton signals in the 7—8 ppm region indicates increasing equalization of the ligands. In this connection it was particularly important that the three carboxylic protons could be titrated, a finding that indicates the above-designated structure i. As the ionic radius increases from aluminum to indium [$r(Al^{3+})=0.51$ Å, $r(Ga^{3+})=0.62$ Å, and $r(In^{3+})=0.81$ Å] the existence of the H-bridge observed in Al(dips)$_3$ becomes less probable. The metal chelate can then be stabilized only by participation of the central metal atom in the conjugation of the chelate ring[5].

The position of the C=O band in the IR spectrum of Ga(dips)$_3$ and In(dips)$_3$ is exactly the same as for Al(dips)$_3$, as is the shift of the C=O frequency on methylation.

Experimental

3,5-Diisopropylsalicylic acid (3.33 g, 0.015 mol) was dissolved in methanol (25 ml) and added to the metal(III) chloride or nitrate (0.005 mol) in methanol (25 ml). The mixture was treated with 0.1 M methanolic $NaOCH_3$ solution (150 ml) and stirred for 30 min. The solvent was then evaporated in a vacuum and the residual product was dissolved in benzene (100 ml). The resulting solution was cooled to 0 °C to facilitate complete crystallization of the NaCl or $NaNO_3$. The precipitate was separated and the solution was evaporated in a vacuum. To free the resulting metal chelate from benzene it was redissolved in diethyl ether, then freed from solvent in a vacuum and finally dried in a high vacuum.

Received: September 12, 1972 [Z 721 IE]
German version: Angew. Chem. *84*, 1151 (1972)

[1] *H. F. Eicke* and *V. Arnold*, Ber. Bunsenges. phys. Chem., in press.
[2] *J. L. Hales, J. I. Jones*, and *A. S. Lindsay*, J. Chem. Soc. *1954*, 3145.
[3] *K. W. F. Kohlrausch*: Hand- und Jahrbuch der Chemischen Physik. Akademische Verlagsgesellschaft, Leipzig 1943, Vol. 9, VI, p. 373.
[4] *D. Peltier* and *A. Pichevin*, Bull. Soc. Chim. Fr. *1960*, 1141.
[5] *G. E. Kimball*, J. Chem. Phys. *8*, 183 (1940).

Preparation and Some Properties of Di[bis(trifluoromethyl)phosphido]mercury Hg[P(CF$_3$)$_2$]$_2$

By *Joseph Grobe* and *Reinhard Demuth*[*]

As part of our investigations on the preparation of (CF$_3$)$_2$E-derivatives (E = P or As) of electropositive main-group

[*] Prof. Dr. J. Grobe and R. Demuth
Eduard Zintl-Institut für Anorganische und Physikalische Chemie der Technischen Hochschule
61 Darmstadt, Hochschulstrasse 4 (Germany)

elements[1,2] we have been able to synthesize a mercury compound $Hg[P(CF_3)_2]_2$ that is suitable for introduction of $(CF_3)_2E$-groups.

Processes analogous to the preparation of the nitrogen compound $Hg[N(CF_3)_2]_2$[3] are here excluded because in the phosphorus case the starting material does not exist. Indications of the desired compound were obtained particularly from the reaction of $Hg[Si(CH_3)_3]_2$ with $(CF_3)_2PH$[2] in which formation of (trimethylsilyl)bis(trifluoromethyl)phosphane $(CH_3)_3SiP(CF_3)_2$ had to be explained as due to decomposition of the intermediate $(CH_3)_3SiHgP(CF_3)_2$. Also an unstable intermediate compound $(CF_3)_2PHgI$ was postulated for the reaction of $(CF_3)_2PI$ with mercury[4] or mercurous iodide[2].

The interesting new compound $Hg[P(CF_3)_2]_2$ *(1)* was formed on treatment of divinylmercury with bis(trifluoromethyl)phosphane in an all-glass apparatus for 16 days at room temperature, the yield being about 60%:

$$Hg[CH{=}CH_2]_2 + 2\,HP(CF_3)_2 \rightarrow \underset{(1)}{Hg[P(CF_3)_2]_2} + 2\,CH_2{=}CH_2$$

The ethylene liberated was determined quantitatively and identified by molecular weight determination and its IR spectrum.

(1) was also obtained, in about 10% yield, by the analogous reaction of dimethylmercury with $HP(CF_3)_2$. However, this reaction is extremely slow (reaction time: 2 years at 20 °C). Fractional condensation in a high vacuum (receiver at 0 °C) affords compound *(1)* in a purity not exceeding 90% and further purification is prevented by the too small differences between the boiling points of this product and its impurities. The compound inflames at once on contact with air; it was identified as follows by reactions in sealed NMR tubes:

a) *(1)* decomposes when heated, with formation of mercury and $P_2(CF_3)_4$.

b) Treatment of *(1)* with hydrogen iodide leads to HgI_2 and $HP(CF_3)_2$:

$$\underset{(1)}{Hg[P(CF_3)_2]_2} + 2\,HI \rightarrow HgI_2 + 2\,HP(CF_3)_2$$

c) Cleavage of the Hg—P bond by iodosilane affords HgI_2 and $H_3SiP(CF_3)_2$.

d) On reaction of *(1)* with an excess of bis(trifluoromethyl)-arsane the $P(CF_3)_2$ groups are replaced by $As(CF_3)_2$ groups:

$$\underset{(1)}{Hg[P(CF_3)_2]_2} + 2\,HAs(CF_3)_2 \rightarrow \underset{(2)}{Hg[As(CF_3)_2]_2} + 2\,HP(CF_3)_2$$

(2) is thermally less stable than *(1)* and decomposes to mercury and $As_2(CF_3)_4$.

The following data were obtained for compounds *(1)* and *(2)* by ^{19}F-NMR measurements (solvent TMS, CCl_3F as external standard): *(1)* $\Phi_F = 37.1$ ppm; $^2J_{PF} = 58$ Hz, $J_{^{13}CF} = 322$ Hz, $J_{FF'} = 7.9$ Hz; *(2)* $\Phi_F = 32.8$ ppm.

The use of $Hg[E(CF_3)_2]_2$ (E = P or As) as reagent for introduction of $(CF_3)_2E$-groups is currently under examination with further examples[**].

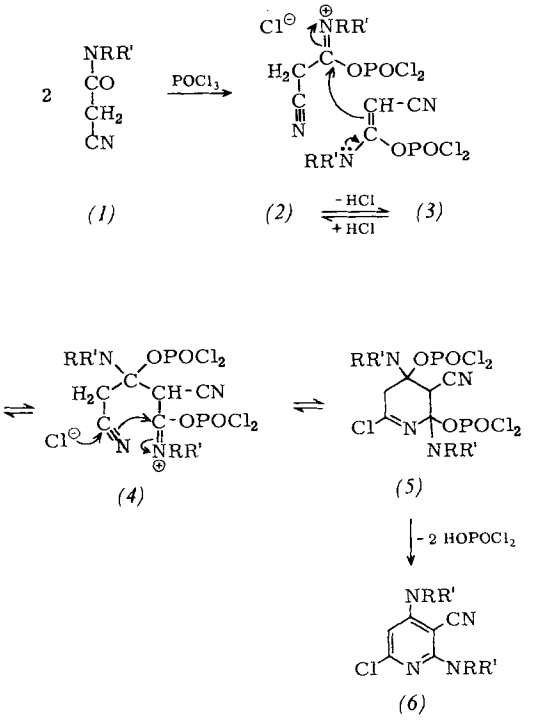
Received: September 18, 1972 [Z 722 IE]
German version: Angew. Chem. *84*, 1153 (1972)

[**] Note added in proof (26. Oct. 72): Further investigations have shown that *(1)* is also formed on reaction of $Hg(CN)_2$ or $Hg(SCH_3)_2$ with $HP(CF_3)_2$, the reaction rate decreasing in the order $Hg(CN)_2 > Hg(CH{=}CH_2)_2 > Hg(SCH_3)_2 > Hg(CH_3)_2$.

The Synthesis of Tetrasubstituted Pyridines from *N,N*-Dialkylcyanoacetamides[1]

By *A. L Cossey, R. L N. Harris, J. L Huppatz,* and *J. N. Phillips*[*]

We wish to report a novel pyridine synthesis based on the reaction between *N,N*-dialkylcyanoacetamides *(1)* and phosphorus oxide trichloride. Thus, when *(1a)* and phosphorus oxide trichloride were heated together at 100 °C a reaction occurred and HCl was evolved. The product



Scheme 1

isolated was a pale yellow crystalline solid, m.p. 108 to 109 °C, whose analysis and mass spectrum indicated that it had the structure *(6a)*[2]. The NMR spectrum ($CDCl_3$) of *(6a)* showed that it contained two dissimilar *N,N*-dimethyl groups ($\delta = 3.13$ and 3.18 ppm, each 6 H/s) and a

[1] *J. Grobe*, Z. Naturforsch. *23b*, 1609 (1968).
[2] *S. Ansari, J. Grobe*, and *P. Schmid*, J. Fluorine Chem. *2*, 281 (1972).
[3] *H. J. Emeléus* and *G. L. Hurst*, J. Chem. Soc. *1964*, 396; *J. A. Young, S. N. Tsoukalas*, and *R. D. Dresdner*, J. Amer. Chem. Soc. *80*, 3604 (1958).
[4] *A. B. Burg* and *W. Mahler*, J. Amer. Chem. Soc. *79*, 4242 (1957).

[*] Dr. R. L. N. Harris, Dr. J. L. Huppatz, Dr. J. N. Phillips, and A. L. Cossey
CSIRO, Division of Plant Industry
Canberra, A.C.T. 2601 (Australia)

single aromatic proton ($\delta = 6.00$, s). The IR spectrum indicated the presence of a conjugated nitrile group. A close examination of the high resolution mass spectrum revealed an $M - CH_3N$ peak, which is characteristic for 2-(*N,N*-dimethylamino)pyridines[3]. In the NMR spectrum of the product of catalytic hydrogenation, m.p. 57—58 °C, two aromatic protons appeared as an AB quartet ($\delta = 6.0$ and 7.82 ppm, $J = 6$ Hz), implying that the chlorine was originally present in a position adjacent to the aromatic proton in the original product.

The substitution pattern in *(6a)* could not be deduced absolutely by spectral means but follows from a consideration of the possible mode of formation of the compound (Scheme 1). This was confirmed in later investigations[4].

Eilingsfeld et al.[5] postulated a similar reaction course for the reaction of simple substituted acetamides in the presence of phosphorus oxide trichloride to give substituted acetoacetamides. The reaction in Scheme 1 is therefore reminiscent of the conversion of malonodinitrile *via* its dimer into 2,4-diamino-5-bromo-4-cyanopyridine on treatment with HBr[6].

The reaction was found to be general for a number of *N,N*-disubstituted cyanoacetamides, representative examples of which are given in Table 1.

Table 1. Pyridines *(6)* from cyanoacetamides *(1)* and $POCl_3$.

Cpd.	R	R'	Yield [%]	M.p. [°C]
(6a)	CH_3	CH_3	84	108—109
(6b)	$-(CH_2)_4-$		86	129—131
(6c)	$-(CH_2)_2-O-(CH_2)_2-$		81	127—128
(6d)	CH_3	C_6H_5	76	115—116

6-Chloro-3-cyano-2,4-bis(N,N-dimethylamino)pyridine

(1a)[7] (11.2 g, 0.1 mol) and $POCl_3$ (33.7 g, 0.22 mol) were mixed and heated on a steam bath under a reflux condenser protected from moisture for 2 h. The orange viscous reaction mixture was cooled, cautiously poured into ice-water, and rendered alkaline with sodium hydroxide solution. The crude product *(6a)* was collected, washed with cold water, and crystallized from aqueous ethanol to give pale yellow needles [9.4 g (84%), m.p. 108—109 °C].

Received: September 5, 1972 [Z 723a IE]
German version: Angew. Chem. *84*, 1183 (1972)

[1] Amide-Acid Chloride Adducts in Organic Synthesis, Part 1.

[2] Very recently this pyridine has been reported to result from the reaction of *N,N*-dimethylcyanoethynylamine with hydrogen chloride [*T. Sasaki* and *A. Kojima*, Tetrahedron Lett. *1971*, 4593] but experimental details of the procedure and physical properties of the compound have not yet been published.

[3] *C. P. Whittle*, Tetrahedron Lett. *1968*, 3689.

[4] *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*, Angew. Chem. *84*, 1184 (1972); Angew. Chem. internat. Edit. *11*, 1099 (1972).

[5] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Chem. Ber. *96*, 2899 (1963).

[6] *R. A. Carboni, D. D. Coffman*, and *E. G. Howard*, J. Amer. Chem. Soc. *80*, 2838 (1958).

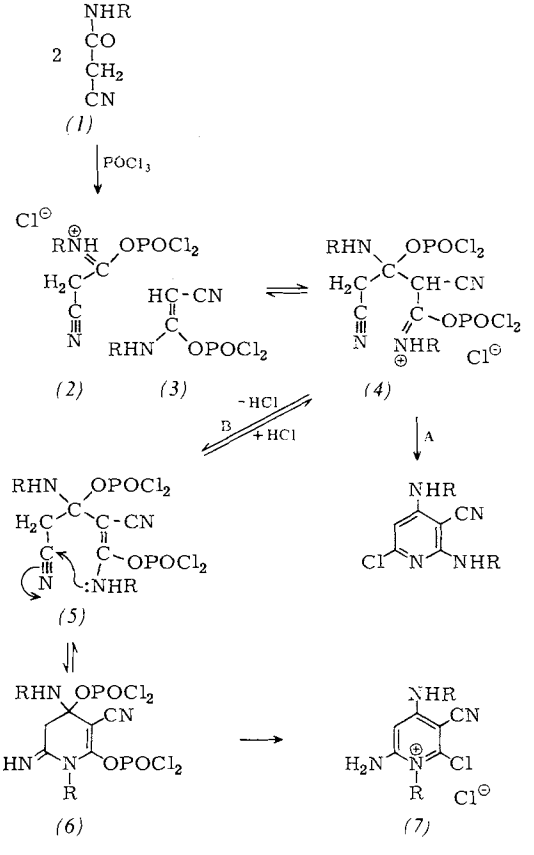
[7] *T. S. Osdene, A. A. Santilli, L. E. McCardle*, and *M. E. Rosenthale*, J. Med. Chem. *10*, 165 (1967).

The Synthesis of *N*-Alkylpyridinium Salts from *N*-Alkylcyanoacetamides[1]

By *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*[*]

N,N-Dialkylcyanoacetamides react in the presence of phosphorus oxide trichloride to give pyridine derivatives[2]. We now describe an extension of this reaction in which *N*-alkylpyridinium salts can be synthesized.

When *N*-methylcyanoacetamide *(1a)* and phosphorus oxide trichloride were heated together in chloroform a yellow precipitate rapidly crystallized out. On isolation the product proved to be a water soluble salt whose analysis indicated the structure *(7a)*. The NMR spectrum (D_6-DMSO) showed signals at $\delta = 2.87$ (3H, doublet collapsing to a singlet on deuteration, $NH-CH_3$), 3.73 ($s/\geqslant N-CH_3$), and 6.00 ppm (s/aromatic H). The presence of a broad variable absorption in the region $\delta = 4.0—7.0$ indicated the presence of other exchangeable protons. The IR spectrum indicated the presence of a conjugated nitrile group and there was strong absorption in the C=N region. The mass spectrum showed a molecular ion for the free base at *m/e* 196 (with Cl = 35).



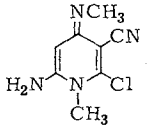
Scheme 1

We believe that the pyridinium salt is formed as shown in Scheme 1. The compound *(4)* may cyclize to the pyridine derivative (route A)[2] or be converted, *via* the intermediates

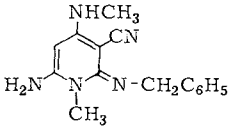
[*] Dr. R. L. N. Harris, Dr. J. L. Huppatz, Dr. J. N. Phillips, and A. L. Cossey
CSIRO, Division of Plant Industry
Canberra, A.C.T. 2601 (Australia)

(5) and *(6)* (route B), into the pyridinium salt *(7)*. It appears that this latter route (a prospect not available with *N,N*-substituted cyanoacetamides) must be favored when it can occur, since in the many examples studied, *N*-alkylcyanoacetamides on treatment with phosphorus oxide trichloride gave only *N*-alkylpyridinium salts of type *(7)*, usually in yields exceeding 80%.

The chemical properties of the salt *(7a)* further substantiated the structure proposed. The free base was readily obtained and on the basis of its NMR spectrum was assigned the 1,4-dihydropyridine structure *(8a)* (in D_6-DMSO both $N-CH_3$ signals appear as singlets at $\delta = 2.6$ and 5.52 ppm). The halogen is readily replaced by nucleophiles; for example, reaction with benzylamine leads to compound *(9a)*, whose 1,2-dihydropyridine structure follows from NMR evidence [in D_6-DMSO one of the $N-CH_3$ groups was observed to be coupled to an exchangeable proton (doublet at $\delta = 2.72$ ppm, collapsing to a singlet on deuteration; α-benzyl protons give a singlet at $\delta = 4.87$ ppm]. The formation of benzyliminopyridines eliminates possible structures in which the chlorine occupies a position *meta* to the ring nitrogen.

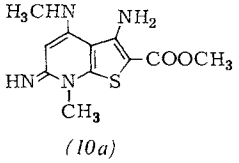


(8a)

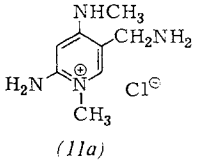


(9a)

Reaction of *(7a)* with methyl thioglycollate results in rapid formation of the fused thieno[2,3-*b*]pyridine *(10a)*. This indicates that the active chlorine in *(7a)* must be adjacent to the nitrile group. Similarly reaction with hydrazine gave the pyrazolo[4,5-*b*]pyridine. Finally, catalytic hydrogenation of *(7a)* gave the pyridinium salt *(11a)*, whose NMR spectrum in D_2O (two singlets for the ring protons at $\delta = 6.02$ and 7.73 ppm) clearly eliminates possible structures for *(7a)* in which the chlorine substituent is adjacent to an unsubstituted position.



(10a)



(11a)

Several examples of compounds of type *(7)* are given in Table 1.

Table 1. *N*-Alkylpyridinium salts *(7)* from *N*-alkylcyanoacetamides *(1)* and $POCl_3$.

Cpd.	R	Yield [%]	M.p. [°C]
(7a)	CH_3	80	>250
(7b)	n-C_4H_9	86	230—231
(7c)	n-C_8H_{17}	75	233—234

6-Amino-2-chloro-3-cyano-1-methyl-4-methylamino-pyridinium chloride (7a)

(1a) (9.8 g, 0.1 mol) was dissolved in chloroform (50 ml) and $POCl_3$ (15.3 g, 0.1 mol) added. The reaction mixture was warmed on a steam bath under reflux for 2 h during which time the product crystallized. It was collected and recrystallized from methanol to give a pale yellow solid m.p. >250°C (9.4 g, 80%).—Higher homologs of *(7a)* are soluble in chloroform; they are isolated by removal of the solvent *in vacuo* and treatment of the residue with cold methanol.

Received: September 5, 1972 [Z 723b IE]
German version: Angew. Chem. *84*, 1184 (1972)

[1] Amide-Acid Chloride Adducts in Organic Synthesis, Part 2.—Part 1: [2].

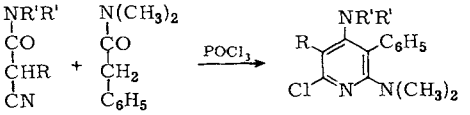
[2] *A. L. Cossey, R. L. N. Harris, J. L. Huppatz* and *J. N. Phillips*, Angew. Chem. *84*, 1183 (1972); Angew. Chem. internat. Edit. *11*, 1098 (1972).

Synthesis of Pentasubstituted Pyridines from *C*-Alkyl-*N,N*-dialkylcyanoacetamides[1]

By *A. L. Cossey, R. L. N. Harris, J. L. Huppatz,* and *J. N. Phillips*[*]

Pyridines are obtained by a one-step synthesis from *N,N*-dialkylcyanoacetamides by reaction with phosphorus oxide trichloride[2]. We now describe an extension of this synthesis leading to pentasubstituted pyridines.

When *C*-methyl or *C*-ethyl-*N,N*-dialkylcyanoacetamides are heated with phosphorus oxide trichloride no pyridines are formed, presumably because the irreversible aromatization step, which would involve alkyl elimination or rearrangement, is energetically less favorable. Inclusion of a suitable substrate, however, allows a mixed condensation to occur; for example, the cyanoacetamide *(1a)* and *N,N*-dimethylphenylacetamide *(2)* react in $POCl_3$ (100°C, 2 h) to give the pentasubstituted pyridine *(3a)* as the only isolable product in 16% yield[3]. Further examples are given in Table 1.



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

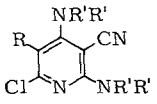
Table 1. Pyridines *(3)* from the reaction of *C*-alkyl-*N,N*-dialkylcyanoacetamides *(1)*, *N,N*-dimethylphenylacetamide *(2)* and $POCl_3$.

Cpd.	R	R′	R′	Yield [%]	M.p. [°C]
(3a)	CH_3	CH_3	CH_3	16	119—120
(3b)	C_2H_5	CH_3	CH_3	17	73— 74
(3c)	CH_3	$-(CH_2)_4-$		35	110—111
(3d)	C_2H_5	$-(CH_2)_4-$		40	84— 85

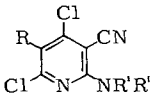
When the compounds *(1)* are substituted at the methylene group by *i*-propyl or benzyl, however, two molecules react with $POCl_3$ with elimination of the *iso*-propyl or benzyl group. For example, *(1f)* reacts in $POCl_3$ (100°C, 2 h) to give a mixture of the two pyridines *(4f)* and *(5f)* (total yield 54%), which can be separated by careful chromatography on silica gel. When the reaction time is extended to 16 hours, the pyridine *(5f)* is the only product isolated

[*] Dr. R. L. N. Harris, Dr. J. L. Huppatz, Dr. J. N. Phillips, and A. L. Cossey
CSIRO, Division of Plant Industry
Canberra, A.C.T. 2601 (Australia)

(88% yield). In contrast, *(1g)* under the same conditions gives only the pyridine *(4g)* (62% yield). Further examples are listed in Table 2.



(4)



(5)

Table 2. Pyridines *(4)* and *(5)* from reaction of *C*-alkyl-*N*,*N*-dialkylcyanoacetamides *(1)* with $POCl_3$.

Cpd.	R	R′	R′	Yield [%] 2 h	Yield [%] 16 h	M.p. [°C]
(4e)	i-C_3H_7	CH_3	CH_3	9	—	80— 81.5
(5e)	i-C_3H_7	CH_3	CH_3	10	75	53— 54
(4f)	i-C_3H_7	$-(CH_2)_4-$		31	—	109—110
(5f)	i-C_3H_7	$-(CH_2)_4-$		23	88	105—106
(4g)	i-C_3H_7	C_2H_5	C_2H_5	—	62	Oil
(5h)	$C_6H_5CH_2$	CH_3	CH_3		60[a]	78— 79

[a] Benzyl chloride was isolated as a by-product in this reaction.

5-Ethyl-6-chloro-2-(N,N-dimethylamino)-3-phenyl-4-pyrrolidinopyridine (3d)

Compounds *(1d)*[4] (3.3 g, 0.02 mol), *(2)*[5] (3.3 g, 0.02 mol), and $POCl_3$ (7.5 g, 0.042 mol) are mixed and heated on a steam bath under a reflux condenser protected from moisture for two hours. The orange reaction mixture is cooled, cautiously poured into ice-water and rendered alkaline with sodium hydroxide solution. The crude product is extracted with chloroform (3 × 50 ml) and the combined extracts are washed once with water and dried (Na_2SO_4). After evaporation of the solvent the remaining dark red, viscous oil (6.3 g) is chromatographed on a silica-gel column (30 × 4 cm) using chloroform-petroleum ether (b.p. 40—60 °C) (1 : 1) as eluent. The first fractions eluted from the column afford a pale yellow oil (2.6 g, 40%) which subsequently solidifies and can be recrystallized from aqueous ethanol (as colourless plates, m.p. 84—85 °C).

Received: September 5, 1972 [Z 723c IE]
German version: Angew. Chem. *84*, 1185 (1972)

[1] Amide-Acid Chloride Adducts in Organic Synthesis, Part 3.—Part 2: *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*, Angew. Chem. *84*, 1184 (1972); Angew. Chem. internat. Edit. *11*, 1099 (1972).

[2] *A. L. Cossey, R. L. N. Harris, J. L. Huppatz*, and *J. N. Phillips*, Angew. Chem. *84*, 1183 (1972); Angew. Chem. internat. Edit. *11*, 1098 (1972).

[3] The structures of all compounds reported are consistent with NMR and mass spectral data.

[4] *H. F. Schwartz, L. F. Worrell*, and *J. N. Delgada*, J. Pharm. Sci. *56*, 80 (1967).

[5] *H. Rapoport* and *R. M. Bonner*, J. Amer. Chem. Soc. *72*, 2783 (1950).

Metalation at Primary, Secondary, and Tertiary Carbon Atoms in Open-Chain and Cyclic Nitrosamines[**]

By *Dieter Seebach* and *Dieter Enders*[*]

We recently reported our successful metalation of dimethylnitrosamine with lithium diisopropylamide and some re-

Table 1. Nitrosamines of types *(5)*—*(9)* [a]. Yields are not optimized. Metalation was by lithium diisopropylamide for 10 min at −80 °C, after which the electrophile was added, and the mixture was stirred for 5—10 h at −80 °C and then worked up [b]

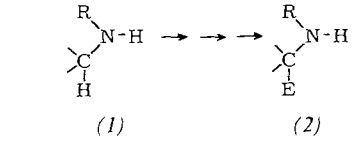
No.	Nitrosamine of type *(3)*	Electrophile	Product type	Yield [%]	M.p. [°C] or b.p. [°C/torr] [c]
1	Ethylmethylnitrosamine	Acetaldehyde	*(7)*	75	80/0.1
2	Isopropylmethylnitrosamine	Acetaldehyde	*(7)*	85	85/0.01
3	Isopropylmethylnitrosamine	Benzyl bromide	*(6)*	90	[b]
4	*tert*-Butylmethylnitrosamine	Acetaldehyde	*(7)*	95	70/0.03
5	Benzylmethylnitrosamine	Acetaldehyde	*(9a)* + *(9b)*	100	120—130/0.01
6	Methylphenylnitrosamine	Acetaldehyde	*(7)* [d]	58	100/0.001
7	Di-*n*-hexylnitrosamine	Benzyl bromide	*(6)*	>95	[g]
8	Diisopropylnitrosamine	Acetaldehyde	*(7)*	40	46.5—47 95/0.01
9	1-Nitrosopyrrolidine	Benzyl bromide	*(6)*	90	130/0.001
10	1-Nitrosopyrrolidine	CO_2	*(5)*	20	>99 (dec.) [h]
11	1-Nitrosopiperidine [f]	Acetaldehyde	*(7)* [e]	90	100/0.001
12	1-Nitrosopiperidine	Benzyl bromide	*(6)*	60	150/0.01
13	1-Methyl-4-nitrosopiperazine	Acetaldehyde	*(7)* [e]	45	120/0.001
14	Perhydro-1-nitrosoazepine	Benzophenone	*(8)*	90	140

[a] The new compounds gave correct elemental analyses. The IR and NMR spectra are in accord with the structures assigned.
[b] See experimental.
[c] Bath-temperature on molecular distillation.
[d] Metalated with lithium cyclohexylisopropylamide or lithium dicyclohexylamide in a mixture of THF, ether, and pentane at −115 °C.
[e] Mixture of diastereoisomers.
[f] Metalation for 3.5 h.
[g] Undistillable oil. Removal of the nitroso group (HCl in benzene) gives the secondary amine as hydrochloride which sinters at 50 °C and melts above 80 °C.
[h] M.p. 97.5—107 °C [3].

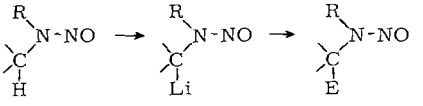
[*] Prof. Dr. D. Seebach and Dipl.-Chem. D. Enders
Institut für Organische Chemie
Fachbereich Chemie der Universität
63 Giessen, Ludwigstrasse 21 (Germany)

[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

actions with electrophiles that involved C—C linkage[1]. We drew the somewhat premature conclusion that this provided a general method *(1)* → *(2)* for chain-extension at the α-C atom of secondary amines.



(1) *(2)*



(3) *(4)*

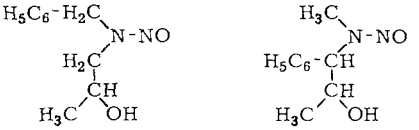
(5), E = COOH
(6), E = C_6H_5-CH_2
(7), E = CH_3-CH(OH)
(8), E = $(C_6H_5)_2C(OH)$

We can now report that the reaction has wide applicability, as shown by H/Li exchange *(3)* → *(4)* on a variety of nitrosamines and subsequent reaction with CO_2, benzyl bromide, acetaldehyde, or benzophenone to give products of types *(5)* to *(8)* (Table 1).

The following should be emphasized:

1. The methylnitrosamines *(3)* may have R = ethyl, isopropyl, *tert*-butyl, benzyl, or phenyl (Table 1, Nos. 1—6).

2. Metalation of ethylmethyl- and isopropylmethyl-nitrosamine occurs selectively at the CH_3 group, but that of benzylmethylnitrosamine is not specific [see *(9a)* and *(9b)* from acetaldehyde].



(9a) *(9b)*

3. Both secondary[2] and tertiary hydrogen of *(3)* can also be replaced electrophilically (Nos. 5, 7, 8).

4. Five- (Nos. 9 and 10), six- (Nos. 11—13), and seven-membered (No. 14) cyclic nitrosamines react in good yield independently of the ring size.

The danger of working with the carcinogenic nitrosamines can be minimized by removing the nitroso group after the reaction without previous workup, as described in the following experimental procedure.

Isopropylphenethylamine from isopropylmethylnitrosamine:

Isopropylmethylnitrosamine (33.0 mmol, 3.06 ml) is added rapidly to a solution of lithium diisopropylamide (34.5 mmol) [from the amine and butyllithium in THF (100 ml)] at −78 °C and is treated 10 min later with benzyl bromide (35 mmol, 4.1 ml). After 3 h the cooling bath is removed and the solvent distilled off. The residue is dissolved in 7% HBr-glacial acetic acid (65 ml) and set aside at room temperature for 30 min, whereafter the amine is isolated by adding the whole cautiously and with cooling to aqueous sodium hydroxide solution covered with a layer of ether and finally precipitating the hydrochloride [m.p. 162.5 to 165.5 °C (168—169 °C[4]), yield 4.79 g, 79%] by passing gaseous hydrogen chloride into the ethereal phase previously separated from the aqueous layer.

Received: September 21, 1972 [Z 724a IE]
German version: Angew. Chem. *84*, 1186 (1972)

[1] *D. Seebach* and *D. Enders*, Angew. Chem. *84*, 350 (1972); Angew. Chem. internat. Edit. *11*, 301 (1972).

[2] Prof. *R. R. Fraser* (Ottawa) informed us of his unpublished results to the effect that dibenzylnitrosamine yields derivatives in high yield by way of the lithium compound, but that cyclic nitrosamines do not react or do so only poorly.

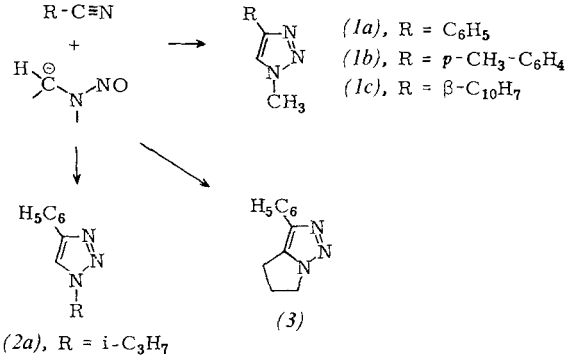
[3] *W. Lijinsky, L. Keefer*, and *J. Loo*, Tetrahedron *26*, 5137 (1970).

[4] *S. L. Shapiro, V. A. Parrino*, and *L. Freedman*, J. Amer. Chem. Soc. *81*, 3728 (1959).

Reaction of Metalated Nitrosamines with Nitriles. A New Method for Preparation of *v*-Triazoles[**]

By *Dieter Seebach* and *Dieter Enders*[*]

Treatment of metalated nitrosamines[1] with nitriles leads to 40—70% yields of *v*-triazoles[2]. 1-Methyl-4-phenyl-1,2,3-triazole *(1a)*, m.p. 122 °C (123 °C[3]) is obtained from benzonitrile and metalated dimethylnitrosamine in this way. Varying the nitrile components afforded the corresponding *p*-tolyl *(1b)* (m.p. 134 °C) and β-naphthyl derivative *(1c)* (m.p. 180 °C); the triazoles *(2a)* (m.p. 43.5 °C), *(2b)* (m.p. 96.4 °C), and *(3)* (m.p. 156 °C) are formed by reaction of benzonitrile with metalated isopropylmethylnitrosamine, *tert*-butylmethylnitrosamine, and 1-nitrosopyrrolidine, respectively. The NMR spectra of compounds *(1)* and *(2)* include a characteristic signal for the proton at position 5 at δ = 7.5—7.9 ppm; *(3)* shows CH_2 multiplets at δ = 2.95, 3.12, and 4.36 ppm.



(1a), R = C_6H_5
(1b), R = *p*-CH_3-C_6H_4
(1c), R = β-$C_{10}H_7$

(2a), R = i-C_3H_7
(2b), R = *tert*-C_4H_9

(3)

Since a great variety of nitrosamines can be metalated[1] this method makes di- and trisubstituted triazoles generally accessible and these are interesting as precursors of azirines[4]; enolizable nitriles are not amenable to the reaction described here[5]. Studies on the mechanism of the reaction and on photolysis and thermolysis of the products are in progress.

[*] Prof. Dr. D. Seebach and Dipl.-Chem. D. Enders
Institut für Organische Chemie
Fachbereich Chemie der Universität
63 Giessen, Ludwigstrasse 21 (Germany)

[**] We thank the Deutsche Forschungsgemeinschaft for financial support.

1-Methyl-4-phenyl-1,2,3-triazole (1a)

Pure dimethylnitrosamine (1.62 ml, 22 mmol) is added with stirring to a solution of lithium diisopropylamide (23 mmol) in anhydrous THF (70 ml) (from 3.22 ml of diisopropylamine and 14.2 ml of *n*-butyllithium; 1.6 M in *n*-hexane) at −78 °C and the mixture is treated 10 min later with benzonitrile (1.03 ml, 10 mmol). After being kept for 10 h at the temperature of Dry Ice, the mixture is treated with a solution of glacial acetic acid (1.32 ml, 23 mmol) in THF (5 ml). Working up with methylene dichloride affords a crystalline crude product that, recrystallized from CCl_4 or ligroin, forms colorless needles, m.p. 122 °C (yield 1.15 g, 72%).

Received: September 21, 1972 [Z 724b IE]
German version: Angew. Chem. *84*, 1187 (1972)

[1] *D. Seebach* and *D. Enders*, Angew. Chem. *84*, 350, 1186 (1972); Angew. Chem. internat. Edit. *11*, 301, 1101 (1972).

[2] *v*-Triazoles have previously been prepared from: a) 1,2-dicarbonyl compounds and hydrazines or hydroxylamine/hydrazines; b) α-diazo carbonyl compounds and primary amines; c) nitriles and diazo compounds; and d) acetylenes and azides (the most important method): *F. R. Benson* and *W. L. Savell*, Chem. Rev. *46*, 1 (1950).

[3] *H. Hoberg*, Liebigs Ann. Chem. *707*, 147 (1967).

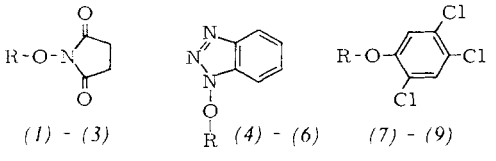
[4] *C. W. Rees et al.*, Chem. Commun. *1971*, 532, 1518, 1519.

[5] For example, acetonitrile gives no triazole on treatment with lithiated dimethylnitrosamine.

Model Reactions for Synthesis of Pharmacologically Active Polymers by Way of Monomeric and Polymeric Reactive Esters[**]

By *Hans-Georg Batz*, *Giselher Franzmann*, and *Helmut Ringsdorf*[*]

Pharmacologically active polymers have aroused increasing interest in recent years[1]. These polymers may act as drugs themselves or only after release of lower-molecular species. The problem is to effect linkage[2] of the drug with monomers and polymers under mild conditions to ensure complete retention of the biological activity and exclusion of side reactions.



(1) - (3) *(4) - (6)* *(7) - (9)*

We have examined reactive esters, of the type known in peptide chemistry[3], for their suitability as precursors of pharmacologically active polymers. By treating unsaturated acid chlorides or anhydrides, esters or isocyanates with *N*-hydroxy compounds and chloro- or nitro-phenols[4] we have prepared the reactive unsaturated esters *(1)* to *(9)* shown in Table 1.

The monomers *(1)*, *(2)*, *(7)*, and *(8)* are resistant to hydrolysis; they react at 0 °C in neutral or weakly alkaline water/dioxane solution with amines, giving amides in yields of up to 80%. The monomers *(4)* and *(5)* react at room temperature with alcohols as well as with amines and are hydrolyzable. Compounds *(3)*, *(6)*, and *(9)* were subjected to reaction only as polymers since the monomers lose acetaldehyde relatively easily[5].

All the monomers were subjected to radical polymerization. The homopolymers of *(1)*—*(4)* and *(6)* are soluble in dimethyl sulfoxide, and the other polymers dissolve also in other polar solvents, *e.g.* tetrahydrofuran and methylene dichloride. Copolymers that dissolve in water or organic solvents were prepared by copolymerization of the monomers *(1)*—*(9)* with 1-vinylpyrrolidone, methacrylamide, acrylamide, or styrene.

Like the monomers, the polymers of active esters react readily with nucleophilic reagents. This makes possible to effect reaction of pharmacologically active compounds

Table 2. Model reactions for synthesis of pharmacologically active polymers [22 °C, in methylene dichloride, polymer 0.4 mol/l (monomer units), cyclohexylamine 0.8 mol/l].

Cpd.	Reagent	Reaction course	Time [d]	Conversion
Poly-*(4)*	Cyclohexylamine	Homogeneous after *ca.* 1 min	1	100
Poly-*(1)*	Cyclohexylamine	Heterogeneous 1 d	5	70
Poly-*(2)*	Cyclohexylamine	Heterogeneous 3 d	5	60
Poly-*(3)*	Cyclohexylamine	Heterogeneous 3 d	5	60—70
Poly-*(8)*	Cyclohexylamine	Homogeneous	5	15
Poly-*(1)*	Ammonia [a]	Heterogeneous 10 h	1	90

[a] Solvent: H_2O. Polymer 0.1 mol/l (monomer units); NH_3 1.3 mol/l.

Table 1. Reactive esters *(1)*—*(9)*.

Cpd.	R	M.p. [°C]	Yield [%]	C=O Bands [cm^{-1}]	NMR δH_A	(Vinyl) δH_B	[ppm] δH_C
(1)	CH_2=CH—CO	68	65	1735, 1775	6.13	6.70	6.50
(2)	CH_2=C(CH_3)—CO	103	76	1730—1770	5.95	6.45	—
(3)	CH_2=CH—NH—CO	111	85	1730—1770	4.39	4.68	6.57
(4)	CH_2=CH—CO	122	30	1705	6.15	6.78	7.38
(5)	CH_2=C(CH_3)—CO	40	30	1785	6.0	6.57	—
(6)	CH_2=CH—NH—CO	140	80	1725	4.51	5.08	6.50
(7)	CH_2=CH—CO	65	70	1750	6.05	6.73	6.32
(8)	CH_2=C(CH_3)—CO	60	65	1740	5.82	6.42	—
(9)	CH_2=CH—NH—CO	130	40	1725	4.45	4.65	6.65

[*] Dr. H.-G. Batz, Dipl.-Chem. G. Franzmann, and Prof. Dr. H. Ringsdorf
Institut für organische Chemie der Universität
65 Mainz, Johann-Joachim-Becher-Weg 18 (Germany)

[**] Part 3 of Pharmacologically active polymers.—Part 2: *H. Ringsdorf, A. G. Heisler, F. H. Müller, E. H. Graul*, and *W. Ruther*, Biol. Aspects Rad. Protect. *1971*, 138.

with polymers without racemization or side reactions. Table 2 shows the model reactions effected with cyclohexylamine and ammonia. Methyl polyacrylate and polymethacrylate do not react under the stated conditions.

The polymers prepared from *(4)*—*(6)* and containing benzotriazole are hydrolyzed in aqueous sodium carbonate solution even at room temperature. If polymeric *(4)*—*(6)* undergoes partial reaction with the model compounds and is then hydrolyzed, polymers are obtained containing carboxyl groups [from poly-*(4)* and poly-*(5)*] or amino groups [from poly-*(6)*]. Neutral polymers are obtained by treatment of the residual active ester groups with an excess of amine or ammonia.

N-Hydroxysuccinimide methacrylate (2)[6]

Triethylamine (0.5 mol) and methacryloyl chloride (0.5 mol), each in 150 ml of CH_2Cl_2, are added dropwise with stirring and ice cooling to *N*-hydroxysuccinimide (0.5 mol) in anhydrous methylene dichloride (200 ml). After 6 hours' stirring at room temperature the precipitated triethylammonium chloride is removed and the filtrate is shaken with, successively, water, a little saturated sodium hydrogen carbonate solution, and again water, dried and evaporated. The residue is recrystallized from ethyl acetate/light petroleum; yield 70 g (77%).

Polymerization

The ester *(2)* (0.1 mol) is kept in anhydrous tetrahydrofuran (200 ml) containing 0.5 mol-% of azodiisobutyronitrile for 8 h at 60 °C. The precipitated polymer is filtered off, digested with tetrahydrofuran, filtered off again, and dried; yield 15 g, 81%.

Reaction with amines: poly-N-acryloylcyclohexylamine

Poly-1-acryloyloxybenzotriazole [poly-*(4)*] (1.89 g, 0.01 mol) is mixed with cyclohexylamine (2.26 ml, 0.02 mol) in methylene dichloride (25 ml). The solution becomes homogeneous after *ca.* 1 min. After 1 day the product is precipitated by ether and reprecipitated from methanol/water. The poly-1-acryloyloxycyclohexylamine was characterized by elemental analyis and its IR and NMR spectra. The conversion amounted to 100%.

Received: June 23, 1972
Supplemented: October 16, 1972 [Z 725 IE]
German version: Angew. Chem. *84*, 1189 (1972)

[1] *H. Lee*, Polymer Reprints *12*, No. 2, p. 73 (1971); *S. J. Kotenko* and *Yu. J. Lisunkin*, Farm. Zh. (Kiev) *26*, 17 (1971); *H. Ringsdorf*, Strahlentherapie *32*, 627 (1967); *K. P. Khomyakov, A. Virnik*, and *Z. Rogovin*, Russ. Chem. Rev. *33*, 462 (1969).

[2] *R. Axen* and *S. Ernback*, Eur. J. Biochem. *18*, 351 (1971); *E. M. Crook, K. Brocklehurst*, and *C. H. Warton* in *S. P. Colowick* and *N. O. Kaplan*: Methods in Enzymology. Academic Press, New York 1971, Vol. 19, pp. 963 ff.; *L. Goldstein, ibid.* pp. 935 ff.; *H. P. Orth* and *W. Brümmer*, Angew. Chem. *84*, 319 (1972); Angew. Chem. internat. Edit. *11*, 249 (1972).

[3] *G. W. Anderson, J. E. Zimmermann*, and *F. M. Callahan*, J. Amer. Chem. Soc. *86*, 1839 (1964); *F. Weygand, D. Hoffmann*, and *E. Wünsch*, Z. Naturforsch. *21b*, 426 (1966); *W. König* and *R. Geiger*, Chem. Ber. *103*, 788 (1970).

[4] *H. Morawetz*, J. Amer. Chem. Soc. *83*, 1738 (1961).

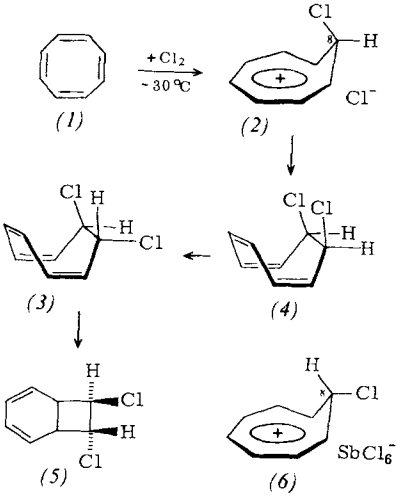
[5] *G. Welzel*, Dissertation, Universität Freiburg 1960; *C. J. Overberger, G. Montando*, and *S. Ishida*, J. Polymer Sci. A 1, *7*, 35 (1969).

[6] *H.-G. Batz*, Dissertation, Technische Universität München 1970.

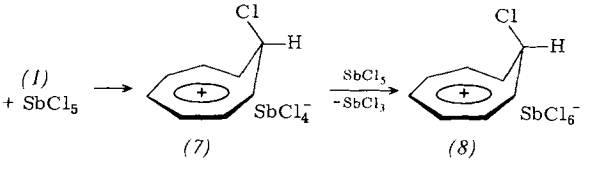
The Primary Step in the Halogenation of Cyclooctatetraene

By *Rolf Huisgen* and *Johann Gasteiger*[*]

The dichloride *(5)* of cyclooctatetraene, isolated by *Reppe, Schlichting, Klager*, and *Toepel*[1], and the corresponding dibromide are the result of a multi-stage reaction sequence that is analogous for chlorination and bromination. We have obtained the dichlorides *(3)* to *(5)* in crystalline form and have elucidated their thermodynamic and kinetic interrelationships[2]. Halogenation of *(1)* is unusually rapid and affords the *cis*-dichloride *(4)* exclusively.



The *endo*-8-chlorohomotropylium chloride *(2)* presumed to be the primary product provided the key to the understanding of the fast rate of chlorination and of the anomalous course leading to the *cis*-compound. The fluorosulfonate *(2)* (FSO_3^- in place of Cl^-) combines with a chloride ion to give the *cis*-dichloride *(4)*, whereas the *exo*-8-chlorohomotropylium salt *(6)* and Cl^- afford the *trans*-dichloride *(3)*[3]. Our attempts to demonstrate the primary *endo*-chlorination *(1)* → *(2)* were not at first entirely successful. Chlorination of *(1)* at −90 °C in the presence of antimony pentachloride afforded mixtures of *endo*- and *exo*-8-chlorohomotropylium hexachloroantimonate[3]; the disturbing formation of *(6)* was ascribed to the subsequent reaction *(4)* + $SbCl_5$ → *(6)*, which occurred quantitatively in a separate experiment[4].

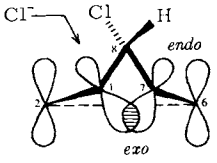


In our search for a chlorinating agent that would stop the reaction of *(1)* reliably at the homotropylium stage *(2)*, we have found that antimony pentachloride itself plays a unique double role as Cl^+ donor and strong Lewis acid. When 2 equivalents of $SbCl_5$ react with *(1)* in methylene chloride at −60 °C the crystalline *endo*-salt *(8)* separates

[*] Prof. R. Huisgen and Dr. J. Gasteiger
Institut für Organische Chemie der Universität
8 München 2, Karlstrasse 23 (Germany)

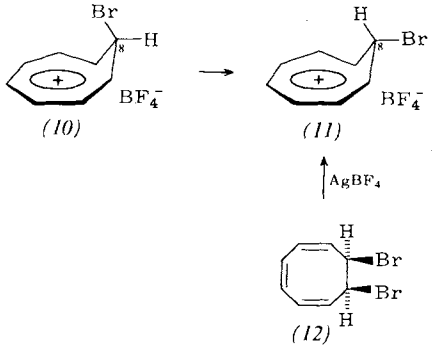
in 94% yield (correct CH analyses); *(8)* was shown by its NMR spectrum to be free from the isomer *(6)*. The conversion *(7)*→*(8)* is a rapid subsequent reaction, as was shown by reaction of *(1)* with 1.2 equivalents of $SbCl_5$ in SO_2 at −55 °C to form *(8)* in 60% yield; 40% of compound *(1)* remained unchanged. The almost complete conversion *(1)*→*(8)* on use of 2 equivalents of $SbCl_5$ provides the missing link for the unusual halogenation mechanism.

The solution of *(8)* in SO_2 reacts quantitatively at −50 °C with 1.1 equivalents of tetramethylammonium chloride to give NMR-pure *cis*-dichloride *(4)*. The two steps, *(1)*→*(8)*, and *(8)*→*(4)*, thus proceed with high stereoselectivity.



(9)

Whilst the cause of the exclusive *endo* attack by chlorine on *(1)* is not yet clear, the model *(9)* for compound *(2)* indicates the reason for the nucleophilic *endo* attack in step *(2)*→*(4)*. The model shows C-atoms 1 and 7 to be moved out of the plane of the trigonal C-atoms 2 to 6[5]. This motion destroys the parallelism of the π orbitals of the homoaromatic ion. The σ-overlap of the orbitals of C-1 and C-7 shown in *(9)* causes an increase in electron density below the ring plane. The electron deficiency in the upper lobes results in increased electrophilicity on the *endo* side.



(10) *(11)* *(12)*

The complex of *(1)* and silver tetrafluoroborate, on reaction with one equivalent of bromide in ethylene dichloride at −35 °C, affords a precipitate of *(10)* and AgBr; the crystalline *endo*-8-bromo-homotropylium fluoroborate *(10)* was obtained with more than 97% stereoselectivity. In the NMR spectrum (SO_2, −40 °C, 60 MHz) the strongly deshielded 8-H appears as a triplet at τ = 2.70 ppm, whereas the homoaromatic 1-H and 7-H give a triplet ($J_{1,2} = J_{1,8} = 6.9$ Hz) at τ = 3.77 ppm.

The *endo*-bromo compound *(10)* isomerizes to the *exo* form *(11)* in SO_2 solution at 20 °C, presumably by ring inversion. The same *exo*-bromo fluoroborate *(11)* is formed on treatment of the *cis*-dibromide *(12)* with $AgBF_4$ at −60 °C. *(11)* gave a correct CH analysis and showed in the NMR spectrum (SO_2, −40 °C) the *endo*-8-H as a triplet at τ = 8.76 ppm. The high Δτ = 6 ppm of the *endo*-8-H in *(11)* and the *exo*-8-H in *(10)* is characteristic for homotropylium salts[4, 6].

Received: October 19, 1972 [Z 726 IE]
German Version: Angew. Chem. *84*, 1187 (1972)

[1] *W. Reppe, O. Schlichting, K. Klager,* and *T. Toepel*, Liebigs Ann. Chem. *560*, 1 (1948).

[2] *R. Huisgen, G. Boche, W. Hechtl,* and *H. Huber*, Angew. Chem. *78*, 595 (1966); Angew. Chem. internat. Edit. *5*, 585 (1966).

[3] *R. Huisgen, G. Boche,* and *H. Huber*, J. Amer. Chem. Soc. *89*, 3345 (1967).

[4] *G. Boche, W. Hechtl, H. Huber,* and *R. Huisgen*, J. Amer. Chem. Soc. *89*, 3344 (1967).

[5] The same structure was deduced by *P. Warner, D. L. Harris, C. H. Bradley,* and *S. Winstein*, Tetrahedron Lett. *1970*, 4013, from the 251-MHz spectrum.

[6] *J. L. v. Rosenberg, J. E. Mahler,* and *R. Pettit*, J. Amer. Chem. Soc. *84*, 2842 (1962); *S. Winstein, H. D. Kaesz, C. G. Kreiter,* and *E. C. Friedrich, ibid. 87*, 3267 (1965).

Hendecacesium Trioxide, $Cs_{11}O_3$[**]

By *Arndt Simon* and *Edgar Westerbeck*[*]

Metal-rich oxides (suboxides) of cesium entered the literature long ago as Cs_7O, Cs_4O, Cs_7O_2, and Cs_3O[1], but few investigations of these compounds have been reported[2, 3] although the unusual stoichiometry leads one to expect interesting bonding relations. Further, there have been references[4] to the possible technical importance of alkali-metal suboxides: The cesium layers evaporated on to superficially oxidized silver or on to Cs_2O layers in current photocathodes are found experimentally[5] to react on subsequent heating ('forming') with suboxide formation, so that chemical causes can effect the altered photoeffects (spectral shift, sensitivity) of such composite cathodes.

Recent studies[4, 6, 7] have shown that the suboxides of rubidium and cesium belong to a structurally homogeneous type that is designated by the concept 'complex metal'[6]. The suboxide hitherto formulated as Cs_2O_3 has, according to the results of thermoanalytical and X-ray measurements the formula $Cs_{11}O_3$ and shows a close structural relation to the compounds Cs_7O, Rb_6O and Rb_9O_2 which have been studied in more detail.

$Cs_{11}O_3$ forms permanganate-colored crystalline needles that are extremely sensitive to air and melt incongruently at 52 °C. Phase width could not be detected. In the presence of an excess of cesium, millimeterlong single crystals can be grown in a capillary which enable the structure to be determined[8]. The compound crystallizes monoclinically, space group $Pc(C_s^2)$, with $Z = 4$, $a_0 = 17.610$, $b_0 = 9.218$, $c_0 = 24.047$ Å, $\beta = 100.24°$, $d_{exp} = 2.61$, $d_{calc} = 2.610\ g \cdot cm^{-3}$. The lattice parameters were obtained from modified[9] Guinier photographs of poly- and single-crystalline samples.—The structural model is based on 1386 independent *h0l* to *h3l* reflections ('Pailred' diffractometer; corrected for absorption, anisotropically refined; $R = 0.09$, $R' = 0.11$). Figure 1 shows the projection of the atom

[*] Prof. Dr. A. Simon and Dipl.-Chem. E. Westerbeck
Anorganisch-chemisches Institut der Universität
44 Münster, Gievenbecker Weg 9 (Germany)

[**] Part 5 of Alkali-metal Suboxides. This work was supported by the Deutsche Forschungsgemeinschaft.— Part 4: [5].

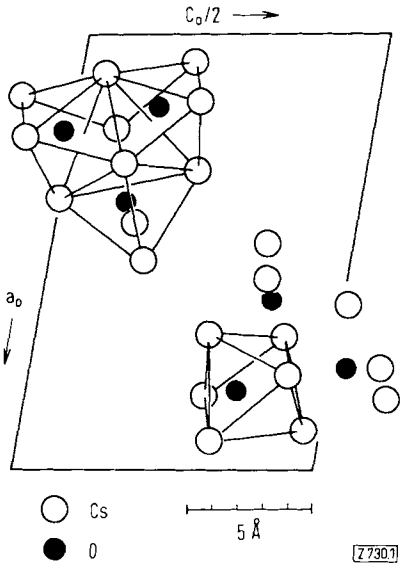


Fig. 1. Half unit cell of the crystal structure of $Cs_{11}O_3$, projection of the atomic centers of gravity along [010].

centers of gravity in $Cs_{11}O_3$ along [010]. The striking feature of this structure is the exclusive occurrence of discrete $[Cs_{11}O_3]$ groups in which the oxygen atoms are in quasitrigonal arrangement. Each oxygen is surrounded by a distorted octahedron of cesium atoms. The $[Cs_{11}O_3]$ unit results from face sharing of coordination octahedra in the manner of a polynuclear metallo complex.

Units of this geometry were first found in Cs_7O[4], in which they are surrounded by purely metallic, close-packed structural regions. Thus there is a close relation between $Cs_{11}O_3$ and $[Cs_{11}O_3]Cs_{10}=Cs_7O$, completely analogous to the relation between Rb_9O_2 and $[Rb_9O_2]Rb_3=Rb_6O$[6, 7]. $Cs_{11}O_3$ is the structural analog of Rb_9O_2.

Received: October 18th, 1972 [Z 7301E]
German version: Angew. Chem. *84*, 1190 (1972)

[1] *E. Rengade*, Bull. Soc. Chim. Fr. [4] *5*, 994 (1909).
[2] *G. Brauer*, Z. Anorg. Chem. *255*, 101 (1947).
[3] *K.-R. Tsai, P. M. Harris*, and *E. N. Lassettre*, J. Chem. Phys. *60*, 345 (1956).
[4] *A. Simon*, Naturwissenschaften *58*, 622 (1971).
[5] *A. Simon*, Z. Anorg. Allg. Chem., in press.
[6] *A. Simon*, Naturwissenschaften *58*, 623 (1971).
[7] *A. Simon*, Naturwissenschaften *58*, 623 (1971).
[8] *E. Westerbeck*, Diplomarbeit, Universität Münster 1971.
[9] *A. Simon*, J. Appl. Cryst. *3*, 11, 18 (1970); *4*, 138 (1971); cf. also Angew. Chem. *83*, 216 (1971); Angew. Chem. internat. Edit. *10*, 831 (1971).

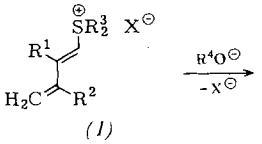
CONFERENCE REPORTS

Two Unusual Sulfur Groups: Butadienylsulfonium Salts and Sulfur Diimides

By *Günter Kresze*[*]

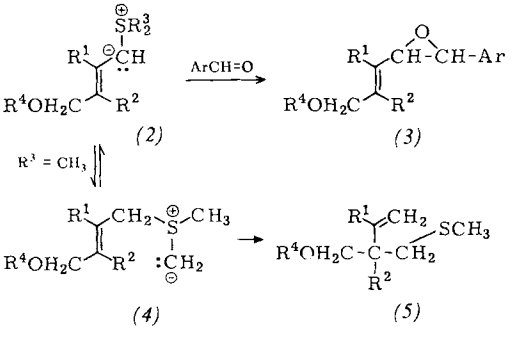
1. *trans*-1,3-Butadienylsulfonium salts such as *(1)* are best prepared by reaction of *trans*-1,4-dihalo-2-butenes with dialkyl sulfides and treatment of the resulting 1,4-bis(dialkylsulfonio)-2-butene dihalides with sodium methoxide.

Thermolysis of the butadienylsulfonium salts *(1)* provides a useful synthesis of *trans*-1-(alkylthio)butadienes. Nucleophilic addition of alkoxides gives as intermediates sulfonium ylides *(2)*, which with aromatic aldehydes afford 3-(3-alkoxy-1-propenyl)-2-aryloxiranes *(3)* and moreover (in the case of the dimethylsulfonium compounds, $R^3=CH_3$) are in equilibrium with alkylsulfonium methylides *(4)* whose sigmatropic rearrangement leads to 3-butenyl sulfides *(5)*.

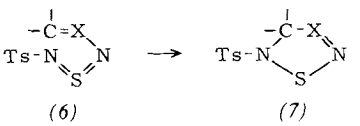


(1)

2. Sulfur diimides RN=S=NR also display ylide-like character in some reactions: α,β-Unsaturated NSN compounds of type *(6)*, derived from primary vinylamines, hydrazones, or hydrazine derivatives usually occur only as intermediates; they cyclize to *(7)* in reactions corresponding to *(4)* → *(5)*.



(2) *(3)* *(4)* *(5)*

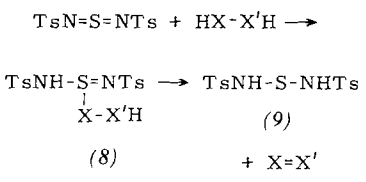


(6) *(7)*

Sulfur bis(tosylimide) not only undergoes the usual additions (*e.g.* of alcohols or secondary amines) to one S=N

[*] Prof. Dr. G. Kresze
Organisch-Chemisches Laboratorium der Technischen Universität
8 München, Arcisstrasse 21 (Germany)

bond but also, in a series of cases, can act as dehydrogenating agent, with formation of bis(tosylamino)sulfane *(9)*. For example, reaction in aprotic media afforded azobenzenes from hydrazobenzene, quinones from hydroquinones, benzylidenemalonic esters from benzylmalonic esters, diphenyl sulfide from thiophenol, and naphthalene from 1,2- or 1,4-dihydronaphthalene. The first step in these dehydrogenations is to be formulated as an addition [in some case an ene reaction], and the second [because of the ylide character of the S=N bond in the adduct *(8)*] is considered as elimination of a sulfonium salt or, in some cases, as 1,5-H shift.



Lecture at Mainz on June 29, 1972 [VB 352 IE]
German version: Angew. Chem. *84*, 1154 (1972)

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Isotope separation by electrical migration in molten salts forms the theme of a report by *V. N. Lyubimov*. An introductory review of the underlying theoretical principles of the process is followed by an account of the application of this method to the separation of stable isotopes. Fused salts are used since here the mass effect is greater than in aqueous solutions. The author describes apparatus, methods of measurement, and experimental conditions, both for laboratory-scale investigations and for plant-scale production. The report contains a comprehensive table of experimental results for 20 elements. In connection with this work the following topics are also dealt with: Determination of ionic mobilities in molten salts, the structure of molten salts, and the mechanism of ionic migration in an electric field. [Separation of Isotopes by Electrical Migration and Determination of Ionic Mobilities in Molten Salts. Russ. Chem. Rev. *41*, 222—249 (1972); 31 references]

[Rd 587 IE –Q]

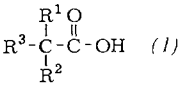
Analytical methods screening of drugs and narcotics are discussed by *M. Riedmann*. The rather expensive methods of mass spectrometry, nuclear magnetic resonance, spectrofluorimetry, and IR and UV spectrometry are not necessary for rapid testing of drugs. Thin-layer and, particularly, gas chromatography are quite suitable since they provide reliable results within a few minutes, which is of decisive importance in cases of acute poisoning and when dealing with a large number of samples (doping control at sports meetings!). Because of its high selectivity, an N-sensitive flame ionization detector is used for the detection of doping agents and drugs such as opiates, phenylalkylamines, indole alkaloids, benzilic acid esters, barbiturates, methadon, and lysergides. If the result is positive, then identification of the doping agent is confirmed by the gas chromatographic retention time. UV spectroscopy and thin-layer and gas chromatography are used for the analysis of cannabis products such as hashish and marijuana. The author also deals with the identification of opium alkaloids and barbiturates and with the importance of testing for drug misuse. [Analytische Methoden des Nachweises von Drogen und Giftstoffen. Naturwissenschaften *59*, 306–310 (1972); 19 references]

[Rd 595 IE –M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Film-forming polymer masses that are suitable for use as a resin base for hair-fixing preparations because of their solubility and film-forming properties consist of vinyl acetate, crotonic acid, and at least one vinyl ester of an α-branched, saturated, aliphatic monocarboxylic acid containing 5—10 carbon atoms in the carboxylic acid unit, which has the general formula *(1)*, where R^1 and R^2 denote alkyl and R^3 denotes hydrogen, alkyl, or aryl. The terpolymer consists of about 7 to 89% of vinyl acetate, about 6 to



(1)

13% of crotonic acid, and about 5 to 80% of vinyl ester, based on the total weight, and exhibits good solubility both in the typical organic solvents for use in hair sprays and in the typical aqueous solvent systems used for wave setting preparations. The terpolymer is also very compatible with the typical hydrocarbon propellants used for hair sprays. [DOS 1745208; National Starch and Chemical Corp., New York]

[PR 36 IE—E]

Nitration and Aromatic Reactivity. By *J. G. Hoggett, R. B. Moodie, J. R. Penton,* and *K. Schofield.* Cambridge University Press, London 1971. 1st edit., xii, 246 pp., £ 5.—.

Of the aromatic substitution reactions, nitration has been studied with particular thoroughness. It is not only of central importance in preparative organic chemistry, but has also played a decisive part in molding the development and progress of theoretical chemistry. Full account is taken of this in the present book. The authors have succeeded in exemplary fashion in giving the reader a closer look at the current problems in physical organic chemistry, using nitration as an example. They show their deep knowledge of the subject in their discussion of the relationship between structure, reactivity, and selectivity of electrophilic nitration reagents, in relation to nucleophilic substrates. Even more praiseworthy is the exposition (the need for which has been felt for a long time) on mixing and encounter controlled reactions and their disguising effect on the selectivity of chemical processes.

The contents of the book are arranged as follows:

1. Introduction; 2. Nitrating systems: A. mineral acids; 3. Nitrating systems: B. inert organic solvents; 4. Nitrating systems: C. miscellaneous (nitration with nitrogen pentoxide, nitration *via* nitrosation, nitration with nitronium salts in organic solvents); 5. Nitrating systems: D. benzoyl nitrate and systems formed from nitric acid and acetic anhydride; 6. The process of substitution. The remaining four chapters are devoted to the topic of nitration and aromatic reactivity: 7. Theoretical background; 8. Nitration of bases; 9. Nitration of monocyclic compounds; 10. Nitration of bicyclic and polycyclic compounds.

The book has author, subject, and compounds indexes and gives an impressive survey of the literature up to 1970. It can be recommended without reservations to any chemist of modern outlook.

Paul Rys [NB 88 IE]

Handbuch der Analytischen Chemie (Handbook of Analytical Chemistry). Part 3, Vol IIIa. Quantitative Analysis, Aluminium. By *W. Fresenius* and *G. Jander*, revised by *H. Bensch.* Springer-Verlag, Heidelberg—Berlin—New York, 1972. 2nd Edit., xix, 716 pp., 47 figs., bound DM 198.—.

With the appearance of the present edition, this well tried handbook has been expanded by a further important chapter. The author, who is a recognized specialist in the field of the analysis of aluminum, must be congratulated on his splendidly comprehensive contribution (no less than 2521 references!).

In addition to the two main sections on determination techniques (550 pp.) and separation techniques (80 pp.), the book contains an introduction to the principles of the chemistry of the aluminum ion in aqueous systems and a short section on special techniques, which consist essentially of techniques for the determination of aluminum metal, *e. g.* in metal powders or dross, and the determination of aluminum oxide in aluminum and its alloys and in iron and steel.

The chapter on determination techniques is subdivided into gravimetric, titrimetric, photometric, fluorometric, nephelometric, polarographic, spectrochemical and radiochemicals methods, and deals not only with the usual methods but also with a large number of other possibilities. The chapter on separation methods is subdivided into techniques involving precipitation of aluminum itself, separation by precipitation of the accompanying elements, by masking the aluminum or by complex formation, extraction techniques, separation by electrolysis on a mercury cathode, chromatographic techniques, and separation by evaporation in a current of hydrogen chloride or chlorine.

The material is concisely presented and contains a large number of clearly formulated operating procedures, useful notes being given wherever possible to indicate their accuracy, the possibility of interference, and the range of application. This is a genuine treasure house and no analytical laboratory should be without it.

Günther Kraft [NB 99 IE]

Diffusion Data. By *F. Wöhlbier.* Trans Tech Publications, Clausthal 1971. 1st edit., 269 pp., bound, $ 44.—.

"Diffusion Data" is a review of experimental results in the field of migration phenomena in crystalline and amorphous solids, and also in liquids that are solid at normal temperatures. Despite the brevity of the individual items it is comprehensive, and the results appear only a short time after their initial publication. Apart from work on diffusion as such, there are reports on the isotope effect in diffusion, on thermo- and electrotransport, ionic conductivity, permeation of gases, experimental methods for determining these effects, *etc.* Consideration is given to atomic transport processes in crystal lattices, along grain boundaries or dislocations, on surfaces and interfaces, and in thin films. The data are arranged in alphabetical order of the matrix substance concerned for each material grouping, *e.g.* metals and their alloys, semiconductors oxides, halides, organic crystals, *etc.* In conjunction with the author, subject, and subject field indexes, this breakdown enables the reader rapidly to find the information he wants. The bibliography is also broken down by material groupings.

The brief discussion on each article contains not only the actual experimental data, which are often advantageously supplemented by graphical presentations, but also information on the experimental method and the material used and the author's interpretation of the transport mechanisms, anomalies, *etc.* involved.

Vol. 5, No. 1 (1971) has an Appendix consisting of a complete author, subject, and subject field index to the first four volumes, which makes the present edition a miniature work of reference in its own right. For anyone requiring information on current results and experimental techniques in the field of migration phenomena, "Diffusion Data" offers the best possible method at present available for obtaining such information quickly, conveniently, and reliably.

Christian Herzig [NB 83 IE]

1000 Fragen aus der Chemie (1000 Questions from Chemistry) By *W. Geissler* and *T. Reinholz*. J. F. Lehmanns Verlag, München 1971. 1st ed., v, 210 pp., numerous figures, bound DM 16.—.

About 170 questions on general chemistry, 230 on inorganic and analytical chemistry, and 600 on organic chemistry are given, with short answers, in about 200 pages. According to the preface, the questions are largely authentic examination questions from the medical courses of West German universities. In the reviewer's opinion, however, a number of the questions are rather irrelevant to the budding physician. In view of the tightening-up of the syllabus that is necessitated by the new Education Act, there will be an increasing need in the future for the subject matter of courses to be closely concerned with medicine.

The collection of questions will probably be of little interest to the medical student in the foreseeable future. This is the more regrettable in that the authors have taken a great deal of trouble in the preparation of the book, which they undoubtedly also intended to be of assistance to medical students. (However, the authors cannot be held responsible for the selection of the examination material.) This criticism in no way limits the usefulness of the book to the other groups for whom it is intended. This collection of questions will be a significant and reasonably priced aid to teaching candidates and first-semester chemistry students, and can be recommended with a clear conscience.

Klaus Beyermann [NB 77 IE]

Absorption Spectra in the Ultraviolet and Visible Region. Vol. XV. Edited by *L. Láng*. Academic Press, New York—London 1971. 1st Edit., 408 pp., numerous tables and spectra. Ring-bound, $ 27.50.

The present 15th volume contains almost 200 spectra of a wide variety of compounds (aromatic, heterocyclic, organometallic compounds, *etc.*). The spectra are reproduced as $\log \varepsilon/m\mu$ diagrams on loose A 5 sheets. The reverse of each sheet, in addition to the name of the substance, the molecular formula, the molecular weight, and the melting point, carries information about the instrument with which the spectrum was recorded and data on the solvent, the concentration, the light path, and (in tabulated form) a number of recorded values [wavelength ($m\mu$) and $\log I_0/I$]. The sheets are held together in a ring binder. A clear list of contents contains a substance index, an author index, and a formula index.

Like the entire series, the volume is a collection of spectra that will be useful to any chemist

Egon Fahr [NB 98 IE]

Malting and Brewing Science. By *J. S. Hough, D. E. Briggs,* and *R. Stevens* Chapman & Hall Ltd., London, 1971, 678 pp., about 250 figs., £ 10.—.

As the authors state, this book has been written to provide a suitable textbook for students of brewing sciene in Birmingham. Since a single book obviously cannot cover all the aspects of this subject, the emphasis here is on the scientific side rather than on analytical methods or the use of equipment.

The main topics, treated in 22 chapters, including the biochemistry and technology of malting and drying barley; brewing water; the chemistry and biochemistry of mashing; brewing sugars and sirups; the chemistry of wort preparations and hop extraction; the biology and metabolism of brewers' yeasts; the growth of yeast and the fermentation of beer; and the treatment and quality of beer.

This book gives a detailed account of the field from the British standpoint. It contains about 300 structural formulas and metabolic schemes, 250 illustrations of equipment, and some 1000 references. Unfortunately, the Continental contribution to modern brewing technology is hardly represented and it might have been better perhaps to include some authors who have a command of French, Czech, and German, so as to arrive at a more complete and balanced picture of the field—as has been done in "Barley and Malt" and "The Chemistry and Biology of Yeasts", edited by *A. H. Cook*, which were written by 29 authors.

Anton Piendl [NB 86 IE]

Water and Water Pollution. Vol. 1. Ed. by *L. L. Ciaccio*. Marcel Dekker, Inc., New York 1971. 1st edit., xix, 449 pp., numerous figs., bound $ 27.50.

The editor has succeeded in getting some of the leading American experts in water chemistry for this four-volume handbook. The first volume takes as a starting point the chemical, physical, and biological characteristics of water, and goes on to apply a blend of practical experience and theoretical fundamentals to specific situations such as estuaries and rivers, the influence of pollution on the aquatic ecosystem, and the utilization of water during excessive rainfall or ground water enrichment.

The current position as regards the evaluation of waste waters and their chemical, physical, and biological purification is illustrated.

Although on many points the book concerns itself specifically with the water industry in the USA—which differs in many respects from its West German counterpart—this first volume is still of direct value in the way in which it successfully combines theory and practice. The systematic layout and the extremely careful way in which the bibliographies to the individual chapters have been compiled make this book easy to use. It can be used as a working tool by the student and practising specialist alike. It is also clearly enough written to act as a chemical textbook for civil engineers. It is to be hoped that the remaining three volumes will soon make their appearance.

Wilhelm Husmann [NB 87 IE]

Techniques of Chemistry. Edited by *A. Weissberger*. Vol. 2. **Organic Solvents, Physical Properties and Methods of Purification.** By *J. A. Riddick* and *W. B. Bunger*. Wiley-Interscience, New York–London 1970. 3rd Edit., xiii, 1041 pp., numerous tables, bound £ 11.75.

Our increasing understanding of the influence exerted by solvents on chemical reactions, equilibria, and absorption spectra has led not only to more objective criteria for the selection of suitable solvents but has also resulted in a marked increase in the number of solvents available. While

the first edition of the present handbook[*] described 160 solvents and thereby covered the whole known field, the present, third edition reports the physical properties and methods of purification of 354 solvents.

After a brief classification of organic solvents with regard to their chemical constitution, which is used in the arrangement of the 354 solvents (Chapter 1, 18 pages), Chapter 2 (42 pages) gives a thorough discussion of the tabulated physical constants, the methods by which they are determined, and the criteria for their selection from the literature. Chapter 3 (491 pages) contains in tabular form an overall summary of all the constants characteristic of a solvent. Here are the physical constants needed for identification and checking of purity (melting and boiling points, refractive index, density, *etc.*), and also those required in physicochemical measurements (*e.g.* cryoscopic and ebullioscopic constants). All in all, some 45 individual items of information are provided for each solvent, including literature references to UV, IR, NMR, and mass spectra of the solvent in question, and the Beilstein reference. I found the seven following tables particularly useful; here all the solvents are arranged by increasing boiling point, melting point, and dipole moment, and also by increasing density, ebullioscopic and cryoscopic constants, and dielectric constant. In Chapter 4 (20 pages) there is a brief discussion of the concept of purity of a substance and criteria of purity, together with an enumeration of the general methods used for the determination of water in organic solvents, and for its removal. Finally, in Chapter 5 (306 pages) there is a detailed summary of the general and specific purification methods for all the solvents tabulated in Chapter 3, together with notes on their handling and storage (toxicity, flashpoint, explosion limits). A distinction is made in the methods of purification according to the purpose to which the purified solvent is to be put. This extensive work is concluded by a bibliography of over 5300 references, which covers the literature up to 1968 (Chapter 6, 132 pages), and by a subject index.

The authors have succeeded in taking the almost unmanageably great mass of material on the constants and methods used in the selection and purification of solvents, and assembling it critically in a readily comprehensible form. All the same, certain hopes remain unrealized. There are no data on deuterated solvents, and only a few on the solvent mixtures (ligroin, petroleum ether) commonly used in laboratory practice. A note on the empirical parameter of the solvent polarity would have been useful. Solvents with high dielectric constants dissociate well, but are not necessarily ionizing solvents, as is maintained on p. 57. The ionizing capabilities of a solvent are determined by factors other than the dielectric constant.

In conclusion, it may be said that the present book is a highly successful and considerably extended revision of its well-known predecessor. The assessment of the reviewer of the first edition may be repeated without reservation: "The book should represent an extremely useful source of information for anyone concerned with solvents"[*]

Christian Reichardt [NB 34 IE]

[*] Cf. Angew. Chem. *49*, 213 (1936).

Registered names, trademarks, etc. used in this journal, even without specific indication thereof, are not to be considered unprotected by law.

© Verlag Chemie GmbH, Weinheim 1973. – Printed in Germany by Zechnersche Buchdruckerei, Speyer/Rhein.

All rights reserved (including those of translation into foreign languages). No part of this issue may be reproduced in any form – by photoprint, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers.

Editorial office: Boschstrasse 12, 6940 Weinheim/Bergstr., Germany, Telephone 40 36/40 37, Telex 46 55 16 vchwh d.

Editor: *H. Grünewald* · **Translation Editors:** *A. J. Rackstraw* and *A. Stimson.*

Publishers: Verlag Chemie GmbH. (Managing Directors *Jürgen Kreuzhage* and *Hans Schermer*) Pappelallee 3, 6940 Weinheim/Bergstr., Germany, and Academic Press Inc. (President *Walter J. Johnson*), 111 Fifth Avenue, New York 3, N. Y., USA, and Berkeley Square House, Berkeley Square, London, W. 1., England.

Correspondence concerning advertisements should be addressed to Verlag Chemie GmbH. (Advertising Manager *H. Both*), 6940 Weinheim/Bergstr., Pappelallee 3, P. O. Box 129/149 Germany, Telephone Weinheim (0 62 01) 40 31, Telex 46 55 16 vchwh d.

AUTHOR INDEX

G.E. = Reference to the German Edition of Angewandte Chemie. References are given for Review Articles, Short Communications, and Conference Reports only.

"G.E. –" indicates an Abstract or a Book Review.

AARONSON, M. J. 521 [G.E. 542]
Ache, H. J. 179 [G.E. 234]
Achenbach, H. 434 [G.E. 479]
Adam, W. 540 [G.E. 590]
Addison, C. C. 244
Adloff, J. P. 61
Advena, J. 441 [G.E. 440]
Agarwal, K. L. 451 [G.E. 489]
Albanbauer, J. 319 [G.E. 258]
Albrecht, W. 1051 [G.E. 1077]
Ali, A. 289 [G.E. 259]
Allen, G. C. 65
Allen, G. S. H. 852 [G.E. 901]
Altenbach, H.-J. 935, 937, 939 [G.E. 983, 985, 986]
Appel, R. 927 [G.E. 944]
Arnold, V. 1096 [G.E. 1151]
Arpe, H. J. 722, 723, 723 [G.E. 767, 767, 767]
Arranz, F. 339 [G.E. 361]
Arzoumanian, H. 245
Ashkenazi, P. 1027 [G.E. 1106]
Asinger, F. 62 [G.E. 37]
Aumann, R. 522 [G.E. 583]
Auterhoff, H. 345
Ayrey, G. 65

BACHHUBER, H. 829 [G.E. 889]
Bächmann, K. 69
Backes, J. 513 [G.E. 534]
Bacq, Z. M. 157
Bailey, R. A. 65
Balasubramanian, S. 341 [G.E. 363]
Baldas, J. 648
Baldwin, R. L. 66
Bandi, P. 848 [G.E. 830]
Barnard, D. 65
Barnes, D. S. 945
Barnett, B. L. 137 [G.E. 121]
Basile, L. J. 447
Batrakov, V. V. 1037
Battelle, L. F. 138 [G.E. 164]
Battersby, A. R. 734
Batz, H.-G. 1103 [G.E. 1189]
Bau, R. 138 [G.E. 164]
Baumann, M. 52 [G.E. 62]
Baumgärtner, A. 334 [G.E. 356]
Beattie, C. J. 648
Becher, H. J. 26 [G.E. 8]
Beck, A. K. 443 [G.E. 476]
Beck, E. A. 446
Beck, F. 760 [G.E. 798]
Beck, W. 527 [G.E. 584]
Becke-Goehring, M. 69, 72, 449, 548
Becker, H.-P. 850 [G.E. 894]
Beeby, P. J. 833 [G.E. 896]
Behrendt, W. 534 [G.E. 549]
Beijer, B. 929 [G.E. 957]
Bellüs, D. 65
Bennetto, H P. 447
Bensch, H. 1108
Bentham, J. E. 640 [G.E. 683]
Berger, K. C. 334 [G.E. 356]
Bergmann, G. 1032 [G.E. 1101]
Bernal, I. 632 [G.E. 640]
Berndt, U. 515 [G.E. 537]
Bestmann, H.-J. 59, 296, 508 [G.E. 65, 293, 528]
Betts, J. 64
Beuter, A. 1020 [G.E. 1099]
Beyer, W. 140 [G.E. 154]
Beyersmann, D. 947
Bickelhaupt, F. 924 [G.E. 993]
Bier, G. 63 [G.E. 69]
Bikerman, J. J. 549
Billups, W. E. 637 [G.E. 684]
Biltz, H. 71
Binder, H. 1028 [G.E. 1107]
Binger, P. 309, 433 [G.E. 352, 483]
Biswas, M. 945
Black, D. St. C. 47 [G.E. 34]
Blasenbrey, S. 334 [G.E. 356]
Blasius, E. 547
Bloom, B. R. 1038
Boch, M. 289 [G.E. 265]
Boche, G. 724 [G.E. 768]
Bock, H. 150, 436, 927 [G.E. 119, 436, 944]
Bockris, J. O'M. 67, 67
Bode, W. 334 [G.E. 357]
Boeris, F. J. 1034
Bogdanorić, B. 1023 [G.E. 1070]
Böhm, L. L. 340 [G.E 362]
Böhmer, V. 335 [G.E. 357]
Bolton, P. D. 447
Bonati, F. 429 [G.E. 482]
Bond, A. M. 65
Borchard, W. 335 [G.E. 357]
Both, W. 296 [G.E. 293]
Boucher, L. J. 447
Boué, S. 320 [G.E. 314]
Bourguignon, J. J. 339 [G.E. 361]
Brandenburg, D. 335 [G.E. 358]
Brandt, J. 375 [G.E. 400]
Braterman, P. S. 545
Brauer, H.-D. 531 [G.E. 546]
Braun, M. 49, 443 [G.E. 60, 476]
Bray, R. C. 945
Breitmeier, E. 539 [G.E. 589]
Brenner, B. 336 [G.E. 359]
Bresler, S. E. 549
Briggs, D. E. 1109
Brinkwerth, W. 848 [G.E. 830]
Brogli, F. 538 [G.E. 551]
Bronstert, B. 637 [G.E. 638]
Brown, D. G. 1035
Brown, H. C. 692 [G.E. 702]
Brubaker, G. R. 344
Bruckmann, P. 524 [G.E. 543]
Brümmer, W. 249 [G.E. 319]
Brunner, H. 418, 923 [G.E. 442, 955]
Buddrus, J. 1041 [G.E. 1173]
Buehler, C. A. 65, 70
Buisson, D. H. 1025 [G.E. 1103]
Bunger, W. B. 1110
Bunnett, J. F. 734
Burchard, W. 63 [G.E. 69]
Burger, K. 47, 223, 319 [G.E. 35, 212, 258]
Bürvenich, C. 539 [G.E. 589]
Burzin, K. 151 [G.E. 108]

CAIS, M. 1025, 1027, 1028 [G.E. 1104, 1106, 1107]
Calderon, N. 646, 855
Calligaris, M. 733
Cameron, T. S. 510 [G.E. 530]
Cantow, H.-J. 336 [G.E. 358]
Carstensen-Oeser, E. 422 [G.E. 434]
Carter, M. E. 647
Cashion, P. J. 451 [G.E. 489]
Casper, K. 357 [G.E. 381]
Cerný, M. 1035
Chakravarty, D. 945
Chance, B. 544 [G.E. 553]
Chatzidakis, A. 506 [G.E. 526]
Chekanova, V. D. 66
Cheng, C. Y. 510 [G.E. 530]
Chompff, A. J. 859
Christensen, J. J. 66, 343
Christophorou, L. 1038
Ciaccio, L. L. 1109
Coker, D. T. 64
Collard, J. 917 [G.E. 993]
Colton, R. 64
Conia, J. M. 447
Corey, E. J. 446
Cossey, A. L. 1098, 1099, 1100 [G.E. 1183, 1184, 1185]
Cox, M. 157
Crabbé, P. 69
Cramer, F. 717 [G.E. 710]
Cremer, D. 935 [G.E. 983]
Cremer, H.-D. 217 [G.E. 207]

DAHM, J. 1032 [G.E. 1101]
Dahm, M. 990 [G.E. 1001]
Daly, J. J. 630 [G.E. 679]
Damaskin, B. B. 1037
Dane, E. 246
Darken, J. 157
Davis, B. R. 632 [G.E. 640]
Davis, D. G. 1014 [G.E. 1072]
de Boer, T. J. 321 [G.E. 303]
Dehmlow, E. V. 322 [G.E. 304]
Delbrück, M. 1 [G.E. 1]
Delventhal, J. 435, 830 [G.E. 435, 832]
de Meijere, A. 56 [G.E. 63]
Demir, T. 510 [G.E. 530]
Demuth, R. 1097 [G.E. 1153]
Dickerson, R. 651
Diebler, H. 731 [G.E. 773]
Dietschmann, H. 142 [G.E. 110]
Dimroth, K. 506, 631, 1090, 1091 [G.E. 526, 636, 1145, 1146]
Distler, W. 59 [G.E. 65]
Dolgij, I. E. 929 [G.E. 946]
Dollhopf, W. 334 [G.E. 356]
Dorian, A. F. 651
Dreeskamp, H. 1088 [G.E. 1143]
Dreiding, A. S. 236 [G.E. 170]
Dürr, H. 224, 225, 422 [G.E. 215, 215, 434]
Düwel, H. 217 [G.E. 207]
Dyachenko, A. I. 507 [G.E. 527]

EATON, D. R. 245
Ebsworth, E. A. V. 640 [G.E. 683]
Edwards, R. 245
Effenberger, F. 61, 299, 300, 922 [G.E. 37 294, 295, 954]
Eglinton, G. 446
Ehrig, V. 127 [G.E. 107]
Eichstedt-Nielsen, B. 239 [G.E. 219]
Eicke, H. F. 1096 [G.E. 1151]
Eidenschink, R. 292 [G.E. 292]
Eisner, U. 732
Eiter, K. 60 [G.E. 67]
Eliel, E. L. 739 [G.E. 779]
Eliezer, I. 447
Enderer, K. 151 [G.E. 108]
Enders, D. 301, 1102, 1103 [G.E. 350, 1186, 1187]
Engel, J. 568 [G.E. 615]
Engel, P. S. 156
Engelhard, M. 310 [G.E. 346]
Englert, M. 136 [G.E. 120]
Epple, G. 299, 300 [G.E. 294, 295]
Erdmann, B. 515 [G.E. 537]
Ewing, G. E. 486 [G.E. 570]
Eyring, H. 1040

FAESSLER, A. 34 [G.E. 51]
Fahrenholz, F. 289 [G.E. 259]
Falbe, J. 155 [G.E. 172]
Fayos, J. 58 [G.E. 27]

Fehn, J. 47, 223, 319 [G.E. 35, 212, 258]
Feix, G. 336 [G.E. 359]
Feldmann, R. 217 [G.E. 207]
Ferraro, J. R. 447
Fery, N. 337 [G.E. 359]
Fialkov, A. S. 66
Field, L. 732
Fink, G. 336 [G.E. 359]
Fischer, E. O. 238, 643, 644 [G.E. 214, 679, 682]
Fischer, E. W. 340 [G.E. 363]
Fischer, G. 829 [G.E. 889]
Fischer, Heinz 846 [G.E. 828]
Fischer, Helmut 644 [G.E. 682]
Fischer, H. A. 68
Fischer, R. D. 675 [G.E. 737]
Fischer, W. 71
Fischler, I. 1088 [G.E. 1143]
Fitzky, H. G. 979 [G.E. 1037]
Flemming, J. 650
Fluck, E. 1028 [G.E. 1107]
Fodor, G. 919 [G.E. 947]
Foerst, W. 246
Formáček, V. 141 [G.E. 155]
Forster, D. 54 [G.E. 65]
Försterling, H.-D. 651, 821 [G.E. —, 862]
Fortman, J. J. 65
Franck, B. 420, 421 [G.E. 432, 433]
Frank, R. 329 [G.E. 316]
Franzmann, G. 1104 [G.E. 1189]
Freifelder, M. 649
Freist, W. 713 [G.E. 711]
Frensdorff, H. K. 16 [G.E. 16]
Fresenius, W. 1109
Friedl, J. 319 [G.E. 258]
Fröhlich, K. 57 [G.E. 26]
Frump, J. A. 156
Fuhrhop, J. H. 1014 [G.E. 1072]

GAL, J. 919 [G.E. 947]
Galin, J. C. 339 [G.E. 361]
Gansow, O. A. 637 [G.E. 684]
Gantz, D. 420, 421 [G.E. 432, 433]
Gasser, R. P. H. 64
Gassman, P. G. 323 [G.E. 304]
Gasteiger, J. 716, 1104 [G.E. 766, 1187]
Gattner, H.-G. 335 [G.E. 358]
Gattow, G. 534 [G.E. 549]
Geary, W. J. 157
Geiger, R. 244
Geis, I. 651
Geiss, K.-H. 443 [G.E. 476]
Geissler, W. 1110
Gerlach, H. 1030 [G.E. 1110]
Gero, S. D. 148 [G.E. 111]
Geussenhainer, S. 713 [G.E. 712]
Ghosez, L. 852 [G.E. 901]
Ghosh, P. 245
Gieren, A. 223 [G.E. 212]
Gillespie, R. J. 446, 447
Glade, P. R. 1038
Gleiter, R. 1028 [G.E. 1107]
Glemser, O. 1094, 1095 [G.E. 1147, 1149]
Gokel, G. W. 138, 530 [G.E. 164, 587]
Goldbach, G. 337 [G.E. 359]
Greving, B. 848 [G.E. 830]
Grieb, R. 236 [G.E. 170]
Griffith, J. S. 545
Grigat, E. 949 [G.E. 1008]
Grimm, F. L. 642 [G.E. 684]
Grimme, W. 517 [G.E. 539]
Grisebach, H. 159 [G.E. 192]
Grob, C. A. 544 [G.E. 592]
Grobe, J. 1097 [G.E. 1153]
Gröbel, B.-T. 443 [G.E. 476]
Grohmann, K. 314 [G.E. 266]
Grünanger, P. 1039
Grundmann, C. 1039
Grünewald, H. 246
Gschwend, H. W. 294 [G.E. 291]
Günther, H. 217, 517, 861 [G.E. 207, 539, 907]
Gütlich, P. 57 [G.E. 26]
Gutmann, V. 545
Gütlich, P. 57 [G.E. 26]
Gutmann, V. 545
Gyenes, I. 344
Gyure, W. L. 1061 [G.E. 1088]

HABERSAAT, K. 291 [G.E. 262]
Hack, F. 725 [G.E. 769]
Häfelinger, G. 725, 855 [G.E. 769, —]
Hagedorn, I. 307 [G.E. 354]
Hagemann, H. 1011, 1011, 1012 [G.E. 1062, 1063, 1063]
Hagemann, H. J. 333 [G.E. 314]
Halbritter, K. 62 [G.E. 68]
Hall, W. de W. 155
Hamann, K. 337 [G.E. 359]
Hambright, P. 64
Hanack, M. 714 [G.E. 714]
Hardel, K. 173 [G.E. 227]
Harris, R. L. N. 1098, 1099, 1100 [G.E. 1183, 1184, 1185]
Hartke, K. 50 [G.E. 61]
Hartley, F. R. 596 [G.E. 649]
Hartmann, A. 620 [G.E. 668]
Hauptmann, H. 439, 441, 441 [G.E. 438, 439, 440]
Hauska, G. 153 [G.E. 123]
Hegnauer, R. 343
Heier, K.-H. 1016, 1017 [G.E. 1066, 1067]
Heil, G. 426 [G.E. 474]
Heilbronner, E. 538 [G.E. 551]
Heilenz, S. 857
Heimbach, P. 68
Heine, H.-G. 974 [G.E. 1032]
Heinrich, F. 234 [G.E. 263]
Heitz, W. 298 [G.E. 296]
Hekman, M. 926 [G.E. 995]
Heldt, H. W. 792 [G.E. 792]
Heller, J. 236 [G.E. 170]
Hempel, K. 227 [G.E. 255]
Henc, B. 1023 [G.E. 1070]
Henderson, D. 1040
Henneberg, D. 348, 357 [G.E. 371, 381]
Hepler, L. G. 447
Herberhold, M. 730, 1092 [G.E. 773, 1150]
Herbstein, F. H. 1025 [G. E. 1104]
Herr, H.-J. 131, 135 [G.E. 113, 117]
Herrmann, W. A. 418 [G.E. 442]
Heusler, K. 245
Hey, D. H. 446
Heyns, K. 649
Hikino, H. 546
Hill, J. O. 343
Hiriart, J. M. 326 [G.E. 308]
Hocker, J. 964 [G.E. 1022]
Hoene, R. 337 [G.E. 359]
Hoffmann, E. G. 375 [G.E. 400]
Hoffmann, H. M. R. 324 [G.E. 305]
Hoffmann, R. 825 [G.E. 820]
Hoffmann, R. W. 324, 512, 513 [G.E. 306 533, 534]
Hoffmann, U. 346
Höfle, G. 720 [G.E. 716]
Hofmann, H. 346
Hofmann, Hans 423 [G.E. 477]
Hofmann, P. 423 [G.E. 477]
Hofmann, U. 72
Höfner, W. 857
Hoggett, J. G. 1108
Hollaender, J. 850 [G.E. 894]
Hollitzer, O. 720 [G.E. 716]
Holm, R. 979 [G.E. 1037]
Hopf, H. 419 [G.E. 471]
Hoppe, D. 432, 933 [G.E. 435, 956]
Hornstein, I. 650
Horrocks, W. de W. jr. 155
Hough, J. S. 1110
Houseman, T. H. 65
Howard, P. Y. 529 [G.E. 586]
Howlett, K. D. 510 [G.E. 530]
Hübner, W. 338 [G.E. 361]
Hug, W. 244
Huisgen, R. 715, 716 1104, [G.E. 765, 766, 1187]
Hünig, S. 431, 433 [G.E. 480, 481]
Hunt, J. P. 157
Hüper, F. 420 [G.E. 432]
Huppatz, J. L. 1098, 1099, 1100 [G.E. 1183, 1184, 1185]
Huttner, G. 42, 238 [G.E. 29, 214]

IMOTO, M. 855
Iqbal, A. F. M. 634 [G.E. 641]
Iqbal, Z. 545
Irvine, M. V. 648
Issenberg, P. 650
Issleib, K. 527 [G.E. 582]
Izatt, R. M. 66, 343

JACKISCH, J. 844 [G.E. 826]
Jaenicke, O. 532 [G.E. 547]
Jander, G. 547, 1108
Jann, K. 650
Janousek, Z. 916, 917 [G.E. 991, 993]
Jastorff, B. 713 [G.E. 711]
Jerome-Lerutte, S. 545
Jolivet, Y. 339 [G.E. 362]
Jolly, P. W. 136 [G.E. 120]
Jones, M. jr. 733
Jones, W. M. 325 [G.E. 306]
Jost, W. 1040
Jutz, C. 315 [G.E. 299]
Jutzi, P. 53 [G.E. 28]

KADISH, K. 1014 [G.E. 1072]
Kaez, H. D. 1034
Kalvoda, J. 245
Kämmerer, H. 335 [G.E. 357]
Kanter, H. 1090 [G.E. 1145]
Kapon, M. 1025 [G.E. 1104]
Karl, W. 434 [G.E. 479]
Katzin, L. I. 447
Kauffmann, Th. 290, 291, 292, 842, 844, 846, 847, 848 [G.E. 261, 262, 292, 824, 826, 828, 829, 830]
Kaupp, G. 313, 718, 719 [G.E. 259, 718, 719]
Keat, R. 510 [G.E. 530]
Keck, H. 435, 830 [G.E. 485, 832]
Keese, R. 518 [G.E. 540]
Keil, F. 1040
Keller, C. 57, 515 [G.E. 26, 537]
Keller, H. J. 944 [G.E. 998]
Keller, K. 728 [G.E. 712]
Kempter, G. 1038
Kepák, F. 156
Kermer, W.-D. 62 [G.E. 68]
Khorana, H. G. 451 [G.E. 489]
Kimling, H. 932 [G.E. 952]
Kindl, H. 244
King, R. B. 1034
Kinsky, S. C. 448
Kirmse, W. 851 [G.E. 833]
Kirsch, G. 338 [G.E. 360]
Klärner, F. G. 832 [G.E. 892]
Klein, G. 641 [G.E. 643]
Kleine, T. O. 448
Klessinger, M. 524, 525 [G.E. 543, 544]
Klingebiel, U. 1095 [G.E. 1149]
Kloster-Jensen, E. 438 [G.E. 483]
Knabe, J. 345
Knowles, J. R. 854
Knunyants, I. L. 583 [G.E. 623]
Knutsson, L. 329 [G.E. 311]
Köbel, H 158
Köbrich, G. 52, 473 [G.E. 62, 557]
Koch, D. 48 [G.E. 32]
Koenig, J.-J. 152 [G.E. 153]
Koenig, J. L. 1034
Koerner von Gustorf, E. 532, 1088 [G.E. 547, 1143]
Kolb, G. 339 [G.E. 362]
Kölbel, H. 158
Kollmar, H. 635 [G.E. 680]
König, E. 45, 45 [G.E. 33, 33]
König, Eckehard 66
Konz, W. E. 715 [G.E. 765]
Köppelmann, E. 290, 291 [G.E. 261, 262]
Korte, E.-H. 226 [G.E. 218]
Korth, T. 289 [G.E. 265]
Köster, H. 713 [G.E. 712]
Kothe, G. 830 [G.E. 890]

Kowalski, M. 336 [G.E. 358]
Kozak, S. L. 65
Kraus, W. 641 [G.E. 643]
Krause, S. 945
Krebs, A. 932 [G.E. 952]
Krebs, E.-P. 518 [G.E. 540]
Krech, F. 527 [G.E. 582]
Kreissl, F. R. 643 [G.E. 679]
Kreiter, C. G. 141, 643 [G.E. 155, 679]
Kresze, G. 1106 [G.E. 1154]
Kretzschmar, H.-J. 338 [G.E. 361]
Kreutz, W. 551 [G.E. 597]
Kreutzberger, A. 144 [G.E. 109]
Kricheldorf, H. R. 128, 337 [G.E. 107, 360]
Krieg, B. 42 [G.E. 29]
Krieger, K. 719 [G.E. 719]
Kroner, J. 220 [G.E. 210]
Kropf, H. 239 [G.E. 219]
Krozer, S. 336 [G.E. 358]
Krüger, C. 137, 387 [G.E. 121, 412]
Krumholz, P. 66
Kuchen, W. 435, 830 [G.E. 485, 832]
Kühle, E. 244, 344
Kuhn, H. 651, 798, 821 [G.E. —, 838, 862]
Kuhn, J. 244
Kuhn, M. 516 [G.E. 538]
Kurihara, M. 244
Kurz, J. L. 546
Kuss, E. 645 [G.E. 686]
Kuthan, J. 732
Kutty, T. R. N. 244

LABONVILLE, P. 447
Lagowski, J. J. 546
Landgrebe, J. A. 326 [G.E. 307]
Lang, H.-J. 59 [G.E. 65]
Lange, H.-W. 227 [G.E. 255]
Lappus, M. 923 [G.E. 955]
Latscha, H. P. 528 [G.E. 585]
Leach, S. J. 547
Ledwith, A. 734
Leermakers, P. A. 156
Legg, J. I. 344
Legler, J. 846 [G.E. 828]
LeGoff, E. 926 [G.E. 996]
Leibfritz, D. 232 [G.E. 156]
Leiserowitz, L. 514 [G.E. 536]
Leitich, J. 1088 [G.E. 1143]
Lengyel, I. 521 [G.E. 542]
L'Eplattenier, F. 1096 [G.E. 1151]
Lesbre, M. 652
Leugering, H. J. 338 [G.E. 360]
Leupold, I. 722, 723, 723 [G.E. 767, 767, 767]
Levason, W. 733
Ley, K. 1009, 1009, 1010, 1011, 1011, 1012, [G.E. 1060, 1061, 1061, 1062, 1063, 1063]
Lezius, A. 338 [G.E. 360]
Lichtenthaler, R. G. 535 [G.E. 588]
Lightner, D. A. 215 [G.E. 216]
Limacher, H. 920 [G.E. 950]
Lin, L.-P. 637 [G.E. 684]
Lin, T.-P. 1095 [G.E. 1149]
Lincoln, S. F. 65
Livingstone, S. E. 157
Lloyd, D. 404 [G.E. 447]
Logan, N. 244
Logemann, E. 1089, 1089 [G.E. 1144, 1144]
Löhr, G. 340 [G.E. 362]
Lohse, C. 240 [G.E. 220]
Łopusinski, A. 838 [G.E. 896]
Lorenz, H. P. 307 [G.E. 354]
Luber, J. 306 [G.E. 349]
Ludorff, E. 846 [G.E. 828]
Lukacs, G. 148 [G.E. 111]
Lupan, S. 1025 [G.E. 1104]
Lustenberger, N. 227 [G.E. 255]
Lüttke, W. 234, 310 [G.E. 263, 346]
Lyubimov, V. N. 1107

MAASS, G. 428 [G.E. 430]
Maatman, H. 918 [G.E. 947]
MacDonald, R. P. 67
Maercker, A. 542 [G.E. 531]
Málek, J. 1035
Malisch, W. 516 [G.E. 538]
Manecke, G. 338 [G.E. 361]
Manuel, G. 837 [G.E. 899]
Margaretha, P. 327, 1024 [G.E. 308, 1102]
Märkl, G. 439, 441, 441, 1016, 1017, 1019 [G.E. 438, 439, 440, 1066, 1067, 1069]
Marshall, D. R. 404 [G.E. 447]
Martel, B. 326 [G.E. 308]
Martens, D. 724 [G.E. 768]
Martin, C. W. 326 [G.E. 307]
Martin, G. J. 855
Martin, H.-D. 54, 926 [G.E. 65, 995]
Martin, M. L. 855
Mason, W. R. 447
Matthes, D. 1019 [G.E. 1069]
Matusch, R. 50 [G.E. 61]
Mavrodineanu, R. 547
Maxwell, J. R. 446
Mayer, U. 545
Mazánek, J. 293 [G.E. 290]
Mazerolles, P. 652
McAuliffe, C. A. 733
McGirk, R. H. 834 [G.E. 897]
McKenzie, E. D. 66
McKenzie, H. A. 345
McKillop, A. 48 [G.E. 60]
Meier, H. 1035
Meier, Hans 1051 [G.E. 1077]
Meier, H. P. 294 [G.E. 291]
Meister, B. 1023 [G.E. 1070]
Melson, G. A. 245
Menke, H. 43 [G.E. 30]
Menzel, P. 822 [G.E. 954]
Merkel, W. 511 [G.E. 535]
Merten, R. 964 [G.E. 1022]
Metzger, J. 245
Meyer, B. 423 [G.E. 477]
Michalski, J. 838 [G.E. 896]
Michel, U. 231 [G.E. 160]
Michels, R. 298 [G E 296]
Michelsen, T. W. 65
Midland, M. M. 692 [G.E. 702]
Millic, F. 733
Mills, W. N. 65
Minghetti, G. 429 [G.E. 482]
Mitschke, K.-H. 144 [G.E. 165]
Mitschker, A. 847 [G.E. 829]
Mondon, A. 240 [G.E. 220]
Monroe, B. M. 155, 156
Montforts, F.-P. 421 [G.E. 433]
Moodie, R. B. 1108
Mootz, D. 58 [G.E. 27]
Moreau-Colin, M. L. 545
Moretto, H. 640 [G.E. 683]
Morton, M. J. 447
Müller, B. 422 [G.E. 434]
Müller, J. 653 [G.E. 725]
Müller, W. 1030 [G.E. 1110]
Murthy, A. R. V. 244
Musso, H. 45, 45 [G.E. 33, 33]

NADER, F. 514 [G.E. 536]
Nakamoto, K. 666 [G.E. 755]
Nakaya, T. 855
Narayanan, K. V. 156
Nardin, G. 733
Nass, G. 343
Nefedov, O. M. 507, 929 [G.E. 527, 946]
Neilands, J. B. 945
Neuberg, R. 51 [G.E. 36]
Neugebauer, F. A. 830 [G.E. 890]
Neumann, K. H. 857
Neumann, P. 73 [G.E. 75]
Neumann, W. P. 850 [G.E. 894]
Neumüller, O.-A. 947
Newman, S. 859
Nicholls, C. H. 156
Niggli, A. 236 [G.E. 170]
Nilsson, N. H. 295 [G.E. 293]
Nishida, S. 328 [G.E. 309]
Nordling, C. 83 [G.E. 144]
Noren, G. K. 343
Normant, J. F. 448
Nowotny, H. 906 [G.E. 973]

OELKRUG, D. 64
Ohloff, G. 330 [G.E. 311]
Okonnischnikova, G. P. 929 [G.E. 944]
Oltay, E. 918 [G.E. 947]
Oppolzer, W. 728, 1031 [G.E. 712, 1108]
Orth, H. D. 249 [G.E. 319]
Oth, J. F. M. 51, 424, 426 [G.E. 36, 472, 474]
Ottaway, J. M. 64
Oxenius, R. 511 [G.E. 535]
Oyakawa, R. T. 138 [G.E. 164]

PANKE, D. 341 [G.E. 365]
Pant, B. C. 733
Paquette, L. A. 328 [G.E. 310]
Parr, W. 314, 529 [G.E. 266, 586]
Passmore, T. 446
Pauling, H. 1023 [G.E. 1070]
Paulsen, H. 149 [G.E. 112]
Pawliczek, J. B. 517, 1021 [G.E. 539, 1100]
Pearson, D. E. 65, 70
Pechhold, W. 334 [G.E. 356]
Pedersen, C. 241 [G.E. 221]
Pedersen, C. J. 16 [G.E. 16]
Penninger, J. M. L. 918 [G.E. 947]
Penton, J. R. 1108
Periard, J. 339 [G.E. 362]
Peters, F. 428 [G.E. 430]
Petersen, O. 918 [G.E. 946]
Petrii, O. A. 1037
Pettit, G. R. 647
Pettit, L. D. 945
Petz, W. 934 [G.E. 997]
Pfannemüller, B. 645 [G.E. 644]
Pfitzner, H. 312 [G.E. 351]
Pfüller, H. 508 [G.E. 528]
Phillips, B. A. 919 [G.E. 947]
Phillips, J. N. 1098, 1099, 1100 [G.E. 1183, 1184, 1185]
Pike, D. 289 [G.E. 265]
Pillinger, C. T. 446
Pistorius, R. 841 [G.E. 893]
Plinke, G. 424 [G.E. 472]
Pohl, F. M. 894 [G.E. 931]
Polansky, O. E. 532 [G.E. 547]
Poralla, K. 343
Porsch, P.-H. 429 [G.E. 478]
Porte, A. L. 510 [G.E. 530]
Porter, Q. N. 648
Pradhan, N. K. 64
Preetz, W. 243 [G.E. 267]
Preston, K. Jr. 279 [G.E. 280]
Prince, R. H. 408 [G.E. 461]
Prinzbach, H. 131, 133, 135, 296, 940, 942 [G.E. 113, 115, 117, 297, 988, 990]
Prout, C. K. 510 [G.E. 530]
Pustoslemsek, P. 142 [G.E. 110]
Pütter, H. 431, 433 [G.E. 480, 481]
Pütter, R. 826 [G.E. 822]

QUAST, H. 229 [G.E. 316]
Quinkert, G. 637, 1072 [G.E. 638, 1157]
Quistad, G. B. 215 [G.E. 216]

RADIMERSKI, P. 288 [G.E. 345]
Radola, B. J. 445
Randaccio, L. 733
Rankin, D. W. H. 640 [G.E. 683]
Rapp, E. 326 [G.E. 307]
Rappe, C. 329 [G.E. 311]
Rassat, A. 303 [G.E. 353]
Rawlinson, D. J. 446
Razavi, A. 1092 [G.E. 1150]
Reader, R. D. 648
Rebsch, M. 302 [G.E. 344]
Reddy, A. K. N. 67, 67
Redlich, H. 1021 [G.E. 1100]
Reel, H. 1013 [G.E. 1064]
Reetz, M. T. 129, 130 [G.E. 161, 163]
Regel, W. 131 [G.E. 113]
Regler, D. 238 [G.E. 214]
Rehage, G. 335 [G.E. 357]

Reichardt, C. 62 [G.E. 68]
Reiher, M. 947
Reinholz, T. 1109
Reisdorff, J. 218 [G.E. 208]
Rembold, H. 1061 [G.E. 1088]
Rempp, P. 339 [G.E. 361]
Reslova, S. 1035
Rewicki, D. 44 [G.E. 31]
Riddick, J. A. 1110
Ried, W. 142, 511, 997 [G.E. 110, 535, 1048]
Riediger, B. 736
Riedmann, M. 1107
Riess, G. 339 [G.E. 362]
Rinehart, K. L. jr. 448
Ringsdorf, H. 1103 [G.E. 1189]
Risler, H. 727 [G.E. 770]
Roberts, T. D. 858
Robey, R. L. 48 [G.E. 60]
Roesky, H. W. 642, 642, 918 [G.E. 684, 685, 946]
Rosenkranz, H.-J. 974 [G.E. 1032]
Rothe, M. 293 [G.E. 290]
Rothenwöhrer, W. 641 [G.E. 643]
Röttele, H. 426 [G.E. 474]
Rottler, R. 336 [G.E. 359]
Röwemeier, P. 844 [G.E. 826]
Rowland, C. 92 [G.E. 86]
Rüde, E. 650
Rudolph, H. 974 [G.E. 1032]
Rudolph, J. 247
Ruge, B. 225 [G.E. 215]
Rüger, W. 883 [G.E. 961]
Runquist, O. 157
Rys, P. 246, 874 [G.E. —, 921]
Rytting, J. H. 66

SACKMANN, G. 339 [G.E. 362]
Sadlo, H. 641 [G.E. 643]
Saillant, R. B. 1034
Saladin, E. 229 [G.E. 158]
Salaun, J. R. 447
Salem, L. 92 [G.E. 86]
Salzer, A. 930 [G.E. 949]
Sangmeister, E. 620 [G.E. 668]
Sanz, F. 630 [G.E. 679]
Sarhan, A. 341 [G.E. 304]
Sartorius, R. 531 [G.E. 546]
Sasse, K. 260 [G.E. 271]
Satge, J. 652
Sauter, H. 133, 296 [G.E. 115, 297]
Sawada, H. 855
Sawodny, W. 1020 [G.E. 1099]
Sawyer, A. K. 1039
Schaal, M. 527 [G.E. 584]
Schaefer, D. P. 344
Schäfer, H. 48, 841 [G.E. 32, 893]
Schäfer, W. 512, 631, 836, 924 [G.E. 533, 636, 898, 993]
Schaffer, O. 506, 1091 [G.E. 526, 1146]
Schaller, E. 434 [G.E. 479]
Schallner, O. 56 [G.E. 63]
Schauer, R. 7 [G.E. 41]
Scheffold, R. 229, 231 [G.E. 158, 160]
Scherer, O. J. 529 [G.E. 585]
Scheuer, P J. 244
Scheurlen, H. 947
Schiess, P. 288 [G.E. 345]
Schill, G. 248, 1089, 1089 [G.E. —, 1144, 1144]
Schleyer, P. v. R. 330 [G.E. 316]
Schmalzried, H. 445
Schmid, G. 934, 1034 [G.E. 997, 1111]
Schmid, R. 159 [G.E. 192]
Schmidbaur, H. 144, 145, 516, 944 [G.E. 165, 166, 538, 957]
Schmidpeter, A. 306 [G.E. 349]
Schmidt, A. H. 142, 997 [G.E. 110, 1048]
Schmidt, B. 576 [G.E. 649]
Schmidt, P. 513 [G.E. 534]
Schmidt, U. 632 [G.E. 640]
Schmidt, W. 221 [G.E. 168]
Schmidtchen, F. 421 [G.E. 433]
Schmieder, K. R. 637 [G.E. 638]
Schmitt, E. 329 [G.E. 316]
Schnecko, H. 853 [G.E. 902]
Schnegg, U. 715 [G.E. 765]
Schnell, D. 336 [G.E. 359]
Schofield, K. 1108
Schöllkopf, U. 311, 429, 432 [G.E. 289, 478, 435]
Schomburg, G. 248, 366 [G.E. 371, 390]
Schöne, A. 647
Schott, H. 824 [G.E. 819]
Schrader, B. 226 [G.E. 218]
Schröder, G. 51, 424, 426 [G.E. 36, 472, 474]
Schröder, R. 311 [G.E. 289]
Schroeder, B. 850 [G.E. 894]
Schroth, G. 375 [G.E. 400]
Schubert, R. 840 [G.E. 888]
Schulte-Elte, K. H. 330 [G.E. 311]
Schulz, G. V. 340 [G.E. 362]
Schulze, J. 158
Schulze, W. 858
Schutte, C. J. H. 66
Schüttler, R. 512 [G.E. 533]
Schwarz, G. 568 [G.E. 615]
Schwarzhans, K. E. 535 [G.E. 587]
Schwedova, I. B. 929 [G.E. 946]
Schweig, A. 512, 536, 537, 631, 836, 837, 924, 1033 [G.E. 533, 550, 551, 636, 898, 899, 993, 1074]
Schweizer, E. 154 [G.E. 124]
Schwesinger, R. 940, 942 [G.E. 988, 990]
Schwyzer, R. 854 [G.E. 902]
Scott, L. T. 733
Seebach, D. 49, 127, 301, 443, 1102, 1103 [G.E. 60, 107, 350, 476, 1186, 1187]
Seeger, R. 1028 [G.E. 1107]
Seelig, J. 920 [G.E. 950]
Seeliger, W. 287 [G.E. 343]
Selley, N. J. 858
Sellmann, D. 534 [G.E. 549]
Seng, F. 1009, 1009, 1010 [G.E. 1060, 1061, 1061]
Senning, A. 295 [G.E. 293]
Seppelt, K. 630, 723 [G.E. 212, 715]
Sepulchre, A.-M. 148 [G.E. 111]
Sergio, R. 224 [G.E. 215]
Seyferth, D. 448
Sharma, D. K. 244
Shaw, R. A. 510 [G.E. 530]
Sicher, J. 200 [G.E. 177]
Sieveking, H. U. 303 [G.E. 353]
Sievers, R. E. 65
Sigel, H. 851, 1025 [G.E. 833, 1103]
Simmons, E. L. 157
Simon, A. 1105 [G.E. 1190]
Singh, N. *528 [G.E. 585]*
Sinnwell, V. 149 [G.E. 112]
Skorianetz, W. 330 [G.E. 311]
Skrabal, P. 874 [G.E. 921]
Smid, J. 112 [G.E. 127]
Smith, H. O. 635 [G.E. 680]
Sokolski, G. A. 583 [G.E. 623]
Solar, S. 1024 [G.E. 1102]
Solouki, B. 436, 927 [G.E. 436, 944]
Sommer, H. 717 [G.E. 710]
Sommerfeld, H.-D. 939 [G.E. 986]
Sondheimer, F. 546, 833, 834, 926 [G.E. —, 896, 897, 996]
Sosnovsky, G. 446
Spangler, R. J. 216 [G.E. 206]
Srinivasan, R. 320, 858 [G.E. 314, —]
Stadler, P. 149 [G.E. 112]
Stark, I. 307 [G.E. 354]
Stegemeyer, H. 731 [G.E. 720]
Steglich, W. 720 [G.E. 716]
Steiger, H. 535 [G.E. 587]
Stein, R. S. 646
Steinmetzer, H.-C. 540 [G.E. 590]
Steinsträsser, R. 633 [G.E. 636]
Stempfle, W. 375 [G.E. 400]
Sterzel, H. J. 340 [G.E. 363]
Steudel, R. 302 [G.E. 344]
Stevens, R. 1109
Stille, J. K. 343
Stohrer, W.-D. 825 [G.E. 820]
Stotz, R. W. 245
Strack, W. 220 [G.E. 210]
Streit, W. 542 [G.E. 531]
Streitberger, H.-J. 847 [G.E. 829]
Strong, H. M. 446
Stühler, H. 145 [G.E. 166]
Subramanian, L. R. 714 [G.E. 714]
Suchet, J. P. 859
Suhr, H. 781 [G.E. 876]
Sustmann, R. 838, 840 [G.E. 887, 888]
Sutton, J. C. 216 [G.E. 206]
Swaminathan, S. 156
Swann, J. C. 945
Swern, D. 859

TAKEMOTO, T. 546
Tanabe, K. 649
Taylor, E. C. 48 [G.E. 60]
Teranishi, R. 650
Tews, K.-H. 821 [G.E. 862]
Thinius, K. 449
Thompson, D. W. 64
Thomson, A. J. 1035
Thyret, H. 520 [G.E. 581]
Tokura, N. 343
Torssell, K. 241 [G.E. 222]
Toth, L. E. 947
Traunmüller, R. 68
Trill, H. 838 [G.E. 887]
Trömel, G. 246, 246
Tsay, Y.-H. 137 [G.E. 121]
Tschirwitz, U. 1051 [G.E. 1077]
Tsuji, J. 855
Tubiana, W. 640 [G.E. 642]
Tuchscherer, C. 44 [G.E. 31]
Turro, N. J. 331 [G.E. 312]

UERPMANN, E.-P. 335 [G.E. 357]
Ugi, I. 71, 138, 530, 929 [G.E. —, 164, 587, 957]
Ullrich, V. 689 [G.E. 701]
Ulmen, J. 517 [G.E. 539]
Unger, K. 267 [G.E. 331]
Urry, D. W. 448
Uzbek, M. U. 144 [G.E. 109]

VAN SPRONSEN, J. 948
van Vyve, T. 916 [G.E. 991]
Vass, G. 148 [G.E. 111]
Venkataraman, K. 547, 737
Verbit, L. 945
Vermeer, H. 924 [G.E. 993]
Vetter, W. 1089 [G.E. 1144]
Viehe, H. G. 344, 916, 917 [G.E. —, 991, 993]
Vieweg, R. 947
Voelter, W. 539 [G.E. 589]
Vogel, E. 217, 218, 935, 937, 939, 1013 [G.E. 207, 208, 983, 985, 986, 1064]
Vogt, H.-H. 737
Vogt, W. 341 [G.E. 363]
Vögtle, F. 73, 535, 727 [G.E. 75, 588, 770]
Völker, T. 342 [G.E. 364]
von Ammon, R. 675 [G.E. 737]
von Bünau, G. 392 [G.E. 418]
von Hinrichs, E. 929 [G.E. 957]
von Schnering, H.-G. 43 [G.E. 30]
von Sturm, F. 140 [G.E. 154]
Vorbrüggen, H. 304, 305 [G.E. 347, 348]
Voss, J. 242 [G.E. 223]

WAEGELL, B. 640 [G.E. 642]
Wagner, G. 150 [G.E. 119]
Wagner, K. 990 [G.E. 1001]
Wagner, R. M. 315 [G.E. 299]
Wagnière, G. 244
Waldau, E. 826 [G.E. 822]
Wall, C. 447
Wallwork, S. C. 244
Warren, K. D. 65
Wasserman, H. H. 332 [G.E. 312]
Weast, R. C. 449
Weber, W. P. 530 [G.E. 587]
Webster, O. W. 153 [G.E. 173]
Weeke, F. 366 [G.E. 390]
Wegler, R. 71
Wegner, G. 340 [G.E. 363]

Weidlein, J. 144 [G.E. 165]
Weidner, U. 146, 536, 537, 837 [G.E. 167, 550, 551, 899]
Weimann, B. 366, 375 [G.E. 390, 400]
Weinstein, B. 289 [G.E. 259]
Weiss, A. 607 [G.E. 498]
Weissberger, A. 1110
Weissenhorn, R. G. 725 [G.E. 769]
Weitemeyer, C. 56 [G.E. 63]
Wendisch, D. 979 [G.E. 1037]
Wendtlandt, W. W. 157
Wentorf, jr., R. H. 446
Wermuth, C.-G. 152 [G.E. 153]
Werner, G. 68
Werner, H. 644, 930, 945 [G.E. 682, 949, —]
Westerbeck, E. 1105 [G.E. 1190]
Westermayer, G. 725 [G.E. 769]
Wiberg, K. B. 332 [G.E. 313]
Wiberg, N. 829 [G.E. 889]
Wick, E. 650
Wiemers, N. 340 [G.E. 363]
Wies, R. 529 [G.E. 585]
Wilke, G. 136, 347, 1023 [G.E. 120, 370, 1070]
Wilkins, B. T. 221 [G.E. 168]
Wille, F. 246
Wille, G. 527 [G.E. 582]
Williams, D. 650
Williams, R. J. P. 1035
Willmot, A. R. 447
Winkler, E. 238 [G.E. 214]
Winkler, R. 545
Winter, G. 751 [G.E. 866]
Winterfeldt, E. 289 [G.E. 265]
Wirsum, U. E. 333 [G.E. 314]
Witkop, B. 156
Witte, H. 287 [G.E. 343]
Wittmer, P. 341 [G.E. 363]
Wöhlbier, F. 1108
Wollmer, A. 335 [G.E. 358]
Woltermann, A. 842, 844 [G.E. 824, 826]
Woodland, J. M. 1035
Woolley, P. R. 408 [G.E. 461]
Worrell, J. H. 344
Wörsdörfer, K. 335 [G.E. 357]
Wulff, G. 341 [G.E. 364]
Wunderlich, W. 341 [G.E. 365]

YAMAZAKI, A. 451 [G.E. 489]
Yannas, I. V. 854
Yoda, N. 244
Young, R. 649

ZÄHNER, H. 343
Záhorszky, U.-I. 45, 45 [G.E. 33, 33]
Zaw, K. 245
Ziegler, E. 348, 366, 375 [G.E. 371, 390, 400]
Zimmermann, E. 496 [G.E. 451]
Zimmermann, H. 830 [G.E. 890]
Zinnius, A. 58 [G.E. 27]
Zischkale, W. 246
Zollinger, H. 246, 874 [G.E. —, 921]
Züchner, K. 1094 [G.E. 1147]
Zürcher, C. 1089 [G.E. 1144]
Zweifel, H. 342 [G.E. 364]

SUBJECT INDEX

FP = Full paper (review article) CR = Conference report
SC = Short communication LA = Literature abstract
PR = Patent abstract
G.E. = Reference to the German Edition of Angewandte Chemie. References are given for Review Articles, Short Communications, and Conference Reports only.

ABSOLUTE CONFIGURATION, of a 1,2-disubstituted ferrocene derivative with two different chiral substituents (SC) 138 [G.E. *84*, 164 (1972)]
Determination in (+)-pentahelicene (SC) 296 [G.E. *84*, 293 (1972)]

Absorption spectra, of tetragonal fluorides from the first transition metal series (LA) 64

Acetamide, syn-Planar conformation of oxalic acid: crystal structure of the oxalic acid-~ complex (SC) 514 [G.E. *84*, 536 (1972)]
Reaction of secondary ~-s with N-dichloromethylene-N,N-dimethylammonium chloride (SC) 917 [G.E. *84*, 993 (1972)]

Acetonitrile, Reaction with cyclohexanone (SC) 722 [G.E. *84*, 797 (1972)]

Acetylcholinesterase, Reactivation of phosphorylated ~ - dependence upon activator acidity (SC) 307 [G.E. *84*, 354 (1972)]

Acetylenes, Metal-olefin and -acetylene bonding in complexes (FP) 596 [G.E. *84*, 649 (1972)]
2-Cyclopropene-1-carboxylic acids from trimethylsilyl-~ (SC) 929 [G.E. *84*, 946 (1972)]
Transition-metal complexes of olefins and ~ (LA) 945
Chemistry of ~ (Book Review) 344

Acids, Transition states as ~ and bases (LA) 546
Solid ~ and bases (Book Review) 649

Acoustical holography, Advances in (FP) 279 [G.E. *84*, 280 (1972)]

Acridinium betaines, Novel method for synthesis (SC) 59 [G.E. *84*, 65 (1972)]

N-Acylaminopyrrolidinone, New ~ derivatives (PR) 1036

Acylating agents, Trifluoromethanesulfonic-carboxylic anhydrides, highly active ~ (SC) 299 [G.E. *84*, 294 (1972)]

Acylation, Catalytic Friedel-Crafts ~ of aromatic compounds (SC) 300 [G.E. *84*, 295 (1972)]

Acyloxylation, One-step substitutive ~ at carbon (LA) 446

(1-Adamantyl)-α-peroxylactone, Synthesis, kinetics, and luminescence (SC) 540 [G.E. *84*, 590 (1972)]

Adenosines, Simple new synthesis of N^6-substituted ~ and 2-amino-~ (SC) 304 [G.E. *84*, 347 (1972)]

Adenosine 3',5'-cyclophosphate, New analogs (SC) 713 [G.E. *84*, 711 (1972)]

Adenosine 3',5'-monophosphate, Mode of action of hormones (FP) 7 [G.E. *84*, 41 (1972)]

Adenosine 5'-triphosphate, Protection of ~ toward hydrolysis by the formation of a mixed-ligand metal ion complex (SC) 1025 [G.E. *84*, 1103 (1972)]

Adsorbents, Structure of porous ~ (FP) 267 [G.E. *84*, 331 (1972)]
Coordination-polymeric metal complexes of bifunctional dithiophosphinic acids and their use as ~ in chromatography (SC) 435 [G.E. *84*, 485 (1972)]

Adsorption, Photochemical and spectroscopic properties of organic molecules in the adsorbed state (LA) 156
~ and colloidal properties of radioactive elements (LA) 156
~ of organic compounds on electrodes (Book Review) 1037

Alanine, Preparation containing L-3-(4-hydroxy-3-methoxyphenyl)-~ and having antiparkinsonian action (PR) 856

Alcohols, Synthesis of hydroxy-deuterated ~ (LA) 945

Aldgarose (SC) 1021 [G.E. *84*, 1100 (1972)]

Alkali metal complexes, Formation in solution (LA) 545

Alkaloids, The ~ (Book Review) 860

n-Alkanes, The influence of haloalkanes on the ^{13}C-NMR spectra of ~ (SC) 1032 [G.E. *84*, 1101 (1972)]

Alkenes, Stereochemistry of cycloaddition of 1,3-diphenyl-2-azaallyllithium to ~ at 0 °C (SC) 290 [G.E. *84*, 261 (1972)]
Oxidation with mercury(II) salts (LA) 245

Alkylation, Anodic oxidation of trihexylmethoxyborate in presence of butadiene (SC) 48 [G.E. *84*, 32 (1972)]
Side-chain ~ of toluene with ethylene (SC) 918 [G.E. *84*, 947 (1972)]

Allenes, Reaction with a $L_2Ni(0)$ system (SC) 136 [G.E. *84*, 120 (1972)]
Dimerization of optically active 1,3-diphenylallene (CR) 322 [G.E. *84*, 304 (1972)]

Allyl anion, Ring opening of a cyclopropyl anion and cycloaddition of ~ (SC) 724 [G.E. *84*, 768 (1972)]

Aluminates, The reduction of organic compounds by alkoxyhydrido~ (LA) 1035

Aluminum complexes, Relation between structure and proton donor strength of octahedrally coordinated tris(3,5-diisopropylsalicylato)-~ (III), -gallium(III) and -indium(III) (SC) 1096 [G.E. *84*, 1151 (1972)]

Aluminum compounds, 2,3:3,4:4,2-Tri-μ-carbonyl-2,2,3,3,4,4-hexacarbonyl-1-aluminotricobalt: Preparation and spectroscopic findings (SC) 535 [G.E. *84*, 587 (1972)]
[Bis(dimethylamino)aluminoxy]dimethylaminocarbene as a complex ligand (SC) 934 [G.E. *84*, 997 (1972)]

Amalgam electrodes, Electrochemical measurements with ~ (LA) 447

Amination, Simple ~ of aromatic hydroxy-nitrogen heterocycles (SC) 305 [G.E. *84*, 348 (1972)]

Amine oxides, Photochemistry of aromatic ~ (CR) 240 [G.E. *84*, 220 (1972)]

Amines, C—C-Bond formation in the α-position to nitrogen in secondary ~. Lithiodimethylnitrosamine (SC) 310 [G.E. *84*, 350 (1972)]
Conjugation in aromatic ~ and phosphanes (SC) 836 [G.E. *84*, 898 (1972)]

Amino acid antagonists, Mode of action of ~ of biological origin (LA) 343

Amino acids, Analysis on the picomole scale (SC) 227 [G.E. *84*, 255 (1972)]
Simple method for the synthesis of some boc-~ (SC) 289 [G.E. *84*, 259 (1972)]
Rapid method for determination of optical purity (SC) 529 [G.E. *84*, 586 (1972)]
Rearrangement and polymerization mechanisms of DTE-~ and 2-thioxo-5-oxazolidones (CR) 337 [G.E. *84*, 360 (1972)]
Aromatic ~ in the metabolism of higher plants (LA) 244

2-Aminoadenosines, Simple new synthesis of N^6-substituted adenosines and ~ (SC) 304 [G.E. *84*, 347 (1972)]

Aminobenzenes, σ-Complexes in halogenation of ~ - isolation and secondary reactions (SC) 922 [G.E. *84*, 954 (1972)]

Aminoethanesulfonyl derivatives, New ~ (PR) 946

Aminopentalenecarbonitriles, a group of stable pentalenes (SC) 50 [G.E. *84*, 61 (1972)]

Ammonolysis, Neighboring group effects in ~ of acetic esters of polynuclear phenolic compounds (CR) 335 [G.E. *84*, 357 (1972)]

Analysis, Chemical ~ in extractive metallurgy (Book Review) 649

Analytical chemistry, Handbuch der Analytischen Chemie (Book Review) 1108

Analytical reagents, Use of radioisotopically labeled ~ (LA) 65

Annulenes, Simple synthesis and NMR spectroscopic behavior of 1,2-dihalo[18]-annulene (SC) 51 [G.E. *84*, 36 (1972)]
Bridged hetero[11]-~ (SC) 217 [G.E. *84*, 207 (1972)]
2-Hydroxy-4,9-methano[11]annulenone, a 10π-electron analog of tropolone (SC) 218 [G.E. *84*, 208 (1972)]
Oxa[17]-~ (SC) 424 [G.E. *84*, 472 (1972)]
Aza[17]-~ (SC) 426 [G.E. *84*, 474 (1972)]
Synthesis of aromatic bridged didehydroaza[17]-~ bearing alkyl substituents within the cavity of the π-electron cloud (SC) 833 [G.E. *84*, 896 (1972)]
Synthesis of stereoisomeric bisdehydrothia[17]-~ and their dioxides (SC) 834 [G.E. *84*, 897 (1972)]
Synthesis of 1-meth oxy-4,5:10,11-bis(tetramethylene)-6,8-didehydro[13]annulenyl anion, an aromatic 13-membered carbocyclic system (SC) 926 [G.E. *84*, 996 (1972)]
The ~ (LA) 546

Anorectics, N-Thienylalkyl-β-phenyl-ethylamines (LA) 736

Ansamycins (LA) 448

Anthracene, [2+4]- and [4+4]-Photoaddition to cyclopentadiene (SC) 718 [G.E. *84*, 718 (1972)]

Antibiotics, Chemistry and biochemistry of branched-chain sugars (FP) 159 [G.E. *84*, 192 (1972)]
Ansamycins (LA) 448

Antibody-complement interaction, Investigation with lipid model membranes (LA) 448

Anti-inflammatory agents, Perspectives in nonsteroidal ~ (FP) 460 [G.E. *84*, 512 (1972)]
4-(2-Benzoxazolyl)phenylacetic acids, alcohols, esters, and amides (LA) 736

Antiparkinsonian action, Preparation containing L-3-(4-hydroxy-3-methoxyphenyl)alanine and having ~ (PR) 856

Aquo complexes, Kinetic data on water exchange between ~ and solvent water (LA) 157

Archeology, Study of prehistoric metallurgy (FP) 620 [G.E. *84*, 668 (1972)]

Arenology principle, Linkage of alkyl groups through arenofunctional groups (SC) 842 [G.E. *84*, 824 (1972)]
Protophanes by oxidative coupling of "transposed dithiols" (SC) 844 [G.E. *84*, 826 (1972)]
Synthesis and properties of azole-pyridine combinations: problem of the hydrolytic cleavage of hetarene combinations (SC) 846 [G.E. *84*, 828 (1972)]

Aromatic, An alternative approach to the nomenclature of cyclic conjugated polyolefins, together with some observations on the use of the term "~" (FP) 404 [G.E. *84*, 447 (1972)]

Aromatic compounds, Synchronous six-electron cyclization of hexatriene systems as a new synthetic principle for preparation of ~ and hetero-~ (SC) 315 [G.E. *84*, 299 (1972)]

Aromatic substitutions, Structure and stereochemistry of the transition states and intermediates of heterolytic ~ (FP) 874 [G.E. *84*, 921 (1972)]

Aromatization of cyclohexylideneacetonitrile (SC) 723 [G.E. *84*, 767 (1972)]

Arsabenzenes, General synthesis of arylsubstituted ~ (SC) 441 [G.E. *84*, 440 (1972)]
Photoelectron spectroscopy and conjugation – direct proof of the unusual sequence of the two highest occupied π-molecular orbitals in the phosphorin (phosphabenzene) and the arsenin (arsabenzene) system (SC) 924 [G.E. *84*, 993 (1972)]

Arsanes, Stereochemistry of the halocarbonyl-phosphanes and ~ of molybdenum and tungsten (LA) 64

Arsenic compounds, $CH_3AsS_2N_2$, a five-membered arsenic-sulfur-nitrogen ring (SC) 529 [G.E. *84*, 585 (1972)]

Arsenides, $Ge_{38}P_8I_8$ and $Ge_{38}As_8I_8$, a new class of compounds with clathrate structure (SC) 43 [G.E. *84*, 30 (1972)]

Arsenin, X-ray structure analysis of 2,3,6-triphenyl-~ (SC) 630 [G.E. *84*, 679 (1972)]
Photoelectron spectroscopy and conjugation—direct proof of the unusual sequence of the two highest occupied π-molecular orbitals in the phosphorin (phosphabenzene) and the ~ (arsabenzene) system (SC) 924 [G.E. *84*, 993 (1972)]

Arsoles, Cleavage of 1-aryl-~ by alkali metals (SC) 439 [G.E. *84*, 483 (1972)]
Unusual substitution in an arsole ring (SC) 441 [G.E. *84*, 439 (1972)]

1-Arylarsoles, Cleavage by alkali metals (SC) 439 [G.E. *84*, 483 (1972)]

Asymmetric synthesis, A catalyzed ~ synthesis (SC) 1023 [G.E. *84*, 1070 (1972)]

Atoms, How are metal ~ formed in flames? (LA) 64

Autoradiography, Autoradiographie (Book Review) 68

Autoxidation, Kinetics of ~ of hydrocarbons in the liquid phase (LA) 64

2-Azaallyllithium, Stereochemistry of cycloaddition of 1,3-diphenyl-~ lithium to alkenes at 0°C (SC) 290 [G.E. *84*, 261 (1972)]
Ring opening of N-lithio-2,3(cis)-diphenylaziridine to 1,3(cis, trans)-diphenyl-~ and its rearrangement to the trans, trans-form (SC) 291 [G.E. *84*, 262 (1972)]

Aza[17]annulenes (SC) 426 [G.E. *84*, 474 (1972)]
Synthesis of aromatic bridged didehydro-~ bearing alkyl substituents within the cavity of the π-electron cloud (SC) 833 [G.E. *84*, 896 (1972)]

2-Aza-1,3-butadienes, Addition of phosphanes and phosphites to trifluoromethyl-substituted ~ (SC) 319 [G.E. *84*, 258 (1972)]

1-Aza-4-phosphabenzene, 2,6-Diphenyl-~ (SC) 1019 [G.E. *84*, 1069 (1972)]

3-Aza-2,4-trans-hexadiene, Structure of 2:1 cycloaddition product of diazomethane and 1,1,1-trifluoro-2-trifluoromethyl-~ (SC) 223 [G.E. *84*, 212 (1972)]

Aziridine, 2-Cyano-~ (SC) 151 [G.E. *84*, 108 (1972)]
Ring opening of N-lithio-2,3(cis)-diphenyl-~ to 1,3(cis,trans)-diphenyl-2-azaallyllithium and its rearrangement to the trans, trans-form (SC) 291 [G.E. *84*, 262 (1972)]
Effect of protonation on ~ and oxirane bond strengths (SC) 825 [G.E. *84*, 820 (1972)]

Azo compounds, Structurally isomeric metal chelates of unsymmetrical o,o′-dihydroxy-~ (SC) 312 [G.E. *84*, 351 (1972)]

Azodicarboxylic acid, Synthesis of isocyanides from N-monosubstituted formamides, phosphanes, and ~ derivatives (SC) 929 [G.E. *84*, 957 (1972)]

Azodicarboxylic imide, 1,4-Cycloaddition of azodicarboxylic phenylimide (4-phenyl-1,2,4-triazoline-3,5-dione) to cyclooctatetraene and its halogen derivatives (SC) 715 [G.E. *84*, 765 (1972)]

Azole, Synthesis and properties of ~-pyridine combinations: problem of the hydrolytic cleavage of hetarene combinations (SC) 846 [G.E. *84*, 828 (1972)]

Azomethines, N-Carbonylureas from ~ and N-chlorocarbonyl isocyanate (SC) 1011 [G.E. *84*, 1062 (1972)]
Cyclization of ~ by N-chlorocarbonyl isocyanate (SC) 1011 [G. E. *84*, 1063 (1972)]

Azulene, New routes to the ~ system (SC) 135 [G.E. *84*, 117 (1972)]

BACTERIA, Formation, structure, and function of the flagella of ~ (CR) 334 [G.E. *84*, 357 (1972)]

Bactericides, Fungicidal and bactericidal 4,5-dicyano-2-sulfonylimido-1,3-dithiacyclopentenes (PR) 946

Bacteriostatic fibers, Polymer based synthetic fibers with antibacterial properties (LA) 734

Barrelene, Bridgehead reactivities of trishomo-~ and trishomobullvalene (SC) 56 [G.E. *84*, 63 (1972)]

Bases, Basic behavior of epoxides in the presence of halide ions (FP) 1041 [G.E. *84*, 1157 (1972)]
Transition states as acids and ~ (LA) 546
Solid acids and ~ (Book Review) 649

Benzaldehyde, Photoisomerization of 2-[2-(N-ethoxycarbonyl-N-allylamino)ethyl]-~ (SC) 728 [G.E. *84*, 712 (1972)]

Benzene oxides, 1,4-Dioxocin (SC) 935 [G.E. *84*, 983 (1972)]
Valence tautomerism of 1,4-dioxocin with syn-benzene dioxide (SC) 937 [G.E. *84*, 985 (1972)]
Valence isomerization of syn-benzene trioxide to cis, cis, cis-1,4,7-trioxacyclononatriene; anti-benzene trioxide (SC) 939 [G.E. *84*, 986 (1972)]
trans-σ-Bis- and -tris-homobenzene derivatives; synthesis of cycloheptatriene-3,4-dicarboxylic acid derivatives (SC) 940 [G.E. *84*, 988 (1972)]
cis-Trioxatris-σ-homobenzene (cis-"benzene trioxide") (SC) 942 [G.E. *84*, 990 (1972)]

Benzenes, Ionization potentials of substituted ~ (SC) 525 [G.E. *84*, 544 (1972)]

Benzimidazolin-2-ones, Reaction of benzofuroxan with formaldehyde (SC) 1009 [G.E. *84*, 1060 (1972)]

Benzo[c]cinnolines, biaryls, stilbenes, and dibenz[c,mn]acridines from sulfonamides (SC) 826 [G.E. *84*, 822 (1972)]

Benzocyclopropene, X-ray structure analysis of a ~ derivative (SC) 422 [G.E. *84*, 434 (1972)]

Benzofuroxan, Reaction of ~ with formaldehyde (SC) 1009 [G.E. *84*, 1060 (1972)]

6,7-Benzomorphans, New racemic and optically active 2-cyclobutylmethyl-5-phenyl-~ (LA) 735

1,4-Benzoquinones, Aliphatic 1,2,3-triketones by ozonolysis of dialkyl-1,4-benzoquinones (SC) 1089 [G.E. *84*, 1144 (1972)]

p-Benzoquinones, Flash-vacuum thermolysis (CR) 333 [G.E. *84*, 314 (1972)]

Benzothiazylthioalkyl groups, Phenols substituted with ~ (PR) 1036

1-Benzothiepins, Synthesis of stable ~ (SC) 423 [G.E. *84*, 477 (1972)]

1,2,4-Benzotriazine 1,4-dioxide, Simple synthesis of 3-amino-~ (SC) 1900 [G.E. *84*, 1061 (1972)]

Benzoxazinones,4-(Dialkylamino)quinolines and 3,3-disubstituted 4(3H)-quinolones from 4H-3,1-~ and ynamines (SC) 720 [G.E. *84*, 716 (1972)]

Benzoxazole, 4-(2-Benzoxazolyl)phenylacetic acids, alcohols, esters, and amides (LA) 736

Benzyl cyanide, Aromatization of cyclohexylideneacetonitrile (SC) 723 [G.E. *84*, 767 (1972)]

Biallenyl, Cyclopropanation products (SC) 234 [G.E. *84*, 263 (1972)]

Biaryls, stilbenes, benzo[c]cinnolines, and dibenz[c,mn]acridines from sulfonamides (SC) 826 [G.E. *84*, 822 (1972)]

Bicycloheptafulvene, Methylenenorbornadiene, a ~ (SC) 512 [G.E. *84*, 533 (1972)]

Bicyclo[4.1.0]hept-1-ene, Bridged methylenecyclopropanes as test cases for Bredt's rule: 2,5,5,7,7-pentamethyl-~ (SC) 52 [G.E. *84*, 62 (1972)]

Bicyclo[4.2.1]nonane series, Reductive fragmentation of 3,3-dihalotricyclo[4.2.1.$0^{2,4}$]-non-2-yl acetates: a new route to the ~ (SC) 641 [G.E. *84*, 643 (1972)]

cis-Bicyclo[6.1.0]nona-2,4,6-triene, Degenerate rearrangement (SC) 832 [G.E. *84*, 892 (1972)]

Bicyclo[4.4.1]octane, Synthesis of 7,7-dimethyl-~-3-one by pinacolic rearrangement (SC) 640 [G.E. *84*, 642 (1972)]

Bilayers, Folding of fatty acid chains in liquid crystalline ~ (SC) 920 [G.E. *84*, 950 (1972)]

Biguanides, New ~ (PR) 856

Biochemical mechanisms, Exploration by tritium labeling (LA) 734

Biochemistry, Biochemisches Praktikum (Book Review) 857

Biography, The avenue of years — a memoir of Sir James Irvine (Book Review) 648

Biology, Die biologische Zukunft des Menschen (Book Review) 550

Biomembranes, Structural principles (FP) 551 [G.E. *84*, 597 (1972)]

Biopolymers, Kinetics of cooperative conformational transitions of linear ~ (FP) 568 [G.E. *84*, 615 (1972)]

Biphenylene, A squaric diamidine and an aza analog of ~ (SC) 433 [G.E. *84*, 481 (1972)]

7,7-Bis(alkylthio)norcaranes, Solvolysis of ~. A new method of homologation (SC) 49 [G.E. *84*, 50 (1972)]

Bischler-Napieralski reaction, Mechanism (SC) 919 [G.E. *84*, 947 (1972)]

Bishomoquinone, Synthesis and X-ray structure analysis of anti-1-bromotricyclo-[5.1.0.$0^{3,5}$]octane-2,6-dione (anti-1-bromo-~ (SC) 236 [G.E. *84*, 170 (1972)]

Block polymers, High-impact plastics formed by two phases. Adjustment of the degree of dispersion and of the interfacial adhesion by ~ (CR) 339 [G.E. *84*, 362 (1972)]

Blood coagulation, Molecular deficiencies in humans (LA) 446

Bond, Thermochemistry of the chemical ~ (LA) 545

Bonding, X-ray spectroscopic investigation of chemical ~ in solids (FP) 34 [G.E. *84*, 51 (1972)]
Metal-olefin and -acetylene ~ in complexes (FP) 596 [G.E. *84*, 649 (1972)]
Application of magnetic resonance methods in the elucidation of ~ in transition metal compounds (LA) 245
Current views of ~ in carbonylmetal compounds (LA) 545
~ in inorganic pseudohalides (LA) 545

Bond strengths, Effect of protonation on aziridine and oxirane ~ (SC) 825 [G.E. *84*, 820 (1972)]

9-Boraanthracene, Preparation of 9-phenyl-~ anion (SC) 53 [G.E. *84*, 28 (1972)]

Boranes, Organic syntheses via free-radical displacement reactions (FP) 692 [G.E. *84*, 702 (1972)]

Borates, Anodic oxidation of trihexylmethoxyborate in presence of butadiene (SC) 48 [G.E. *84*, 32 (1972)]

Boron compounds, Structure of $(CH_3OBC_5H_5)_2Co$, a derivative of the aromatic hydridoborinate anion (SC) 42 [G.E. *84*, 29 (1972)]

Bredt's rule, Bridged methylenecyclopropanes as test cases for ~: 2,5,5,7,7-pentamethylbicyclo[4.1.0]-hept-1-ene (SC) 52 [G.E. *84*, 62 (1972)]

Brewing science, Malting and ~ (Book Review) 1109

Bullvalene, Bridgehead reactivities of trishomobarrelene and trishomo-~ (SC) 56 [G.E. *84*, 63 (1972)]

Butadiene, Chemical syntheses with metal atoms: preparation of bis (~)iron complexes and ~-tetracarbonylchromium (SC) 532 [G.E. *84*, 547 (1972)]

3-Butenyl Grignard reagents, Rearrangement: anionic or radical? (SC) 542 [G.E. *84*, 531 (1972)]

CALCULATIONS, Insights into small ring carbocations provided by MO ~ (CR) 330 [G.E. *84*, 316 (1972)]

Camptothecin, Biogenetically oriented total synthesis of ~ and 7-chloro-~ (SC) 289 [G.E. *84*, 265 (1972)]

Carbanions, Silicon as a carbanion substituent in ylides (CR) 944 [G.E. *84*, 957 (1972)]

Carbene complexes, Unusual ^{13}C chemical shifts of transition metal-~ (SC) 141 [G.E. *84*, 155 (1972)]
Transition metal-~ as π-ligands — [ethoxy-(2,6-dimethoxyphenyl)carbenetetracarbonyliron(0)]tricarbonyliron(0) (SC) 238 [G.E. *84*, 214 (1972)]
Dimethylphosphane(phenylmethoxy)-methylenepentacarbonylchromium(0) — a route from ~ to ylide complexes (SC) 643 [G.E. *84*, 679 (1972)]
Demonstration of isomers and intramolecular isomerization of ~ of chromium (SC) 644 [G.E. *84*, 682 (1972)]

Carbene reactions, Carbonyl ylides and dichlorooxiranes in ~ (CR) 326 [G.E. *84*, 307 (1972)]

Carbene rearrangements, Cycloheptatrienylidene: structure and role in carbene-~ (CR) 325 [G.E. *84*, 306 (1972)]

Carbenes, DTA studies on formation of dehydrobenzene and dichlorocarbene from haloorganolithium compounds (SC) 507 [G.E. *84*, 527 (1972)]
[Bis(dimethylamine)aluminoxy]dimethylaminocarbene as a complex ligand (SC) 934 [G.E. *84*, 997 (1972)]
Carbenoids, ~, and nitrenes as polymerization initiators (LA) 855

Carbenoids, Chemistry of ~ and other thermolabile organolithium compounds (FP) 473 [G.E. *84*, 557 (1972)]
Organomercury ~ for the synthesis of cyclopropane derivatives (SC) 231 [G.E. *84*, 160 (1972)]
~, carbenes, and nitrenes as polymerization initiators (LA) 855
Carbides, Crystal chemistry of complex ~ and related compounds (FP) 906 [G.E. *84*, 973 (1972)]
Transition metal ~ and nitrides (Book Review) 947

Carbocations, Insights into small ring ~ provided by MO calculations (CR) 330 [G.E. *84*, 316 (1972)]

Carbocycles, Synthesis of five-membered ~ by [1,3]-anionic cycloaddition (SC) 292 [G.E. *84*, 292 (1972)]

Carbodiimidium compounds as reagents in organic chemistry (SC) 229 [G.E. *84*, 158 (1972)]

Carbohydrase, Enzymic synthesis of homogeneous stereoregular polymers (CR) 645 [G.E. *84*, 644 (1972)]

Carbohydrate esters, Rearrangements with anhydrous hydrofluoric acid (CR) 241 [G.E. *84*, 221 (1972)]

Carbohydrates, Chemistry and biochemistry of branched-chain sugars (FP) 159 [G.E. *84*, 192 (1972)]
Synthesis and pulse Fourier transform ^{13}C-NMR spectra of brached-chain ~ (SC) 148 [G.E. *84*, 111 (1972)]
Synthesis of branched ~ with aldehyde side chains. – Simple synthesis of L-streptose and D-hamamelose (SC) 149 [G.E. *84*, 112 (1972)]
Complex shift reagent for ^{13}C-NMR studies on ~ (SC) 539 [G.E. *84*, 589 (1972)]
Aldgarose (SC) 1021 [G.E. *84*, 1100 (1972)]

Carbon, Preparation, properties, and applications of vitreous ~ (LA) 66

Carbonate, Methyl hydrogen ~ (SC) 534 [G.E. *84*, 549 (1972)]

Carbon disulfide, Conversion of cyclic nitrones to thiolactams by reaction with ~ (SC) 47 [G.E. *84*, 34 (1972)]

Carbonic anhydrase, Metal ion function in ~ (FP) 408 [G.E. *84*, 461 (1972)]

Carbon monoxide, Catalytic deoxygenation of aromatic nitro compounds by ~ in presence of diphenylacetylene (SC) 634 [G.E. *84*, 641 (1972)]

Carbonyl compounds, 1-Formylamino-1-arylsulfonyl alkenes from α-metalated isocyanomethyl aryl sulfones and ~; conversion of a carbonyl compound into the next higher carboxylic acid (SC) 311 [G.E. *84*, 289 (1972)]
1,3-Oxazolidine-2-thiones from alkyl isothiocyanates and ~ (SC) 933 [G.E. *84*, 956 (1972)]

Carbonylmetal compounds, Current views of bonding (LA) 545

Carbonyl olefination, Ketene thioacetals by "Peterson-~" with metalated formyl trimethylsilyl thioacetals (SC) 443 [G.E. *84*, 476 (1972)]

N-Carbonylureas from azomethines and N-chlorocarbonyl isocyanate (SC) 1011 [G.E. *84*, 1062 (1972)]

Carbonyl ylides and dichlorooxiranes in carbene reactions (CR) 326 [G.E. *84*, 307 (1972)]

Carboxylic acid, 1-Formylamino-1-arylsulfonyl alkenes from α-metalated isocyanomethyl aryl sulfones and carbonyl compounds; conversion of a carbonyl compound into the next higher ~ (SC) 311 [G.E. *84*, 289 (1972)]

Carboxylic anhydrides, Trifluoromethanesulfonic-~, highly active acylating agents (SC) 299 [G.E. *84*, 294 (1972)]

Carbylamine reaction, Phase transfer catalysis in the Hofmann ~ (SC) 530 [G.E. *84*, 587 (1972)]

Carrier, Novel ~ for solid phase synthesis of oligomers (SC) 713 [G.E. *84*, 712 (1972)]

Carrier-bound biologically active substances and their applications (FP) 249 [G.E. *84*, 319 (1972)]

Catalysis, Phase transfer ~ in the Hofmann carbylamine reaction (SC) 530 [G.E. *84*, 587 (1972)]
~ by phthalocyanine complexes (CR) 239 [G.E. *84*, 219 (1972)]

Catalysts, Carrier-bound biologically active substances and their applications (FP) 249 [G.E. *84*, 319 (1972)]

Catalytic hydrogenation, Practical ~. Techniques and applications (Book Review) 649

Catenane, Ozonolytic degradation of a ~ (SC) 1089 [G.E. *84*, 1144 (1972)]

~s, rotaxanes and knots (Book Review) 248

Cathodic dimerization (FP) 760 [G.E. *84*, 798 (1972)]

Cation radicals in electron transfer reactions (LA) 734

Cations and radicals from cyclopropanone adducts (CR) 321 [G.E. *84*, 303 (1972)]

Cement, Zement, Herstellung und Eigenschaften (Book Review) 1040

Cesium oxide, Hendecacesium trioxide, $Cs_{11}O_3$ (SC) 1105 [G.E. *84*, 1190 (1972)]

Chelates, Structurally isomeric metal ~ of unsymmetrical o,o'-dihydroxy azo compounds (SC) 312 [G.E. *84*, 351 (1972)]
Structure and bonding properties of β-diketone ~ (LA) 64
Isomerization of metal β-diketone ~ (LA) 65

Chemistry, Knauers Buch der modernen Chemie (Book Review) 247

Chemotaxonomy, Recent trends in ~ of plants (LA) 343

Chiroptical methods, Introduction to ~ in chemistry (Book Review) 69

Chlorine oxide pentafluoride, Reaction of ClF_5 with OF_2 Preparation and properties of chlorine oxide trifluoride and the existence of ~ (SC) 1094 [G.E. *84*, 1147 (1972)]

Chlorine oxide trifluoride, Reaction of ClF_5 with OF_2 Preparation and properties of ~ and the existence of chlorine oxide pentafluoride (SC) 1094 [G.E. *84*, 1147 (1972)]

Chlorobiphenyls, Occurrence of poly-~ and their environmental significance (LA) 245

N-Chlorocarbonyl isocyanate, N-Carbonylureas from azomethines and ~ (SC) 1011 [G.E. *84*, 1062 (1972)]
Cyclization of azomethines by N-chlorocarbonyl isocyanate (SC) 1011 [G.E. *84*, 1063 (1972)]

α-Chloroenamines: new reagents for organic synthesis (CR) 852 [G.E. *84*, 901 (1972)]

Chloroplasts, Comparative studies of the topography of the membranes of mitochondria and ~ (CR) 153 [G.E. *84*, 123 (1972)]

Chondroitin sulfate proteins, Structure, biosynthesis, and heterogeneity (LA) 448

Chromatography, Coordination-polymeric metal complexes of bifunctional dithiophosphinic acids and their use as adsorbents in ~ (SC) 435 [G.E. *84*, 485 (1972)]
Coordination-polymeric metal complexes as stationary phases in gas ~ (SC) 830 [G.E. *84*, 832 (1972)]
New dihydroxyboryl-substituted polymers for column-chromatographic separation of ribonucleoside-deoxyribonucleoside mixtures (SC) 824 [G.E. *84*, 819 (1972)]

Chromium complexes, Chemical syntheses with metal atoms: preparation of bis(butadiene)iron complexes and butadiene-tetracarbonylchromium (SC) 532 [G.E. *84*, 547 (1972)]
Demonstration of isomers and intramolecular isomerization of carbene complexes of chromium (SC) 644 [G.E. *84*, 682 (1972)]
Dimethylphosphane(phenylmethoxy) methylenepentacarbonylchromium(0) – a route from carbene- to ylide complexes (SC) 643 [G.E. *84*, 679 (1972)]
Tetranitrosylchromium $[Cr(NO)_4]$ (SC) 1092 [G.E. *84*, 1150 (1972)]

Chromium compounds, Gmelins Handbuch der anorganischen Chemie (Book Review) 449

Chromosomes, Structure and function of chromosomal nucleohistones (FP) 496 [G.E. *84*, 451 (1972)]

Circular dichroism of cobalt(III) chelates (LA) 447

Claisen condensation, Synthesis of non-enolizable β-diketones by acid-catalyzed intramolecular ~ (SC) 1030 [G.E. *84*, 1110 (1972)]

Clathrates, $Ge_{38}P_8I_8$ and $Ge_{38}As_8I_8$, a new class of compounds with chlathrate structure (SC) 43 [G.E. *84*, 30 (1972)]

Clinical chemistry, Standard methods of ~ (Book Review) 67

Cobalt(III) chelates, Circular dichroism (LA) 447

Cobalt complexes, Stereochemistry of ~ with flexible tetradentate ligands (LA) 344

Cobalt compounds, Structure of $(CH_3OBC_5H_5)_2Co$, a derivative of the aromatic hydridoborinate anion (SC) 42 [G.E. *84*, 29 (1972)]
2,3:3,4:4,2-Tri-μ-carbonyl-2,2,3,3,4,4-hexacarbonyl-1-aluminotricobalt: preparation and spectroscopic findings (SC) 535 [G.E. *84*, 587 (1972)]

Collagen, Properties of ~ and gelatin in the solid state (LA) 854

Colloidal properties and adsorption of radioactive elements (LA) 156

Complexes, Macrocyclic polyethers and their ~ (FP) 16 [G.E. *84*, 16 (1972)]
Metal-olefin and -acetylene bonding in ~ (FP) 596 [G.E. *84*, 649 (1972)]
Decomposition of organometallic ~ in the mass spectrometer (FP) 653 [G.E. *84*, 725 (1972)]
Metal isotope effects on metall-igand vibrations (FP) 666 [G.E. *84*, 755 (1972)]
The mesityl group as a ring current probe in transition metal 1,2-diimine chelates (SC) 725 [G.E. *84*, 769 (1972)]
Coordination-polymeric metal ~ as stationary phases in gas chromatography (SC) 830 [G.E. *84*, 832 (1972)]
σ-~ in halogenation of aminobenzenes – isolation and secondary reactions (SC) 922 [G.E. *84*, 954 (1972)]
Protection of adenosine 5'-triphosphate toward hydrolysis by the formation of a mixed-ligand metal ion complex (SC) 1025 [G.E. *84*, 1103 (1972)]
Transition-metal π-~ with activated olefins (CR) 730 [G.E. *84*, 773 (1972)]
Kinetics and mechanism of the formation of transition-metal ~ (CR) 731 [G.E. *84*, 773 (1972)]
Structural aspects of metal ion-ligand interaction (CR) 851 [G.E. *84*, 833 (1972)]
Crystalline transition-metal ~ with strongly anisotropic physical properties (CR) 944 [G.E. *84*, 998 (1972)]
Short-lived molecules as ligands in coordination compounds (CR) 1034 [G.E. *84*, 1111 (1972)]
Infrared spectra of pseudo-halide ~ (LA) 65
Electronic spectra of hexafluoro ~ (LA) 65
Methods for calculation of stability constants of metal ~ in solution (LA) 65
Structure of metal ~ of some quadridentate Schiff bases (LA) 733
Organic syntheses with transition metal ~ (LA) 855
Ring ligand substitution reactions of aromatic-metal ~ (LA) 945
Transition-metal ~ of olefins and acetylenes (LA) 945
Possible interactions of transition metal ~ with biological macromolecules (LA) 1035
Komplexchemie (Book Review) 72

Computers, The computer in chemical research–an introduction (FP) 347 [G.E. *84*, 370 (1972)]
Computer systems for chemical research (FP) 348 [G.E. *84*, 371 (1972)]
Data processing in gas chromatography (FP) 366 [G.E. *84*, 390 (1972)]
Use in nuclear magnetic resonance NMR spectroscopy (FP) 375 [G.E. *84*, 400 (1972)]
Computer-aided analysis of organic mass spectra (FP) 357 [G.E. *84*, 381 (1972)]
Automated X-ray structure determination as an analytical method (FP) 387 [G.E. *84*, 412 (1972)]
Application to MO theory and chemical kinetics (FP) 393 [G.E. *84*, 418 (1972)]
Computer-assisted analysis of complex synthetic problems (LA) 446

Computer terms (FP) 403 [G.E. *84*, 429 (1972)]

Conductivity measurements in organic solvents (LA) 157

Conformational analysis, in hetero-cyclic systems: recent results and applications (FP) 739 [G.E. *84*, 779 (1972)]
EPR spectroscopy as a method of ~ (CR) 242 [G.E. *84*, 223 (1972)]

Conformational transitions, Kinetics of cooperative ~ of linear biopolymers (FP) 568 [G.E. *84*, 615 (1972)]
Cooperative ~ in globular proteins (FP) 894 [G.E. *84*, 931 (1972)]

Conjugation, in aromatic amines and phosphanes (SC) 836 [G.E. *84*, 898 (1972)]
Photoelectron spectroscopy and ~–direct proof of unusual sequence of two highest occupied π-molecular orbitals in the phosphorin (phosphabenzene) and the arsenin (arsabenzene) system (SC) 924 [G.E. *84*, 993 (1972)]

Contraception reliability of the minipill (PR) 857

Control engineering, Regeln und Steuern (Book Review) 647

Cooperative conformational transitions, Kinetics of ~ of linear biopolymers (FP) 568 [G.E. *84*, 615 (1972)]
~ in globular proteins (FP) 894 [G.E. *84*, 931 (1972)]

Coordination compounds, Photochemical reactions of solid ~ (LA) 157

Copolymerization, Determination of kinetic constants of homopolymerization by measurement of ~-s (CR) 341 [G.E. *84*, 363 (1972)]

Copolymers, Chemical reactions on single crystals of ~ (CR) 340 [G.E. *84*, 363 (1972)]

Synthesis of ethylene-olefin ~ by means of soluble organometal catalysis (CR) 853 [G.E. *84*, 902 (1972)]

Copper(I) compounds, Versatility of organo-~ and organocuprates (LA) 448

Coumarins, Structural studies on constituents of Umbelliferae (CR) 239 [G.E. *84*, 219 (1972)]

Crotonic esters, Reversible isomerization in β-isocyanato-~ (SC) 128 [G.E. *84*, 107 (1972)]

Crystal chemistry, of complex carbides and related compounds (FP) 906 [G.E. *84*, 973 (1972)]

~ and semiconduction (Book Review) 859

Crystal structure, syn-Planar conformation of oxalic acid: ~ of the oxalic acid-acetamide complex (SC) 514 [G.E. *84*, 536 (1972)]

Cyanic esters, New reactions with ~ (FP) 949 [G.E. *84*, 1008 (1972)]

Cyanoacetamides, The synthesis of tetrasubstituted pyridines from N,N-dialkyl~ (SC) 1098 [G.E. *84*, 1183 (1972)]

The synthesis of N-alkylpyridinium salts from N-alkyl~ (SC) 1099 [G.E. *84*, 1184 (1972)]

Synthesis of pentasubstituted pyridines from C-alkyl-N,N-dialkyl~ (SC) 1100 [G.E. *84*, 1185 (1972)]

2-Cyanoaziridine (SC) 151 [G.E. *84*, 108 (1972)]

γ-Cyano-α-isocyanoalkanoates, Ethyl ~from α-metalated ethyl isocyano-acetates or -propionates and acrylonitriles (SC) 429 [G.E. *84*, 478 (1972)]

Cyclization, Synchronous six-electron ~ of hexatriene systems as a new synthetic principle for preparation of aromatic and heteroaromatic compounds (SC) 315 [G.E. *84*, 299 (1972)]

Cycloaddition, Structure of the 2:1 ~ product of diazomethane and 1,1,1-trifluoro-2-trifluoromethyl-3-aza-2,4-trans-hexadiene (SC) 223 [G.E. *84*, 212 (1972)]

Spiroheptatrienes by [1+2]-~ (SC) 225 [G.E. *84*, 215 (1972)]

Intramolecular $[_\pi 4+_\pi 2]$-~: preparative and kinetic aspects (SC) 294 [G.E. *84*, 291 (1972)]

Synthesis of five-membered carbocycles by [1,3]-anionic ~ (SC) 292 [G.E. *84*, 292 (1972)]

1,4-~ of azodicarboxylic phenylimide [4-phenyl-1,2,4-triazoline-3,5-dione] to cyclooctatetraene and its halogen derivatives (SC) 715 [G.E. *84*, 765 (1972)]

1,4-~ of tetracyanoethylene to methoxy- and phenoxy-cyclooctatetraene (SC) 716 [G.E. *84*, 766 (1972)]

Ring opening of cyclopropyl anion and ~ of allyl anion (SC) 724 [G.E. *84*, 768 (1972)]

Substituent effects in 1,3-dipolar ~-s of phenyl azide (SC) 838 [G.E. *84*, 887 (1972)]

Intramolecular ~-s of C,O and C,N multiple bonds to orthoquinodimethanes (SC) 1031 [G.E. *84*, 1108 (1972)]

~-s and rearrangements of 2-oxyallyl systems (CR) 324 [G.E. *84*, 305 (1972)]

~ of cyclopropylethylenes with tetracyanoethylene (CR) 328 [G.E. *84*, 309 (1972)]

Cycloalkynes, The synthesis of stable, isolable ~ having 7- to 12-membered rings (LA) 1035

Cyclobutabenzene, Photochemistry of dimethyl 1,2-dihydro-~-1,2-diylidenediacetate (SC) 216 [G.E. *84*, 206 (1972)]

Cyclobutadiene, Synthesis of a ~ stabilized by steric effects (SC) 932 [G.E. *84*, 952 (1972)]

Cyclobutane, Photoelectron spectra of unsaturated systems containing cyclopropane and ~ rings (SC) 524 [G.E. *84*, 543 (1972)]

~ ring contractions not involving carbonium ions (LA) 447

Cyclobutanones, Photoreactions in solution (CR) 331 [G.E. *84*, 312 (1972)]

Cyclobutenediones, The chemistry of phenylcyclobutenediones (FP) 997 [G.E. *84*, 1048 (1972)]

3-Cyclobutene-1,2-dione, 3-Mercapto-4-phenyl-~ (SC) 142 [G.E. *84*, 110 (1972)]

Cyclobutenes, General synthetic route to seven-membered heterocycles from ~ and 1,3-dipoles (SC) 926 [G.E. *84*, 995 (1972)]

1-Cyclobutenyl nonafluorobutanesulfonate, Solvolysis (SC) 714 [G.E. *84*, 714 (1972)]

Cyclodimerization, of methylene cyclopropane on a Ni(0) catalyst (SC) 309 [G.E. *84*, 352 (1972)]

~ of heated methylenecyclopropane (SC) 433 [G.E. *84*, 483 (1972)]

Light-induced [2+4]-~ in crystalline state (SC) 434 [G.E. *84*, 479 (1972)]

Cyclodipeptides, Side-reactions arising on formation of ~ in solid-phase peptide synthesis (SC) 293 [G.E. *84*, 290 (1972)]

Cycloheptatrienylidene: structure and role in carbene-carbene rearrangements (CR) 325 [G.E. *84*, 306 (1972)]

Cyclohexadienone, Three isomerization routes originating from different electronic states of a linearly-conjugated ~ (SC) 637 [G.E. *84*, 638 (1972)]

Cyclohexanone, Reaction with acetonitrile (SC) 722 [G.E. *84*, 767 (1972)]

Cyclohexylideneacetonitrile, Aromatization (SC) 723 [G.E. *84*, 767 (1972)]

Cyclooctasulfur oxide, Preparation (SC) 302 [G.E. *84*, 344 (1972)]

Cyclooctatetraene, 1,4-Cycloaddition of azodicarboxylic phenylimide [4-phenyl-1,2,4-triazoline-3,5-dione] to ~ and its halogen derivatives (SC) 715 [G.E. *84*, 765 (1972)]

1,4-Cycloaddition of tetracyanoethylene to methoxy- and phenoxy-~ (SC) 716 [G.E. *84*, 766 (1972)]

The primary step in the halogenation of ~ (SC) 1104 [G.E. *84*, 1187 (1972)]

Cycloolefins, Polymerization (LA) 855

Cyclopentadiene, [2+4]- and [4+4]-Photoaddition to anthracene (SC) 718 [G.E. *84*, 718 (1972)]

Cyclophanes, Stereochemistry of [2.2]meta-~ (FP) 73 [G.E. *84*, 75 (1972)]

Simple synthesis of [2.2]para-~ (SC) 419 [G.E. *84*, 471 (1972)]

~ possessing cavities (SC) 535 [G.E. *84*, 588 (1972)]

Cyclopolymerization with intramolecular formation of lactone rings (CR) 339 [G.E. *84*, 362 (1972)]

Cyclopropanation products of biallenyl (SC) 234 [G.E. *84*, 263 (1972)]

Cyclopropane, Organomercury carbenoids for synthesis of ~ derivatives (SC) 231 [G.E. *84*, 160 (1972)]

Cyclodimerization of methylene-~ on a Ni(0) catalyst (SC) 309 [G.E. *84*, 352 (1972)]

Photoelectron spectra of unsaturated systems containing ~ and cyclobutane rings (SC) 524 [G.E. *84*, 543 (1972)]

New direct synthesis of monobromo-~-s (CR) 326 [G.E. *84*, 308 (1972)]

Cyclopropanone, Cations and radicals from ~ adducts (CR) 321 [G.E. *84*, 303 (1972)]

Recent aspects of ~ chemistry (CR) 332 [G.E. *84*, 312 (1972)]

~-s and the Favorskii rearrangement. An unexpectedly large secondary isotope effect (CR) 329 [G.E. *84*, 311 (1972)]

Cyclopropanimines (CR) 329 [G.E. *84*, 316 (1972)]

2-Cyclopropene-1-carboxylic acids from trimethylsilylacetylenes (SC) 929 [G.E. *84*, 946 (1972)]

Cyclopropenylethylenes, Cycloaddition with tetracyanoethylene (CR) 328 [G.E. *84*, 309 (1972)]

Cyclopropyl anion, Ring opening of ~ and cycloaddition of allyl anion (SC) 724 [G.E. *84*, 768 (1972)]

Cyclothiazenes, Oxohalo~ (SC) 1095 [G.E. *84*, 1149 (1972)]

Cysteine, Studies of intramolecular proton transfer to ~ and related compounds by relaxation kinetics (SC) 428 [G.E. *84*, 430 (1972)]

DEAMINATION, Concerted and non-concerted ~ (CR) 851 [G.E. *84*, 833 (1972)]

Dehydrobenzene, DTA studies on formation of ~ and dichlorocarbene from haloorganolithium compounds (SC) 507 [G.E. *84*, 527 (1972)]

Deoxygenation, Catalytic ~ of aromatic nitro compounds by carbon monoxide in presence of diphenylacetylene (SC) 634 [G.E. *84*, 641 (1972)]

Deoxyribonucleic acid, Dynamic structure of a synthetic ~ (CR) 338 [G.E. *84*, 360 (1972)]

Deuterium compounds, Synthesis of hydroxy-deuterated alcohols (LA) 945

Diamond crystals, Growth of large ~ (LA) 446

Diazaphosphorine, Synthesis of 2,2-dichloro-1,5-dimethyl-4,6-dioxo-1,4,5,6-tetrahydro-1,5,2 λ^5-~ (SC) 528 [G.E. *84*, 585 (1972)]

Diazepinones, Synthesis of new ~ (SC) 152 [G.E. *84*, 153 (1972)]

2,3-Diazido-2,3-dimethylbutane, Photolysis of ~ (SC) 1024 [G.E. *84*, 1102 (1972)]

1-Diazoindene and spiro[indene-1,7'-norcaradiene] (SC) 44 [G.E. *84*, 31 (1972)]

Diazomethane, Structure of the 2:1 cycloaddition product with 1,1,1-trifluoro-2-trifluoromethyl-3-aza-2,4-trans-hexadiene (SC) 223 [G.E. *84*, 212 (1972)]

Diazonium salts, Phenyldiimine in reduction of ~ by sodium tetrahydridoborate (SC) 45 [G.E. *84*, 33 (1972)]

Reactions of λ^3-Phosphorins with arenediazonium (SC) 1091 [G.E. *84*, 1146 (1972)]

Dibenz[c,mn]acridines, biaryls, stilbenes, and benzo[c]cinnolines, from sulfonamides (SC) 826 [G.E. *84*, 822 (1972)]

Dibenzoazastannines, Electron-impact induced rearrangements in ~ (SC) 521 [G.E. *84*, 542 (1972)]

1,n-Dicarboxylic diesters, Single-step synthesis by Kolbe electrolysis of oxalic and malonic half esters in the presence of olefins (SC) 841 [G.E. *84*, 893 (1972)]

Dichlorocarbene, DTA studies on formation of dehydrobenzene and ~ from haloorganolithium compounds (SC) 507 [G.E. *84*, 527 (1972)]

N-Dichloromethylene-N,N-dimethylammonium chloride, Reactions with enamines (SC) 916 [G.E. *84*, 991 (1972)]
Reaction with secondary acetamides (SC) 917 [G.E. *84*, 993 (1972)]

Dichlorooxiranes and carbonyl ylides in carbene reactions (CR) 326 [G.E. *84*, 307 (1972)]

Dictionary of science and technology German-English (Book Review) 651

Dicyclohepta [cd, gh]pentalene, a new pyrene isomer (SC) 1013 [G.E. *84*, 1064 (1972)]

Diels-Alder additions, Substituent effects (SC) 840 [G.E. *84*, 888 (1972)]

α,α-Diferrocenylmethyliumion, Structure and properties of ~ (SC) 1025 [G.E. *84*, 1104 (1972)]
Partial charge on the iron in the diferrocenylmethylium ion (SC) 1028 [G.E. *84*, 1107 (1972)]
Diffusion data (Book Review) 1108

Difluoromethyl-1,2,2,3,3-pentafluoropropyl ether (PR) 1035

1,2-Dihalo[18]annulene, Simple synthesis and NMR spectroscopic behavior (SC) 51 [G.E. *84*, 36 (1972)]

Dihydropyridines, Chemistry of ~ (LA) 732

Diimine, Phenyl-~ in the reduction of diazonium salts by sodium tetrahydridoborate (SC) 45 [G.E. *84*, 33 (1972)]
Isolation of pure ~ (SC) 829 [G.E. *84*, 889 (1972)]

1,2-Diimine chelates, The mesityl group as a ring current probe in transition metal ~ (SC) 725 [G.E. *84*, 769 (1972)]

Diiminosuccinonitrile, Hydrogen cyanide chemistry: synthesis of ~ (CR) 153 [G.E. *84*, 173 (1972)]

β-Diketones, Synthesis of non-enolizable ~ by acidcatalyzed intramolecular Claisen condensation (SC) 1030 [G.E. *84*, 1110 (1972)]

β-Diketone chelates, Structures and bonding properties (LA) 64
Isomerization of metal ~ (LA) 65

Dimerization, Cathodic ~ (FP) 760 [G.E. *84*, 798 (1972)]

6,6-Dimethylfulvene, Dye-sensitized photooxygenation of ~; a new 1,2-dioxolane rearrangement (CR) 330 [G.E. *84*, 311 (1972)]

Diols, Polycondensation of diethyl phosphite with aliphatic ~ (CR) 341 [G.E. *84*, 363 (1972)]

1,4-Dioxocin (SC) 935 [G.E. *84*, 983 (1972)]
Valence tautomerism with syn-benzene dioxide (SC) 937 [G.E. *84*, 985 (1972)]

1,2-Dioxolane rearrangement, Dye-sensitized photooxygenation of 6,6-dimethylfulvene; a new ~ (CR) 330 [G.E. *84*, 311 (1972)]

1,3-Diphenylallene, Dimerization of optically active ~ (CR) 322 [G.E. *84*, 304 (1972)]

1,3-Dipoles, General synthetic route to seven-membered heterocycles from cyclobutenes and ~ (SC) 926 [G.E. *84*, 995 (1972)]

Diradicals, Electronic properties (FP) 92 [G.E. *84*, 86 (1972)]

Displacement reactions, Organic syntheses via free-radical ~ (FP) 692 [G.E. *84*, 702 (1972)]

Disulfides, Chirooptical properties of the cystine disulfide bond (CR) 854 [G.E. *84*, 902 (1972)]

Disulfur monoxide, Chemistry of ~ (LA) 244

1,3-Dithiacyclopentenes, Fungicidal and bactericidal 4,5-dicyano-2-sulfonylimido-~ (PR) 946

Dithiazepine, New principle for preparation of bicyclic ~ systems (SC) 511 [G.E. *84*, 535 (1972)]

Dithiophosphinic acids, Coordination-polymeric metal complexes of bifunctional ~ and their use as adsorbents in chromatography (SC) 435 [G.E. *84*, 485 (1972)]

Double bond, Reactivity of ~ in higher olefins depending upon position and geometrical configuration (CR) 62 [G.E. *84*, 37 (1972)]
Reactions of ~-s activated by methoxy groups (CR) 324 [G.E. *84*, 306 (1972)]
Stereochemistry of ~-s (LA) 855

Drugs, Analytical methods of detection of ~ and poisons (LA) 1107

Dyes, Industrial application of the semiconductor properties of ~ (FP) 1051 [G.E. *84*, 1077 (1972)]
The chemistry of synthetic ~ (Book Review) 547, 737
Leitfaden der Farbstoffchemie (Book Review) 246

Dyotropic rearrangements, a new class of orbital-symmetry controlled reactions. Type I. (SC) 129 [G.E. *84*, 161 (1972)]
~, a new class of orbital-symmetry controlled reactions. Type II. (SC) 130 [G.E. *84*, 163 (1972)]

ELECTRIC fields, Properties of molecules in ~ (CR) 1033 [G.E. *84*, 1074 (1972)]

Electrochemistry, Cathodic dimerization (FP) 760 [G.E. *84*, 798 (1972)]
Anodic oxidation of trihexylmethoxyborate in presence of butadiene (SC) 48 [G.E. *84*, 32 (1972)]
Single-step synthesis of 1,n-dicarboxylic diesters by Kolbe electrolysis of oxalic and malonic half esters in the presence of olefins (SC) 841 [G.E. *84*, 893 (1972)]
Modern ~ (Book Review) 67,

Electrodes, Electrochemical measurements with amalgam ~ (LA) 447
Adsorption of organic compounds on ~ (Book Review) 1037

Electronic states, Three isomerization routes originating from different ~ of a linearly-conjugated cyclohexadienone (SC) 637 [G.E. *84*, 638 (1972)]

Electronic theory of cyclic $(pd)_\pi$-systems (LA) 855

"Electron lone pairs" in organic sulfides and disulfides (SC) 150 [G.E. *84*, 119 (1972)]

Electron-rich olefins, Reactions with proton-active compounds (FP) 964 [G.E. *84*, 1022 (1972)]

Electron spectroscopy for chemical analysis: ESCA (FP) 83 [G.E. *84*, 144 (1972)]

Electron transfer reactions, Cation radicals in ~ (LA) 734

Electron transport, Energy coupling and ~ (CR) 544 [G.E. *84*, 553 (1972)]

Electrophilic substitution, Model reactions for ~ of aromatic compounds (CR) 61 [G.E. *84*, 37 (1972)]
Unusual aromatic ~ (LA) 65

Eliminations, The syn and anti steric course in bimolecular olefin-forming ~ (FP) 200 [G.E. *84*, 177 (1972)]

Enamines, Reactions with N-dichloromethylene-N,N-dimethylammonium chloride (SC) 916 [G.E. *84*, 991 (1972)]

Energetics, Chemical ~ (Book Review) 858

Energy coupling and electron transport (CR) 544 [G.E. *84*, 553 (1972)]

Enone lactones, Synthesis and photochemical behavior (CR) 327 [G.E. *84*, 308 (1972)]

Enzymes, Carrier-bound biologically active substances and their applications (FP) 249 [G.E. *84*, 319 (1972)]
Enzymatic hydroxylations with molecular oxygen (FP) 701 [G.E. *84*, 689 (1972)]
Enzymic synthesis of homogeneous stereoregular polymers (CR) 645 [G.E. *84*, 644 (1972)]
~ containing molybdenum (LA) 945

Epoxides, Basic behavior in presence of halide ions (FP) 1041 [G.E. *84*, 1173 (1972)]

7,8-cis-Epoxy-2-methyloctadecane, Novel total synthesis of the sex attractant of Porthetria dispar (~) (SC) 60 [G.E. *84*, 67 (1972)]

Erythrinanes, Rearrangements of spirolactams with synthetic cis- and trans-~ as example (CR) 240 [G.E. *84*, 220 (1972)]

ESR spectroscopy, ESR measurements for the 2,2',6,6'-tetrachloro derivative of Chichibabin's hydrocarbon (SC) 531 [G.E. *84*, 546 (1972)]
1,3,5-Benzenetriyltris(1,5-diphenyl-3-verdazyl): A radical having a nearly degenerate doublet-quartet ground state (SC) 830 [G.E. *84*, 890 (1972)]
~ as a method of conformational analysis (CR) 242 [G.E. *84*, 223 (1972)]

Ester migrations, Sigmatropic [1,5]-~ (SC) 513 [G.E. *84*, 534 (1972)]

Esters, Model reactions for synthesis of pharmacologically active polymers by way of monomeric and polymeric reactive ~ (SC) 1103 [G.E. *84*, 1189 (1972)]

Ethylene, Side-chain alkylation of toluene with ~ (SC) 918 [G.E. *84*, 947 (1972)]

Ethylene-olefin copolymers, Synthesis by means of soluble organometal catalysts (CR) 853 [G.E. *84*, 902 (1972)]

Evolution, Self-organization of molecular systems and ~ of the genetic apparatus (FP) 798 [G.E. *84*, 838 (1972)]
Computer model of the formation of self-organizing systems (FP) 821 [G.E. *84*, 862 (1972)]

FATTY acid chains, Folding in liquid crystalline bilayers (SC) 920 [G.E. *84*, 950 (1972)]

Fatty acid synthetase, Genetic organization of the ~ complex of yeast (CR) 154 [G.E. *84*, 124 (1972)]

Favorskii rearrangement, Cyclopropanones and the ~. An unexpectedly large secondary isotope effect (CR) 329 [G.E. *84*, 311 (1972)]

Fenton's reagent, Free-radical alkylation with sulfoxides and ~ (CR) 241 [G.E. *84*, 222 (1972)]

Ferredoxins, X-ray photoelectron spectroscopy of iron-containing proteins – Valency of iron in ~ (SC) 232 [G.E. *84*, 156 (1972)]

Ferrocene, Absolute configuration of a 1,2-disubstituted ~ derivative with two different chiral substituents (SC) 138 [G.E. *84*, 164 (1972)]
Structure and properties of α,α-diferrocenylmethylium ion (SC) 1025 [G.E. *84*, 1104 (1972)]
Reaction of ferrocenylmethylium ions with nitrosobenzene (SC) 1027 [G.E. *84*, 1106 (1972)]
Partial charge on the iron in the diferrocenylmethylium ion (SC) 1028 [G.E. *84*, 1107 (1972)]

Ferrocenylmethylium ions, Reaction with nitrosobenzene (SC) 1027 [G.E. *84*, 1106 (1972)]

Fiber chemistry, Essential ~ (Book Review) 647

Fibers, Polycrystalline inorganic ~ – production, properties, applications (FP) 751 [G.E. *84*, 866 (1972)]
Polymer based synthetic ~ with antibacterial properties (LA) 734
A new composite fiber (LA) 735
Crosslinked, carbon-loaded polyolefin textile ~ (PR) 856
Improved polyester ~ suitable for dyeing under high-temperature conditions (PR) 855

Flagella, Formation, structure, and function of ~ of bacteria (CR) 334 [G.E. *84*, 357 (1972)]

Flames, How are metal atoms formed in ~? (LA) 64

Flame spectroscopy, Analytical ~ – selected topics (Book Review) 547

Flash-vacuum thermolysis of p-benzoquinones (CR) 333 [G.E. *84*, 314 (1972)]

Flavor research principles and techniques (Book Review) 650

Fluorides, Preparation of non-noble metals (Li, Ca, Sr, Ba, Am, Cf) by reduction of their oxides and ~ with hydrogen (SC) 515 [G.E. *84*, 537 (1972)]
Absorption spectra of tetragonal ~ from the first transition metal series (LA) 64

Fluorinated β-sultones (FP) 583 [G.E. *84*, 623 (1972)]

Fluorine compounds, 1-Cyclopentadienyldifluorophosphane: a new fluxional molecule (SC) 644 [G.E. *84*, 683 (1972)]
4-(Difluorooxophosphoranyl)-1λ⁴,3,5,2,-4,6-trithiatriazine (SC) 642 [G.E. *84*, 684 (1972)]

Fluoro complexes, Preparation and structure of $Rb[Mo_2O_2F_9]$ 1020 [G.E. *84*, 1099 (1972)]

Fluorophosphoranes, Tetraorgano-~ (SC) 144 [G.E. *84*, 165 (1972)]

Fluxional molecule, 1-Cyclopentadienyldifluorophosphane: a new ~ (SC) 640 [G.E. *84*, 683 (1972)]

Folding of fatty acid chains in liquid crystalline bilayers (SC) 920 [G.E. *84*, 950 (1972)]

Force constants, Calculation of vibrational frequencies and ~ (LA) 66

Formaldehyde, Reaction with benzofuroxan (SC) 1009 [G.E. *84*, 1060 (1972)]

Formamides, Synthesis of isocyanides from N-monosubstituted ~, phosphanes and azodicarboxylic acid derivatives (SC) 929 [G.E. *84*, 957 (1972)]

Formimidates, New 1-carbamoyl-N-carbamoyloxy-~ (PR) 946

α-Formylamino-β-hydroxy-acid esters, Ethyl ~(β-substituted N-formylserine esters) from ethyl 2-oxazoline-4-carboxylates (SC) 432 [G.E. *84*, 435 (1972)]

N-Formylserine esters, Ethyl α-formylamino-β-hydroxy-acid esters (β-substituted ~) from ethyl 2-oxazoline-4-carboxylates (SC) 432 [G.E. *84*, 435 (1972)]

Fragmentation, Reductive ~ of 3,3-dihalotricyclo[4.2.1.$0^{2,4}$]non-2-yl acetates: a new route to the bicyclo[4.2.1]nonane series (SC) 641 [G.E. *84*, 643 (1972)]

Friedel-Crafts acylation, Catalytic ~ of aromatic compounds (SC) 300 [G.E. *84*, 295 (1972)]

Fries rearrangement, Photo-~ (LA) 65

Fulvalenes, Sesqui-~ from dihydro-~ (SC) 133 [G.E. *84*, 115 (1972)]
Vinylogous fulvalene: synthesis and electrocyclic reaction (SC) 296 [G.E. *84*, 297 (1972)]

Fulvenes, Vinylogous hepta-~ from vinylogous ~ (SC) 131 [G.E. *84*, 113 (1972)]

Fungicides, Fungicidal and bactericidal 4,5-dicyano-2-sulfonylimido-1,3-dithiacyclopentenes (PR) 946

GALLIUM complexes, Relation between structure and proton donor strength of octahedrally coordinated tris(3,5-diisopropylsalicylato)-aluminum(III), -gallium(III), and -indium(III) (SC) 1096 [G.E. *84*, 1151 (1972)]

Gas chromatography, Data processing in ~ (FP) 366 [G.E. *84*, 390 (1972)]

Gelatin, Properties of collagen and ~ in the solid state (LA) 854

Gel permeation chromatography, Errors in the determination of narrow and broad molecular weight distributions by ~ and their possible elimination (CR) 334 [G.E. *84*, 356 (1972)]

Genetic information, Transcription of ~ and its regulation by protein factors (FP) 883 [G.E. *84*, 961 (1972)]

Genetics, Genetic aspects of hemoglobin synthesis (FP) 576 [G.E. *84*, 649 (1972)]

Geochemistry, Organic ~ (LA) 446

1-Germa-3-cyclopentenes, Photoelectron spectroscopy and transannular interactions – the question of transannular d-π interactions in 1-sila-3-cyclopentenes and ~ (SC) 837 [G.E. *84*, 899 (1972)]

Germanium compounds, $Ge_{38}P_8I_8$ and $Ge_{38}As_8I_8$, a new class of compounds with clathrate structure (SC) 43 [G.E. *84*, 30 (1972)]
Publications on organo-~ (LA) 733
The organic compounds of germanium (Book Review) 652

Glow discharges, Organic syntheses in the plasma of ~ and their preparative application (FP) 781 [G.E. *84*, 876 (1972)]

Glutaronitriles, Simple synthesis of substituted ~ (SC) 723 [G.E. *84*, 767 (1972)]

Gold complexes, Trimeric 1-(cyclohexylimino)methoxymethylgold(I), a new type of organometallic compound (SC) 429 [G.E. *84*, 482 (1972)]

Graft reactions on SiO_2 surfaces (CR) 337 [G.E. *84*, 359 (1972)]

Gramicidin S, Chirooptical properties of the cystine disulfides bond (CR) 854 [G.E. *84*, 902 (1972)]

Grignard reagents, Rearrangement of 3-butenyl ~: anionic or radical? (SC) 542 [G.E. *84*, 531 (1972)]

Growth processes due to reactions in swellable cellular matrixes (FP) 990 [G.E. *84*, 1001 (1972)]

Guanidine, Alkylamino-~ derivatives (LA) 735

HAIR sprays, Film-forming polymer masses (PR) 1107

Halide ions, Basic behavior of epoxides in presence of ~ (FP) 1041 [G.E. *84*, 1173 (1972)]

Haloalkanes, Influence on ^{13}C-NMR spectra of n-alkanes (SC) 1032 [G.E. *84*, 1101 (1972)]

Halogenation, σ-Complexes in ~ of aminobenzenes – isolation and secondary reactions (SC) 922 [G.E. *84*, 954 (1972)]
Primary step in ~ of cyclooctatetraene (SC) 1104 [G.E. *84*, 1187 (1972)]

Halogen cations and interhalogen cations (LA) 447

Halogen compounds, Vibrational spectra of octahedral hexa-~ (LA) 447
Base-catalyzed halogen dance (LA) 734

Halomalonaldehydes, Preparation and reactions (CR) 62 [G.E. *84*, 68 (1972)]

D-Hamamelose, Synthesis of branched carbohydrates with aldehyde side-chains. – Simple synthesis of L-streptose and ~ (SC) 149 [G.E. *84*, 112 (1972)]

Handbook, of chemistry and physics (Book Review) 449
Römpps Chemie Lexikon (Book Review) 947
Handbuch der Analytischen Chemie (Book Review) 1108

Heme, Biosynthesis of ~ and vitamin B_{12} from [α,γ-$^{14}C_2$]-uroporphyrinogen-III (SC) 421 [G.E. *84*, 433 (1972)]

Hemoglobin, Genetic aspects of ~ synthesis (FP) 576 [G.E. *84*, 649 (1972)]

Heptafulvenes, Vinylogous ~ from vinylogous fulvenes (SC) 131 [G.E. *84*, 113 (1972)]

Herbicides, S-Benzyl-N,N-di-sec-butylthiocarbamate (PR) 946

Hetero[11]annulenes, Bridged ~ (SC) 217 [G.E. *84*, 207 (1972)]

Heterocycles, New reactions with cyanic esters (FP) 949 [G.E. *84*, 1008 (1972)]
A general synthetic route to seven-membered ~ from cyclobutenes and 1,3-dipoles (SC) 926 [G.E. *84*, 995 (1972)]
Use of polyphosphoric acid for the synthesis of polymeric aromatic ~ by cyclopolycondensation reactions (LA) 244

Heterocyclic systems, Conformational analysis in ~: recent results and applications (FP) 739 [G.E. *84*, 779 (1972)]

Hexafluoro complexes, Electronic spectra (LA) 65

Hexatriene, Synchronous six-electron cyclization of ~ systems as a new synthetic principle for preparation of aromatic and heteromatic compounds (SC) 315 [G.E. *84*, 299 (1972)]

High-impact plastics formed by two phases. Adjustment of the degree of dispersion and of the interfacial adhesion by block polymers (CR) 339 [G.E. *84*, 362 (1972)]

High pressure properties, and their dependence on molecular structure (CR) 645 [G.E. *84*, 686 (1972)]

Histones, Structure and function of chromosomal nucleo-~ (FP) 496 [G.E. *84*, 451 (1972)]

History, Study of prehistoric metallurgy (FP) 620 [G.E. *84*, 668 (1972)]

Holography, Advances in acoustical ~ (FP) 279 [G.E. *84*, 280 (1972)]

Homobenzene, trans-σ-Bis- and -tris-~derivatives; synthesis of cycloheptatriene-3,4-dicarboxylic acid derivatives (SC) 940 [G.E. *84*, 988 (1972)]
cis-Trioxatris-σ-~ (cis-"benzene trioxide") (SC) 942 [G.E. *84*, 990 (1972)]

Homologation, Solvolysis of 7,7-bis(alkylthio)norcaranes. New method of ~ (SC) 49 [G.E. *84*, 50 (1972)]

Homopolymerization, Determination of kinetic constants of ~ by measurement of copolymerizations (CR) 341 [G.E. *84*, 363 (1972)]

Homotropilidene, Kinetics of the ~ valence tautomerism (SC) 517 [G.E. *84*, 539 (1972)]

Hormones, Mode of action (FP) 7 [G.E. *84*, 41 (1972)]
Arthropod molting ~ of plant origin (LA) 546

Hydrazines, Spirophosphoranes from acyl-~ and phosphorus compounds (SC) 306 [G.E. *84*, 349 (1972)]

Hydride complexes (LA) 1034

Hydrocarbons, Photoelectron spectra of benzenoid ~ $C_{18}H_{12}$ (SC) 538 [G.E. *84*, 551 (1972)]
Kinetics of autoxidation of ~ in the liquid phase (LA) 64
Rearrangements of $(CH)_n$ compounds (LA) 733

Hydrofluoric acid, Rearrangements of carbohydrate esters with anhydrous ~ (CR) 241 [G.E. *84*, 221 (1972)]

Hydroformylation, New aspects of the ~ reaction (CR) 155 [G.E. *84*, 172 (1972)]

Hydrogenation, Practical catalytic ~ .Techniques and applications (Book Review) 649

Hydrogen carriers, Quinoxalines as ~ (PR) 1037

Hydrogen cyanide chemistry: synthesis of diiminosuccinonitrile (CR) 153 [G.E. *84*, 173 (1972)]

Hydroxylations, Enzymatic ~ with molecular oxygen (FP) 701 [G.E. *84*, 689 (1972)]

Hypoiodite reaction (LA) 245

IMIDAZOISOQUINOLINEDIONES (PR) 1036

Immunity, In vitro methods in cell-mediated ~ (Book Review) 1038

Immunochemistry, Einführung in die Immunchemie und Immunologie (Book Review) 650

Immunology, Einführung in die Immunchemie und Immunologie (Book Review) 650

Indene, 1-Diazo-~ and spiro[~-1,7'-norcaradiene] (SC) 44 [G.E. *84*, 31 (1972)]

2H-Indeno[1,2-c]pyridines, 1,3,4,9b-Tetrahydro-~ (PR) 857

Indium complexes, Relation between structure and proton donor strength of octahedrally coordinated tris(3,5-diisopropylsalicylato)-aluminum(III), -gallium(III) and -indium(III) (SC) 1096 [G.E. *84*, 1151 (1972)]

3-Indolylacetic acid, Antiphlogistic N-acyl-~ derivatives (PR) 856

Infrared rotatory dispersion (IRD) (SC) 226 [G.E. *84*, 218 (1972)]

Infrared spectra of pseudo-halide complexes (LA) 65

Inorganic chemistry, Experimentelle Einführung in die Anorganische Chemie (Book Review) 71
Chemie 1, Anorganisch (Book Review) 737

Inorganic fibers, Polycrystalline ~ - production, properties, applications (FP) 751 [G.E. *84*, 866 (1972)]

Insulin, Influence of N-acylation on the three-dimensional structure and the properties of ~ (CR) 335 [G.E. *84*, 358 (1972)]
~ derivatives that cause only slight immunization (PR) *856*
Monoacyl derivatives of ~ with improved physicochemical properties (PR) 856

Insertion reactions, MO calculations on ~ of vinyl cations (SC) 635 [G.E. *84*, 680 (1972)]

Interelectronic repulsion, Assessment of the ~ parameter (LA) 66

Interhalogen cations, Halogen cations and ~ (LA) 447

Intermolecular interactions: van der Waals molecules (FP) 486 [G.E. *84*, 570 (1972)]

Invertebrates, Toxins from marine ~ (LA) 244

Iodine compounds, $Ge_{38}P_8I_8$ and $Ge_{38}As_8I_8$, a new class of compounds with clathrate structure (SC) 43 [G.E. *84*, 30 (1972)]

Ion binding by synthetic macrocyclic compounds (LA) 343

Ionization, Effect of polar substituents on ~ of organic acids (LA) 447

Ionization energies, Geometry and π-~ of alkyl-substituted triketones (SC) 220 [G.E. *84*, 210 (1972)]

Ionization potentials of substituted benzenes (SC) 525 [G.E. *84*, 544 (1972)]

Ion pair solvation complexes, Structure (FP) 112 [G.E. *84*, 127 (1972)]

Iron, Gmelin-Durrer: Metallurgie des Eisens (Book Review) 246, 256

Iron complexes, Cationic γ-oxo-isocyano complexes of iron, ruthenium, and osmium (SC) 527 [G.E. *84*, 584 (1972)]
Chemical syntheses with metal atoms: preparation of bis(butadiene)-~ and butadienetetracarbonylchromium (SC) 532 [G.E. *84*, 547 (1972)]
Dimethylene(2-propenylidene)methanetricarbonyliron (SC) 637 [G.E. *84*, 684 (1972)]
[(η-Phenyl)phenylethylphosphane] (η-2,3-dimethylbutadiene)iron(0), a phosphane complex without coordinated phosphorus (SC) 1088 [G.E. *84*, 1143 (1972)]
Physical chemistry of iron(II) complexes with ligands containing the structural element N=C-C=N (LA) 66

Iron compounds, X-ray photoelectron spectroscopy of iron-containing proteins - Valency of iron in ferredoxins (SC) 232 [G.E. *84*, 156 (1972)]
Transition metal carbene complexes as π-ligands - [ethoxy-(2,6-dimethoxyphenyl)carbenetetracarbonyliron(0)]tricarbonyliron(0) (SC) 238 [G.E. *84*, 214 (1972)]
Tetracarbonyl(π-vinyl alcohol)iron (SC) 520 [G.E. *84*, 581 (1972)]
Occurrence of iron in living nature (LA) 945

β-Isocyanatocrotonate, Reversible isomerization in β-isocyanatocrotonic esters (SC) 128 [G.E. *84*, 107 (1972)]

Isocyanides, Cycloaddition to 4,5-dihydro-1,3,5-oxazaphosph(V)oles (SC) 47 [G.E. *84*, 35 (1972)]
Synthesis from N-monosubstituted formamides, phosphanes, and azodicarboxylic acid derivatives (SC) 929 [G.E. *84*, 957 (1972)]
Polymerization (LA) 733

α-Isocyanoalkanoates, Ethyl γ-cyano-~ from α-metalated ethyl isocyano-acetates or -propionates and acrylonitriles (SC) 429 [G.E. *84*, 478 [1972)]

Isoelectric focusing: present and future state of a new method (CR) 445

Isomerization, Thermally reversible photo-~-s (FP) 1072 [G.E. *84*, 1157 (1972)]
Reversible ~ in β-isocyanatocrotonic esters (SC) 128 [G.E. *84*, 107 (1972)]
Three ~ routes originating from different electronic states of a linearly-conjugated cyclohexadienone (SC) 637 [G.E. *84*, 638 (1972)]
Demonstrations of isomers and intramolecular ~ of carbene complexes of chromium (SC) 644 [G.E. *84*, 682 (1972)]
~ of metal β-diketone chelates (LA) 65

Isonitrile chemistry (Book Review) 71

7-Isopropylidenenorbornadiene (SC) 54 [G.E. *84*, 65 (1972)]

Isothiocyanates, 1,3-Oxazolidine-2-thiones from alkyl ~ and carbonyl compounds (SC) 933 [G.E. *84*, 956 (1972)]

Isotope effects, Metal ~ on metal-ligand vibrations (FP) 666 [G.E. *84*, 755 (1972)]
Cyclopropanones and the Favorskii rearrangement. An unexpectedly large secondary isotope effect (CR) 329 [G.E. *84*, 311 (1972)]

Isotopes, Use of radioisotopically labeled analytical reagents (LA) 65

Isotope separation by electrical migration in molten salts (LA) 1107

KETENE, Thermal formation of 1-propenyl-~ from 2,4-pentadienal (SC) 288 [G.E. *84*, 345 (1972)]

Ketene thioacetals by "Peterson carbonyl olefination" with metalated formyl trimethylsilyl thioacetals (SC) 443 [G.E. *84*, 476 (1972)]

Keto compounds, Aromatic ~ as initiators in photopolymerizations (FP) 974 [G.E. *84*, 1032 (1972)]

Ketones, Synthesis of the lithium enolate of (S)-(+)-sec-butyl methyl ketone and formation of chiral 1,3-di-~ by acylation (SC) 127 [G.E. *84*, 107 (1972)]

Geometry and n-ionization energies of alkyl-substituted tri-~ (SC) 220 [G.E. *84*, 210 (1972)]
Synthesis of non-enolizable β-di-~ by acid-catalyzed intramolecular Claisen condensation (SC) 1030 [G.E. *84*, 1110 (1972)]
Aliphatic 1,2,3-tri-~ by ozonolysis of dialkyl-1,4-benzoquinones (SC) 1089 [G.E. *84*, 1144 (1972)]
Photochemistry of α-dicarbonyl compounds (LA) 155
Metal complexes of thio-β-di-~ (LA) *157*

Kinetics, Application of computers to MO theory and chemical ~ (FP) 393 [G.E. *84*, 418 (1972)]
~ of cooperative conformational transitions of linear biopolymers (FP) 568 [G.E. *84*, 615 (1972)]
~ of the homotropilidene valence tautomerism (SC) 517 [G.E. *84*, 539 (1972)]
Studies of reaction ~ in the solid state: first and second order reaction constants (CR) 445

LABORATORY manual, Kleines Chemisches Praktikum (Book Review) 246

Lactone rings, Cyclopolymerization with intramolecular formation of ~ (CR) 339 [G.E. *84*, 362 (1972)]

Lactones, Synthesis and photochemical behavior of enone ~ (CR) 327 [G.E. *84*, 308 (1972)]

Lead, Gmelins Handbuch der anorganischen Chemie (Book Review) 548

Ligands, Structural aspects of metal ion-ligand interaction (CR) 851 [G.E. *84*, 833 (1972)]
Short-lived molecules as ~ in coordination compounds (CR) 1034 [G.E. *84*, 1111 (1972)]

Liquid crystals, Optical properties of cholesteric ~(CR) 731 [G.E. *84*, 720 (1972)]

Lithiodimethylnitrosamine, C—C-Bond formation in the α-position to nitrogen in secondary amines. ~ (SC) 301 [G.E. *84*, 350 (1972)]

Lithium compounds, Chemistry of carbenoids and other thermolabile organo-~ (FP) 473 [G.E. *84*, 557 (1972)]
Stereochemistry of the cycloaddition of 1,3-diphenyl-2-azaallyllithium to alkenes at 0 °C (SC) 290 [G.E. *84*, 261 (1972)]
Ring-opening of N-lithio-2,3(cis)-diphenylaziridine to 1,3(cis, trans)-diphenyl-2-azaallyllithium and its rearrangement to the trans, trans-form (SC) 291 [G.E. *84*, 262 (1972)]
DTA studies on formation of dehydrobenzene and dichlorocarbene from haloorgano-~ (SC) 507 [G.E. *84*, 527 (1972)]

Lumichrome, New synthesis (SC) 1010 [G.E. *84*, 1061 (1972)]

Luminescence, (1-Adamantyl)-α-peroxylactone: synthesis, kinetics, and ~ (SC) 540 [G.E. *84*, 590 (1972)]

MACROCYCLIC compounds, Ion binding by synthetic ~ (LA) 343

Macromolecular Colloquium (CR) 334 [G.E. *84*, 356 (1972)]

Macromolecules, New aspects of the structure of randomly branched ~ (CR) 63 [G.E. *84*, 69 (1972)]
Possible interactions of transition metal complexes with biological ~ (LA) 1035

Magnetic properties, Theory of ~ of polynuclear transition metal compounds (LA) 545

Magnetic resonance methods in elucidation of bonding properties of transition metal compounds (LA) 245

Malate-lactate transhydrogenase (CR) 852 [G.E. *84*, 901 (1972)]

Maleic anhydride, Anionic polymerization with tertiary phosphanes (CR) 342 [G.E. *84*, 364 (1972)]

Malonaldehydes, Preparation and reactions (CR) 62 [G.E. *84*, 68 (1972)]

Malonates, Single-step synthesis of 1,n-dicarboxylic diesters by Kolbe electrolysis of oxalic and malonic half esters in the presence of olefins (SC) 841 [G.E. *84*, 893 (1972)]

Malting and brewing science (Book Review) 1109

Management, Quantitative ~ in R & D (Book Review) 648

Manganese compounds, Reversible N_2 fixation by dicarbonyl-π-cyclopentadienyl-(tetrahydrofuran)manganese(I) (SC) 534 [G.E. *84*, 549 (1972)]
Chemistry of the higher oxidation states of ~ (LA) 733

Manganese-porphyrin complexes, Literature on ~ (LA) 447

Mannich bases, Dehydro N-~ (SC) 144 [G.E. *84*, 109 (1972)]

Marketing, Der Absatz in der Chemischen Industrie (Book Review) 158

Mass spectrometry, Computer-aided analysis of organic mass spectra (FP) 357 [G.E. *84*, 381 (1972)]
Decomposition of organometallic complexes in the mass spectrometer (FP) 653 [G.E. *84*, 725 (1972)]
~ of heterocyclic compounds (Book Review) 648

Matrix reactions, Growth processes due to reactions in swellable cellular matrixes (FP) 990 [G.E. *84*, 1001 (1972)]

Membranes, Structural principles of bio-~ (FP) 551 [G.E. *84*, 597 (1972)]
Comparative studies of the topography of the ~ of mitochondria and chloroplasts (CR) 153 [G.E. *84*, 123 (1972)]
Investigations of the antibody-complement interaction with lipid model ~ (LA) 448
Investigation of protein conformation in chemically unchanged, functionally and enzymatically active bio-~ by measurement of optical rotation and UV- and visual light absorption (LA) 448

Mercury carbenoids, Organo-~ for synthesis of cyclopropane derivatives (SC) 231 [G.E. *84*, 160 (1972)]

Mercury complexes, Preparation and some properties of di[bis(trifluoromethyl)phosphido]mercury $Hg[P(CF_3)_2]_2$ (SC) 1097 [G.E. *84*, 1153 (1972)]

Mercury compounds, Chemistry of phenyl-(trihalomethyl)-~ (LA) 448

Mercury(II) salts, Oxidation of alkenes with ~ (LA) 245

Mesityl group as a ring current probe in transition metal 1,2-diimine chelates (SC) 725 [G.E. *84*, 769 (1972)]

Mesoionic compounds, Six-membered mesoionic "aromatic" compounds (SC) 1012 [G.E. *84*, 1063 (1972)]

Metabolism, Energy ~ in mitochondria (FP) 792 [G.E. *84*, 792 (1972)]
Foreign compound ~ in mammals (Book Review) 857

[2.2]Metacyclophanes, Stereochemistry (FP) 73 [G.E. *84*, 75 (1972)]

Metalation at primary, secondary, and tertiary carbon atoms in open-chain and cyclic nitrosamines (SC) *1101* [G.E. *84*, 1186 (1972)]

Metal atoms, How are ~ formed in flames? (LA) 64

Metal complexes, Metal ion function in carbonic anhydrase (FP) 408 [G.E. *84*, 461 (1972)]
Coordination-polymeric metal complexes of bifunctional dithiophosphinic acids and their use as adsorbents in chromatography (SC) 435 [G.E. *84*, 485 (1972)]

Metal-ligand vibrations, Metal isotope effects on ~ (FP) 666 [G.E. *84*, 755 (1972)]

Metalloporphyrins, Coordination chemistry (LA) 64

Metallurgy, Study of prehistoric ~ (FP) 620 [G.E. *84*, 668 (1972)]
Chemical analysis in extractive ~ (Book Review) 649

Metal-olefin complexes, Chemie der Metall-Olefin-Komplexe (Book Review) 68

Metals, Preparation of non-noble ~ (Li, Ca, Sr, Ba, Am, Cf) by reduction of their oxides and fluorides with hydrogen (SC) 515 [G.E. *84*, 537 (1972)]

Metal surfaces, Properties of clean ~ and reactions thereon (LA) 64

Metathetic reactions of olefins (LA) 646

4,9-Methano[11]annulenone, 2-Hydroxy-~, a 10 π-electron analog of tropolone (SC) 218 [G.E. *84*, 208 (1972)]

Methanol, Reaction with phenyl radicals (SC) 45 [G.E. *84*, 33 (1972)]

Methoxy groups, Reactions of double bonds activated by ~ (SR) 324 [G.E. *84*, 306 (1972)]

Methylenecyclopropane, Bridged ~-s as test cases for Brendt's rule: 2,5,5,7,7-pentamethylbicyclo[4.1.0]hept-1-ene (SC) 52 [G.E. *84*, 62 (1972)]
Cyclodimerization of ~ on a Ni(0) catalyst (SC) 309 [G.E. *84*, 352 (1972)]
Cyclodimerization of heated ~ (SC) 433 [G.E. *84*, 483 (1972)]

Methylenenorbornadiene, a bicycloheptafulvene (SC) 512 [G.E. *84*, 533 (1972)]

Methyl hydrogen carbonate (SC) 534 [G.E. *84*, 549 (1972)]

Methyl methacrylate copolymers, Structural investigations on polymethyl methacrylate and ~ in solution (CR) 341 [G.E. *84*, 365 (1972)]

Meyer-Schuster rearrangement and Rupe rearrangement (LA) 156

Milk proteins, Chemistry and molecular biology (Book Review) 345

Mineralogy and chemistry (CR) 342 [G.E. *84*, 267 (1972)]

Mitochondria, Energy metabolism in ~ (FP) 792 [G.E. *84*, 792 (1972)]
Comparative studies of the topography of the membranes of ~ and chloroplasts (CR) 153 [G.E. *84*, 123 (1972)]

Molecular biology, Introduction to ~ (Book Review) 549

π-Molecular orbitals, Unusual sequence of the two highest occupied ~ in the phosphorin system (SC) 631 [G.E. *84*, 636 (1972)]

Molecular structure, High-pressure properties and their dependence on ~ (CR) 645 [G.E. *84*, 686 (1972)]

Molecular weight distributions, Errors in the determination of narrow and broad ~ by gel permeation chromatography and their possible elimination (CR) 334 [G.E. *84*, 356 (1972)]
The analysis of narrow ~ as an aid to the kinetic investigation of ionic polymerization processes (CR) 340 [G.E. *84*, 362 (1972)]

Molybdenum complexes, Optically active tungsten complexes and ~ with tetragonal-pyramidal configuration (SC) 418 [G.E. *84*, 442 (1972)]

Molybdenum compounds, Coordination compounds with silicon-molybdenum and silicon-tungsten bonds (SC) 516 [G.E. *84*, 538 (1972)]
Walden inversion at an asymmetric molybdenum atom (SC) 923 [G.E. *84*, 955 (1972)]
Preparation and structure of the fluoro complex $Rb[Mo_2O_2F_9]$ (SC) 1020 [G.E. *84*, 1099 (1972)]
Stereochemistry of halocarbonylphosphanes and arsanes of molybdenum and tungsten (LA) 64
Enzymes containing molybdenum (LA) 945

Monobromocyclopropanes, New direct synthesis (CR) 326 [G.E. *84*, 308 (1972)]

Mössbauer measurements on neptunium-(VII) compounds (SC) 57 [G.E. *84*, 26 (1972)]

MO theory, Application of computers to ~ and chemical kinetics (FP) 393 [G.E. *84*, 418 (1972)]

NATURAL products, New directions of the chemistry of ~ (LA) 156

Neighboring group effects in ammonolysis of acetic esters of polynuclear phenolic compounds (CR) 335 [G.E. *84*, 357 (1972)]

Nematic liquids with positive dielectric anisotropy (SC) 633 [G.E. *84*, 636 (1972)]

Neopentane, Equivalent orbital method of interpreting photoelectron spectra: ~ (SC) 221 [G.E. *84*, 168 (1972)]

Neptunium(VII) compounds, Mössbauer measurements on ~ (SC) 57 [G.E. *84*, 26 (1972)]

Nickel catalyst, Cyclodimerization of methylenecyclopropane on a Ni(0) catalyst (SC) 309 [G.E. *84*, 352 (1972)]

Nickel complexes, Reaction of a $L_2Ni(0)$ system with allenes (SC) 136 [G.E. *84*, 120 (1972)]
Molecular structure of a bridged cis-bis-(π-allyl)nickel system (SC) 137 [G.E. *84*, 121 (1972)]

Nickel compounds, New route to triple-decker sandwich compounds (SC) 930 [G.E. *84*, 949 (1972)]
Spectra and structural properties of complex tetracyanides of platinum, palladium, and nickel (LA) 545

Nitrate groups, Structure of coordinated ~ (LA) 244

Nitration and aromatic reactivity (Book Review) 1108

Nitrenes, Carbenoids, carbenes, and ~ as polymerization initiators (LA) 855

Nitrides, Transition metal carbides and ~ (Book Review) 947

Nitrile oxides, The ~ (Book Review) 1039

Nitriles, Aminopentalenecarbo-~, a group of stable pentalenes (SC) 50 [G.E. *84*, 61 (1972)]
Reaction of metalated nitrosamines with ~. A new method for preparation of v-triazoles (SC) 1102 [G.E. *84*, 1187 (1972)]

Nitro compounds, Catalytic deoxygenation of aromatic ~ by carbon monoxide in the presence of diphenylacetylene (SC) 634 [G.E. *84*, 641 (1972)]

Nitrogen, Reactions and compounds with molecular ~ (CR) 243 [G.E. *84*, 267 (1972)]

Nitrogen compounds, Structure determinations of ~ with the aid of NQR, NMR, and ESCA spectroscopy (FP) 979 [G.E. *84*, 1037 (1972)]
$CH_3AsS_2N_2$, a five-membered arsenic-sulfur-nitrogen ring (SC) 529 [G.E. *84*, 585 (1972)]
Some new redox polymers containing nitrogen (CR) 338 [G.E. *84*, 360 (1972)]
UV spectroscopic properties of simple compounds having N—N and N—O bonds (LA) 244

Nitrogen fixation, Reversible ~ by dicarbonyl-π-cyclopentadienyl(tetrahydrofuran)-manganese(I) (SC) 534 [G.E. *84*, 549 (1972)]

Nitrogen heterocycles, Simple amination of aromatic hydroxy-~ (SC) 305 [G.E. *84*, 348 (1972)]

Nitrones, Conversion of cyclic ~ into thiolactams by reaction with carbon disulfide (SC) 47 [G.E. *84*, 34 (1972)]

Nitrosamine, C—C-Bond formation in the α-position to nitrogen in secondary amines. Lithiodimethyl-~ (SC) 301 [G.E. *84*, 350 (1972)]
Metalation at primary, secondary, and tertiary carbon atoms in open-chain and cyclic ~ (SC) 1101 [G.E. *84*, 1186 (1972)]
Reaction of metalated ~-s with nitriles. A new method for preparation of v-triazoles (SC) 1102 [G.E. *84*, 1187 (1972)]

Nitrosobenzene, Reaction of ferrocenylmethylium ions with ~ (SC) 1027 [G.E. *84*, 1106 (1972)]

NMR spectroscopy, Use of a computer in ~ (FP) 375 [G.E. *84*, 400 (1972)]
Nuclear magnetic resonance in solid-state chemistry (FP) 607 [G.E. *84*, 498 (1972)]
Shift reagents in ~ (FP) 675 [G.E. *84*, 737 (1972)]
^{1}H-NMR spectra of the AA'XX' and AA'BB' type – analysis and classification (FP) 861 [G.E. *84*, 907 (1972)]
Unusual ^{13}C chemical shifts of transition metal-carbene complexes (SC) 141 [G.E. *84*, 155 (1972)]
Synthesis and pulse Fourier transform ^{13}C-NMR spectra of branched-chain carbohydrates (SC) 148 [G.E. *84*, 111 (1972)]
Complex shift reagent for ^{13}C-NMR studies on carbohydrates (SC) 539 [G.E. *84*, 589 (1972)]

The mesityl group as a ring current probe in transition metal 1,2-diimine chelates (SC) 725 [G.E. *84*, 769 (1972)]
Influence of haloalkanes on the C-NMR spectra of n-alkanes (SC) 1032 [G.E. *84*, 1101 (1972)]

Noble gas compounds, Radiochemical investigations on ~ (CR) 61 [G.E. *83*, 986 (1971)]

Nomenclature, An alternative approach to the ~ of cyclic conjugated polyolefins, together with some observations on the use of the term "aromatic" (FP) 404 [G.E. *84*, 447 (1972)]

Norbornadiene, 7-Isopropylidene-~ (SC) 54 [G.E. *84*, 65 (1972)]
Methylene-~, a bicycloheptafulvene (SC) 512 [G.E. *84*, 533 (1972)]

1-Norbornene, Does ~ exist? (SC) 518 [G.E. *84*, 540 (1972)]

Norcaradienes, Photofragmentation of spiropyrazoles. – Stable ~ and spiroheptatrienes (SC) 224 [G.E. *84*, 215 (1972)]

Norcaranes, Solvolysis of 7,7-bis(alkylthio)-~. New method of homologation (SC) 49 [G.E. *84*, 50 (1972)]

Nucleic acid, Chemical synthesis of polynucleotides (FP) 451 [G.E. *84*, 489 (1972)]
Melting of d(T-A)oligomers (LA) 66
Interaction of protons and metal ions with ribo-~, deoxyribo-~ (LA) 66
Nucleinsäuren (Book Review) 947

Nucleohistones, Structure and function of chromosomal ~ (FP) 496 [G.E. *84*, 451 (1972)]

Nucleosides, New dihydroxyboryl-substituted polymers for column-chromatographic separation of ribonucleoside-deoxyribonucleoside mixtures (SC) 824 [G.E. *84*, 819 (1972)]

OLEFINATION, Ketene thioacetals by "Peterson carbonyl ~" with metalated formyl trimethylsilyl thioacetals (SC) 443 [G.E. *84*, 476 (1972)]

Olefin formation, The syn and anti steric course in bimolecular olefin-forming eliminations (FP) 200 [G.E. *84*, 177 (1972)]

Olefins, Metal-olefin and -acetylene bonding in complexes (FP) 596 [G.E. *84*, 649 (1972)]
Reactions of electron-rich ~ with proton-active compounds (FP) 964 [G.E. *84*, 1022 (1972)]
Anodic oxidation of trihexylmethoxyborate in presence of butadiene (SC) 48 [G.E. *84*, 32 (1972)]
Single-step synthesis of 1,n-dicarboxylic diesters by Kolbe electrolysis of oxalic and malonic half esters in presence of ~ (SC) 841 [G.E. *84*, 893 (1972)]
Reactivity of the double bond in higher ~ depending upon position and geometrical configuration (CR) 62 [G.E. *84*, 37 (1972)]
Transition-metal π-complexes with activated ~ (CR) 730 [G.E. *84*, 773 (1972)]
Metathetic reactions of ~ (LA) 646
Transition-metal complexes of ~ and acetylenes (LA) 945

Oligodeoxynucleotides, Synthesis of ~ with 5'-terminal phosphate groups (SC) 717 [G.E. *84*, 710 (1972)]

Oligonucleotides, Novel carrier for solid phase synthesis of oligomers (SC) 713 [G.E. *84*, 712 (1972)]

Optical purity, Rapid method for determination of ~ of amino acids (SC) 529 [G.E. *84*, 586 (1972)]

Optimization, Einführung in die Optimierung (Book Review) 346

Orbitals, Sequence of ~ in sulfones and sulfodiimides (SC) 927 [G.E. *84*, 944 (1972)]

Organic chemistry, Organische Chemie (Book Review) 157
Allgemeine Organische Chemie (Book Review) 649
Organisch-chemisches Praktikum (Book Review) 1038

Organic solvents, Techniques of chemistry (Book Review) 1109

Organic syntheses, Survey of ~ (Book Review) 70

Osmium complexes, Cationic γ-oxo-isocyano complexes of iron, ruthenium, and osmium (SC) 527 [G.E. *84*, 584 (1972)]

Oxa[17]annulenes (SC) 424 [G.E. *84*, 472 (1972)]

Oxalates, Single-step synthesis of 1,n-dicarboxylic diesters by Kolbe electrolysis of oxalic and malonic half esters in the presence of olefins (SC) 841 [G.E. *84*, 893 (1972)]

Oxalic acid, syn-Planar conformation of ~: crystal structure of the ~-acetamide complex (SC) 514 [G.E. *84*, 536 (1972)]

1,3,5-Oxazaphosph(V)oles; Cycloaddition of isocyanides to 4,5-dihydro-~ (SC) 47 [G.E. *84*, 35 (1972)]

4H-1,3-Oxazines, Simple synthesis of 2-substituted 2-oxazolines and 5,6-dihydro-~ (SC) 287 [G.E. *84*, 343 (1972)]

1,3-Oxazolidine-2-thiones from alkyl isothiocyanates and carbonyl compounds (SC) 933 [G.E. *84*, 956 (1972)]

5-Oxazolidones, Rearrangement and polymerization mechanisms of DTE-amino acids and 2-thioxo-~ (CR) 337 [G.E. *84*, 360 (1972)]

2-Oxazoline-4-carboxylates, Ethyl α-formylamino-β-hydroxy-acid esters (β-substituted *N*-formylserine esters) from ethyl ~ (SC) 432 [G.E. *84*, 435 (1972)]

Oxazolines, Simple synthesis of 2-substituted 2-~ and 5,6-dihydro-4H-1,3-oxazines (SC) 287 [G.E. *84*, 343 (1972)]
Survey of the chemistry of ~ (LA) 156

Oxidation states, Unusual ~ of metalloporphyrins; octaethylporphinatosilver-(III)perchlorate (SC) 1014 [G.E. *84*, 1072 (1972)]
Chemistry of the higher ~of manganese compounds (LA) 733

Oxidative coupling, Protophanes by ~ of "transposed dithiols" (SC) 844 [G.E. *84*, 826 (1972)]

Oxides, Preparation of non-noble metals (Li, Ca, Sr, Ba, Am, Cf) by reduction of their ~ and fluorides with hydrogen (SC) 515 [G.E. *84*, 537 (1972)]

Oxirane, Effect of protonation on aziridine and ~ bond strengths (SC) 825 [G.E. *84*, 820 (1972)]

2-Oxyallyl systems, Cycloadditions and rearrangements (CR) 324 [G.E. *84*, 305 (1972)]

Oxygen, Enzymatic hydroxylations with molecular ~ (FP) 701 [G.E. *84*, 689 (1972)]
Polarographic reduction of ~ in the presence of phthalocyanine complexes (SC) 140 [G.E. *84*, 154 (1972)]
Spatial requirements of pyridine N-oxide ~ (SC) 727 [G.E. *84*, 770 (1972)]

Oxygenation, Photochemical ~ of 2,4,6-tri-tert-butyl-λ^3-phosphorin and 2,4,6-tri-tert-butyl-1,1-dimethoxy-λ^5-phosphorin (SC) 506 [G.E. *84*, 526 (1972)]

Ozonolysis, Aliphatic 1,2,3-triketones by ~ of dialkyl-1,4-benzoquinones (SC) 1089 [G.E. *84*, 1144 (1972)]
Ozonolytic degradation of a catenane (SC) 1089 [G.E. *84*, 1144 (1972)]

PAINTS, Anstrichstoffe und ähnliche Beschichtungsstoffe, Pigmente (Book Review) 1037

Palladium compounds, Spectra and structural properties of complex tetracyanides of platinum, palladium, and nickel (LA) 545

[2.2]Paracyclophanes, Simple synthesis (SC) 419 [G.E. *84*, 471 (1972)]

Paramagnetic anisotropy (LA) 155

Pentaacetylene, Preparation of pure triacetylene, tetraacetylene, and ~ and investigation of their electronic spectra (SC) 438 [G.E. *84*, 483 (1972)]

2,4-Pentadienal, Thermal formation of 1-propenylketene from ~ (SC) 288 [G.E. *84*, 345 (1972)]

Pentafluoroorthoselenic acid (SC) 630 [G.E. *84*, 715 (1972)]

(+)-Pentahelicene, Determination of absolute configuration (SC) 296 [G.E. *84*, 293 (1972)]

Pentalenes, Aminopentalenecarbonitriles, a group of stable ~ (SC) 50 [G.E. *84*, 61 (1972)]

Peptides, New biologically active hepta-~ (PR) 856
Synthetic ~ (Book Review) 647

Peptide synthesis, Side-reactions arising on formation of cyclodipeptides in solid-phase ~ (SC) 293 [G.E. *84*, 290 (1972)]
Solid-phase ~ on an inorganic matrix having organic groups on the surface (SC) 314 [G.E. *84*, 266 (1972)]

Peroxides, Organic ~ (Book Review) 859

Pesticides, New 1-carbamoyl-N-carbamoyloxyformimidates (PR) 946

Petroleum, Die Verarbeitung des Erdöls (Book Review) 736

Phanes, Stereochemistry of [2.2]metacyclo-~ (FP) 73 [G.E. *84*, 75 (1972)]

Pharmaceutical chemistry, Lehrbuch der Pharmazeutischen Chemie (Book Review) 345

Phase transitions in polymers (CR) 334 [G.E. *84*, 356 (1972)]

Phenolic compounds, Neighboring group effects in the ammonolysis of acetic esters of polynuclear ~ (CR) 335 [G.E. *84*, 357 (1972)]

Phenols substituted with benzothiazylthioalkyl groups (PR) 1036

Phenyl azide, Substituent effects in 1,3-dipolar cycloadditions of ~ (SC) 838 [G.E. *84*, 887 (1972)]

9-Phenyl-9-boraanthracene, Preparation of ~ anion (SC) 53 [G.E. *84*, 28 (1972)]

Phenylcyclobutenediones, Chemistry (FP) 997 [G.E. *84*, 1048 (1972)]

Phenyldiimine in the reduction of diazonium salts by sodium tetrahydridoborate (SC) 45 [G.E. *84*, 33 (1972)]

Phenyl radicals, Reaction with methanol (SC) 45 [G.E. *84*, 33 (1972)]

Phosphabenzene, Photoelectron spectroscopy and conjugation – direct proof of the unusual sequence of the two highest occupied π-molecular orbitals in the phosphorin (~) and the arsenin (arsabenzene) system (SC) 924 [G.E. *84*, 993 (1972)]

1-Phosphanaphthalene, 1,1-Dibenzyl-2-phenyl-~ (SC) 1016 [G.E. *84*, 1066 (1972)]

2-Phenyl-~ (SC) 1017 [G.E. *84*, 1067 (1972)]

Phosphanes, Addition of ~ and phosphites to trifluoromethyl-substituted 2-aza-1,3-butadienes (SC) 319 [G.E. *84*, 258 (1972)]
1-Cyclopentadienyldifluorophosphane: a new fluxional molecule (SC) 640 [G.E. *84*, 683 (1972)]
Conjugation in aromatic amines and ~ (SC) 836 [G.E. *84*, 898 (1972)]
Synthesis of isocyanides from N-monosubstituted formamides, ~, and azodicarboxylic acid derivatives (SC) 929 [G.E. *84*, 957 (1972)]
[(η-Phenyl)phenylethylphosphane] (η-2,3-dimethylbutadiene)iron(0), a phosphane complex without coordinated phosphorus (SC) 1088 [G.E. *84*, 1143 (1972)]
Anionic polymerization of maleic anhydride with tertiary ~ (CR) 342 [G.E. *84*, 364 (1972)]
Stereochemistry of the halocarbonyl-~ and arsanes of molybdenum and tungsten (LA) 64
Poly(tertiary ~) and their metal complexes (LA) 1034

Phosphides, $Ge_{38}P_8I_8$ and $Ge_{38}As_8I_8$, a new class of compounds with clathrate structure (SC) 43 [G.E. *84*, 30 (1972)]

Phosphites, Addition of phosphanes and ~ to trifluoromethyl-substituted 2-aza-1,3-butadienes (SC) 319 [G.E. *84*, 258 (1972)]
Polycondensation of diethyl phosphite with aliphatic diols (CR) 341 [G.E. *84*, 363 (1972)]

Phosphoranes, Tetraorganofluoro-~ (SC) 144 [G.E. *84*, 165 (1972)]
Tetramethyl(methoxy)-~and related compounds (SC) 145 [G.E. *84*, 166 (1972)]
Formation of macrocyclic polyolefins on autoxidation of bifunctional alkylene-~ (SC) 508 [G.E. *84*, 528 (1972)]
4-(Difluorooxophosphoranyl)-1λ^4,3,5,2,-4,6-trithiatriazine (SC) 642 [G.E. *84*, 684 (1972)]

Phosphorin, Photochemical oxygenation of 2,4,6-tri-tert-butyl-λ^3-~ and 2,4,6-tri-tert-butyl-1,1-dimethoxy-λ^5-~ (SC) 506 [G.E. *84*, 526 (1972)]
Unusual sequence of the two highest occupied π-molecular orbitals in the ~ system (SC) 631 [G.E. *84*, 636 (1972)]
Photoelectron spectroscopy and conjugation – direct proof of the unusual sequence of the two highest occupied π-molecular orbitals in the ~ (phosphabenzene) and the arsenin (arsabenzene) system (SC) 924 [G.E. *84*, 993 (1972)]
1,1-Dihalo-λ^5-~-s (SC) 1090 [G.E. *84*, 1145 (1972)]
Reactions of λ^3-~-s with arene-diazonium salts to give λ^5-~-s (SC) 1091 [G.E. *84*, 1146 (1972)]

Phosphorothiocyanatidate, Synthesis of dineopentyl ~ : the first compound with the P(O)S—C≡N structure (SC) 838 [G.E. *84*, 896 (1972)]

Phosphorus compounds, Spirophosphoranes from acylhydrazines and ~ (SC) 306 [G.E. *84*, 349 (1972)]
Structure and mechanisms of formation of a novel phosphorus-containing heterocycle; P—Cl bond length and ^{35}Cl-NQR frequency (SC) 510 [G.E. *84*, 530 (1972)]
1,3,3,5,5-Pentachloro-1λ^4,2,4,6,3λ^5,5λ^5-thiatriazadiphosphorine (SC) 642 [G.E. *84*, 685 (1972)]
Preparation and some properties of di-[bis(trifluoromethyl)phosphido] mercury $Hg[P(CF_3)_2]_2$ (SC) 1097 [G.E. *84*, 1153 (1972)]

Photoadditions, Cyclovinylogous [2π→2σ]- ~ (SC) 313 [G.E. *84*, 259 (1972)]
[2+4]- and [4+4]-Photoaddition of cyclopentadiene to anthracene (SC) 718 [G.E. *84*, 718 (1972)]

Photochemistry, of dimethyl 1,2-dihydrocyclobutabenzene-1,2-diylidenediacetate (SC) 216 [G.E. *84*, 206 (1972)]
Light-induced [2+4]-cyclodimerization in the crystalline state (SC) 434 [G.E. *84*, 479 (1972)]
Photochemical oxygenation of 2,4,6-tri-tert-butyl-λ³-phosphorin and 2,4,6-tri-tert-butyl-1,1-dimethoxy-λ⁵-phosphorin (SC) 506 [G.E. *84*, 526 (1972)]
Photoprocesses of phenyl-substituted tetrahydropentalenes (SC) 719 [G.E. *84*, 719 (1972)]
~ of aromatic amine oxides (CR) 240 [G.E. *84*, 220 (1972)]
Synthesis and photochemical behavior of enone lactones (CR) 327 [G.E. *84*, 308 (1972)]
~ of α-dicarbonyl compounds (LA) 155
Photochemical and spectroscopic properties of organic molecules in the adsorbed state (LA) 156
Photochemical reactions of solid coordination compounds (LA) 157
Organic photochemical syntheses (Book Review) 858

Photoelectron spectroscopy, Equivalent orbital method of interpreting photoelectron spectra: neopentane (SC) 221 [G.E. *84*, 168 (1972)]
X-ray ~ of iron-containing proteins – Valency of iron in ferredoxins (SC) 232 [G.E. *84*, 156 (1972)]
Photoelectron spectra of unsaturated systems containing cyclopropane and cyclobutane rings (SC) 524 [G.E. *84*, 543 (1972)]
Ionization potentials of substituted benzenes (SC) 525 [G.E. *84*, 544 (1972)]
Evidence for conjugation through a saturated silicon atom (SC) 536 [G.E. *84*, 550 (1972)]
Estimation of spiro-interaction (spiroconjugation) in tetravinylsilane (SC) 537 [G.E. *84*, 551 (1972)]
Photoelectron spectra of benzenoid hydrocarbons $C_{18}H_{12}$ (SC) 538 [G.E. *84*, 551 (1972)]
Conjugation in aromatic amines and phosphanes (SC) 836 [G.E. *84*, 898 (1972)]
~and transannular interactions – question of transannular d-π interactions in 1-sila- and 1-germa-3-cyclopentenes (SC) 837 [G.E. *84*, 899 (1972)]
~ and conjugation – direct proof of the unusual sequence of the two highest occupied π-molecular orbitals in the phosphorin (phosphabenzene) and the arsenin (arsabenzene) system (SC) 924 [G.E. *84*, 993 (1972)]

Photofragmentation of spiropyrazoles. – Stable norcaradienes and spiroheptatrienes (SC) 224 [G.E. *84*, 215 (1972)]

Photo-Fries rearrangement (LA) 65

Photoisomerization, Thermally reversible ~-s (FP) 1072 [G.E. *84*, 1157 (1972)]

~ of 2-[2-(N-ethoxycarbonyl-N-allylamino)-ethyl]benzaldehyde (SC) 728 [G.E. *84*, 712 (1972)]

Photolysis of 2,3-diazido-2,3-dimethylbutane (SC) 1024 [G.E. *84*, 1102 (1972)]

Photooxidation of 3,4-diethyl-2,5-dimethylpyrrole (SC) 215 [G.E. *84*, 216 (1972)]

Photooxygenation, Dye-sensitized ~ of 6,6-dimethylfulvene: a new 1,2-dioxolane rearrangement (CR) 330 [G.E. *84*, 311 (1972)]

Photopolymerizations, Aromatic keto-compounds as initiators in ~ (FP) 974 [G.E. *84*, 1032 (1972)]

Photoreactions of cyclobutanones in solution (CR) 331 [G.E. *84*, 312 (1972)]

Photosensitized reactions, Complications in ~ (LA) 156

Phthalocyanine complexes, Polarographic reduction of oxygen in the presence of ~ (SC) 140 [G.E. *84*, 154 (1972)]
Catalysis by ~ (CR) 239 [G.E. *84*, 219 (1972)]

Physical chemistry, Physikalische Chemie in Experimenten – Ein Praktikum (Book Review) 651
~ – an advanced treatise (Book Review) 1040

Pigments, Anstrichstoffe und ähnliche Beschichtungsstoffe, Pigmente (Book Review) 1037

Pinacolic rearrangement, Synthesis of 7,7-dimethylbicyclo[4.1.1]octan-3-one by ~ (SC) 640 [G.E. *84*, 642 (1972)]

2,5-Piperazinedione, X-ray structural analysis of N,N'-dimethyl-3,6-epitetrathio-~ (SC) 632 [G.E. *84*, 640 (1972)]

Plant protection, Chemical ~ – past, present, and future (FP) 260 [G.E. *84*, 271 (1972)]
Chemie der Pflanzenschutz- und Schädlingsbekämpfungsmittel (Book Review) 71

Plasma, Organic syntheses in the ~ of glow discharges and their preparative application (FP) 781 [G.E. *84*, 876 (1972)]

Plastics Foamed thermoplastic resins (PR) 1036
Stabilisierung und Alterung von Plastwerkstoffen (Book Review) 449

Plastics Handbook, Kunststoff-Handbuch (Book Review) 947

Platinum(IV) complexes, Substitution reactions (LA) 447

Platinum compounds, Spectra and structural properties of complex tetracyanides of platinum, palladium, and nickel (LA) 545

Poisons, Analytical methods of detection of drugs and ~ (LA) 1107

Polarography, Polarographic reduction of oxygen in the presence of phthalocyanine complexes (SC) 140 [G.E. *84*, 154 (1972)]

Polyamide, Development of a new type of ~ (CR) 63 [G.E. *84*, 69 (1972)]

Poly-1-butene, Polymorphic transformations II to I in ~ (CR) 337 [G.E. *84*, 359 (1972)]

Polycarbonate fibers, Crystalline ~ (LA) 734

Polycations of Group VI (LA) 446

Polychlorobiphenyls, Occurrence and environmental significance (LA) 245

Polycyclic molecules, Reactions of highly strained ~ promoted by transition metal complexes (CR) 323 [G.E. *84*, 304 (1972)]

Polyester fibers, Improved ~ suitable for dyeing under high-temperature conditions (PR) 855

Polyethers, Macrocyclic ~ and their complexes (FP) 16 [G.E. *84*, 16 (1972)]

Polyethylene, Deformation (LA) 646

Polyimides, Solid, non-tacky ~ (LA) 735

Polymer compatibility (LA) 945

Polymer emulsions, Aqueous graft and or block copolymer emulsions (LA) 735

Polymeric Wittig reagents (SC) 298 [G.E. *84*, 296 (1972)]

Polymerization, Aromatic keto-compounds as initiators in photo-~ (FP) 974 [G.E. *84*, 1032 (1972)]
Analysis of narrow molecular weight distributions as an aid to the kinetic investigation of ionic ~ processes (CR) 340 [G.E. *84*, 362 (1972)]
~ of vinyl- and related compounds in the presence of sulfur compounds (LA) 245
~ of isocyanides (LA) 733
Thermodynamics of ~ (LA) 855
~ of cycloolefins (LA) 855
~ of N-vinylcarbazole with metal salts (LA) 945

Polymerization initiators, Carbenoids, carbenes, and nitrenes as ~ (LA) 855

Polymer networks – Structural and mechanical properties (Book Review) 859

Polymers, Kinetics of cooperative conformational transitions of linear bio-~ (FP) 568 [G.E. *84*, 615 (1972)]
New dihydroxyboryl-substituted ~ for column-chromatographic separation of ribonucleoside-deoxyribonucleoside mixtures (SC) 824 [G.E. *84*, 819 (1972)]
Model reactions for synthesis of pharmacologically active ~ by way of monomeric and polymeric reactive esters (SC) 1103 [G.E. *84*, 1189 (1972)]
Phase transitions in ~ (CR) 334 [G.E. *84*, 356 (1972)]
Mixtures of ~ having different tacticities with a melting point maximum (CR) 335 [G.E. *84*, 357 (1972)]
Turbidimetric titration of ~ (CR) 336 [G.E. *84*, 358 (1972)]
Use of ~ with enzyme-analogous structures for the resolution of racemates (CR) 341 [G.E. *84*, 364 (1972)]
Enzymic synthesis of homogeneous stereoregular ~ (CR) 645 [G.E. *84*, 644 (1972)]
Compositions containing block ~ of vinyl chloride (LA) 735
Vibrational spectroscopy (LA) 1034
Branched amide-imide-ester ~ for non-hygroscopic electrical insulating varnishes with unlimited storage life (PR) 946
Film-forming polymer masses (PR) 1107

Polymethyl methacrylate, Chemical reactions on ~ (CR) 339 [G.E. *84*, 361 (1972)]
Structural investigations on ~ and methyl methacrylate copolymers in solution (CR) 341 [G.E. *84*, 365 (1972)]

Polynucleotides, Chemical synthesis (FP) 451 [G.E. *84*, 489 (1972)]
Possibilities and limits of the enzymatic synthesis of ~ (CR) 336 [G.E. *84*, 359 (1972)]

Polyolefin fibers, Crosslinked, carbon-loaded ~ (PR) 856

Polyolefins, An alternative approach to the nomenclature of cyclic conjugated ~, together with some observations on the use of the term "aromatic" (FP) 404 [G.E. *84*, 447 (1972)]
Formation of macrocyclic ~ on autoxidation of bifunctional alkylenephosphoranes (SC) 508 [G.E. *84*, 528 (1972)]

Polyphenylenes, High molecular ~ (LA) 343

Polyphosphoric acid, Use for the synthesis of polymeric aromatic heterocycles by

cyclopolycondensation reactions (LA) 244

Polypropylene, Shear-induced crystallization (CR) 338 [G.E. *84*, 360 (1972)]

Polyurethanes, Growth processes due to reactions in swellable cellular matrixes (FP) 990 [G.E. *84*, 1001 (1972)]

Polyvinyl chloride, Easily extrudable plastic mixtures based on ~ suitable for the production of transparent bottles (PR) 1036

Porphyrin complexes, Literature on manganese-~ (LA) 447

Porphyrins, Unusual oxidation states of metallo-~: octaethylporphinatosilver-(III)perchlorate (SC) 1014 [G.E. *84*, 1072 (1972)]

Coordination chemistry of metallo-~ (LA) 64

Porous adsorbents, Structure (FP) 267 [G.E. *84*, 331 (1972)]

Positron, Chemistry of the ~ and of positronium (FP) 179 [G.E. *84*, 234 (1972)]

Positronium, Chemistry of the positron and of ~ (FP) 179 [G.E. *84*, 234 (1972)]

1-Propenylketene, Thermal formation from 2,4-pentadienal (SC) 288 [G.E. *84*, 345 (1972)]

Protein chemistry, Physical principles and techniques of ~, Part B (Book Review) 547

Proteins, Transcription of genetic information and its regulation by protein factors (FP) 883 [G.E. *84*, 961 (1972)]
Cooperative conformational changes in globular ~ (FP) 894 [G.E. *84*, 931 (1972)]
Investigation of protein conformation in chemically unchanged, functionally and enzymatically active biomembranes by measurement of optical rotation and UV- and visual light-absorption (LA) 448
Milk ~, Chemistry and molecular biology (Book Review) 345
Struktur und Funktion der Proteine (Book Review) 651

Protophanes by oxidative coupling of "transposed dithiols" (SC) 844 [G.E. *84*, 826 (1972)]

Protonation, Effect on aziridine and oxirane bond strengths (SC) 825 [G.E. *84*, 820 (1972)]

Proton transfer, Studies of intramolecular ~ to cysteine and related compounds by relaxation kinetics (SC) 428 [G.E. *84*, 430 (1972)]

Pseudohalides, Bonding properties of inorganic ~ (LA) 545
Infrared spectra of pseudohalide complexes (LA) 65

Pteridines, Biochemistry (FP) 1061 [G.E. *84*, 1088 (1972)]

Pyrene, Dicyclohepta[cd,gh]pentalene – a new ~ isomer (SC) 1013 [G.E. *84*, 1064 (1972)]

Pyridine, Synthesis and properties of azole-~ combinations: problem of the hydrolytic cleavage of hetarene combinations (SC) 846 [G.E. *84*, 828 (1972)]
Long-range substituent effects in acylation of thiophene-~ combinations (SC) 847 [G.E. *84*, 829 (1972)]
Synthesis of tetrasubstituted ~-s from N,N-dialkylcyanoacetamide (SC) 1098 [G.E. *84*, 1183 (1972)]
Synthesis of pentasubstituted ~-s from C-alkyl-N,N-dialkylcyanoacetamides (SC) 1100 [G.E. *84*, 1185 (1972)]
Chemistry of dihydro-~-s (LA) 732

Pyridine N-oxide, Spatial requirements of ~ oxygen (SC) 727 [G.E. *84*, 770 (1972)]

Pyridinium salts, Synthesis of N-alkyl-~ salts from N-alkylcyanoacetamides (SC) 1099 [G.E. *84*, 1184 (1972)]

Pyrido[2,3-d]pyrimidine-4(3H)-ones, 2-Amino-~ (PR) 946

Pyridyls, 1,4-Dihydro-1-silyl-~ – A new class of stable radicals (SC) 850 [G.E. *84*, 894 (1972)]

Pyrimidine, Triarenes of the type nucleophile-electrophile-nucleophile containing ~ or s-triazine as central nucleus (SC) 848 [G.E. *84*, 830 (1972)]

Pyrrole, Photooxidation of 3,4-diethyl-2,5-dimethyl-~ (SC) 215 [G.E. *84*, 216 (1972)]

Pyrrolidinone, New N-acylamino-~ derivatives (PR) 1036

QUESTIONS, 1000 Fragen aus der Chemie (Book Review) 1109

Quinodimethanes, Intramolecular cycloadditions of C,O and C,N multiple bonds to ortho-~ (SC) 1031 [G.E. *84*, 1108 (1972)]

Quinolines, 4-(Dialkylamino)-~ and 3,3-disubstituted 4(3H)-quinolones from 4H-3,1-benzoxazinones and ynamines (SC) 720 [G.E. *84*, 716 (1972)]

Quinone, Synthesis and X-ray structure analysis of anti-1-bromotricyclo[5.1.0.-$0^{3,5}$]octane-2,6-dione (anti-1-bromobis-homo-~) (SC) 236 [G.E. *84*, 170 (1972)]

Quinoxalines as hydrogen carriers (PR) 1037

RACEMATES, Use of polymers with enzyme-analogous structures for the resolution of ~ (CR) 341 [G.E. *84*, 364 (1972)]

Radiation physics, Atomic and molecular ~ (Book Review) 1038

Radicals, Electronic properties of di-~ (FP) 92 [G.E. *84*, 86 (1972)]
Organic syntheses via free-radical displacement reactions (FP) 692 [G.E. *84*, 702 (1972)]
A stable aromatic diradical with strong dipolar electronic interaction (SC) 303 [G.E. *84*, 353 (1972)]
1,3,5-Benzenetriyltris(1,5-diphenyl-3-verdazyl): A radical having a nearly degenerate doublet-quartet ground state (SC) 830 [G.E. *84*, 890 (1972)]
1,4-Dihydro-1-silylpyridyls – A new class of stable ~ (SC) 850 [G.E. *84*, 894 (1972)]
Free-radical alkylation with sulfoxides and Fenton's reagent (CR) 241 [G.E. *84*, 222 (1972)]
Some properties of a three-membered cyclic diradical intermediate (CR) 320 [G.E. *84*, 314 (1972)]
Cations and ~ from cyclopropanone adducts (CR) 321 [G.E. *84*, 303 (1972)]

Radioactive elements, Adsorption and colloidal properties of ~ (LA) 156

Radioactive nuclides, Messung radioaktiver Nuklide (Book Review) 69

Radiochemistry, Radiochemie (Book Review) 858

Reaction constants, Studies of reaction kinetics in the solid state: first and second order ~ (CR) 445

Rearrangement, Oxidative ~ of C-sulfonylthioformamides (SC) 295 [G.E. *84*, 293 (1972)]
Electron-impact induced ~-s in dibenzoazastannines (SC) 521 [G.E. *84*, 542 (1972)]
~ of 3-butenyl Grignard reagents: anionic or radical? (SC) 542 [G.E. *84*, 531 (1972)]
Degenerate ~ of cis-bicyclo[6.1.0]nona-2,4,6-triene (SC) 832 [G.E. *84*, 892 (1972)]
~-s of spirolactams with synthetic cis- and trans-erythrinanes as example (CR) 240 [G.E. *84*, 220 (1972)]
~-s of carbohydrate esters with anhydrous hydrofluoric acid (CR) 241 [G.E. *84*, 221 (1972)]
Cycloadditions and ~-s of 2-oxyallyl systems (CR) 324 [G.E. *84*, 305 (1972)]
Catalysis of strained σ-bond ~-s by silver ion (CR) 328 [G.E. *84*, 310 (1972)]
~-s of $(CH)_n$ compounds (LA) 733
Base-catalyzed halogen dance (LA) 734

Receptor sites, Labeling of ~ (LA) 854

Redox polymers, Some new ~ containing nitrogen (CR) 338 [G.E. *84*, 360 (1972)]

Reduction of organic compounds by alkoxyhydridoaluminates (LA) 1035

Reductive fragmentation of 3,3-dihalotricyclo[4.2.1.$0^{2,4}$]non-2-yl acetates: a new route to the bicyclo[4.2.1]nonane series (SC) 641 [G.E. *84*, 643 (1972)]

Repulsion, Assessment of the interelectronic ~ parameter (LA) 66
Influence of non-bonded H atom ~-s (LA) 66

Ring contractions, Cyclobutane ~ not involving carbonium ions (LA) 447

Ring opening of a cyclopropyl anion and cycloaddition of the allyl anion (SC) 724 [G.E. *84*, 768 (1972)]

Rotaxanes, catenanes, ~, and knots (Book Review) 248

Rubidium compounds, Preparation and structure of the fluoro complex Rb-$[Mo_2O_2F_9]$ 1020 [G.E. *84*, 1099 (1972)]

Rupe rearrangement and Meyer-Schuster rearrangement (LA) 156

Ruthenium complexes, Cationic γ-oxo-isocyano complexes of iron, ruthenium, and osmium (SC) 527 [G.E. *84*, 584 (1972)]

SANDWICH compounds, New route to triple-decker ~ (SC) 930 [G.E. *84*, 949 (1972)]

Scandium compounds, Coordination chemistry (LA) 245

Schiff bases, Structure of metal complexes of some quadridentate ~ (LA) 733

Selenate, Xenon bis(pentafluoroortho-~) and xenon fluoride pentafluoroortho-~ (SC) 723 [G.E. *84*, 715 (1972)]

Selenic acid, Pentafluoroortho-~ (SC) 630 [G.E. *84*, 715 (1972)]

Self-organization, of molecular systems and evolution of the genetic apparatus (FP) 798 [G.E. *84*, 838 (1972)]
Computer model of the formation of self-organizing systems (FP) 821 [G.E. *84*, 862 (1972)]

Semiconduction, Crystal chemistry and ~ (Book Review) 859

Semiconductors, Industrial application of the semiconductor properties of dyes (FP) 1051 [G.E. *84*, 1077 (1972)]

Sesquifulvalenes from dihydrofulvalenes (SC) 133 [G.E. *84*, 115 (1972)]

Sex attractant, Novel total synthesis of the ~ of Porthetria dispar (7,8-cis-epoxy-2-methyloctadecane) (SC) 60 [G.E. *84*, 67 (1972)]

Shift reagents, in NMR spectroscopy (FP) 675 [G.E. *84*, 737 (1972)]
Complex shift reagent for ^{13}C-NMR studies on carbohydrates (SC) 539 [G.E. *84*, 589 (1972)]

Signal transducers: Terra incognita of molecular biology (FP) 1 [G.E. *84*, 1 (1972)]

1-Sila-3-cyclopentenes, Photoelectron spectroscopy and transannular interactions – the question of transannular d-π interactions in ~ and 1-germa-3-cyclopentenes (SC) 837 [G.E. *84*, 899 (1972)]

Silane, Nature of the "silicon β-effect" in allyltrimethyl-~ (SC) 146 [G.E. *84*, 167 (1972)]

Silicon compounds, Coordination compounds with silicon-molybdenum and silicon-tungsten bonds (SC) 516 [G.E. *84*, 538 (1972)]
Evidence for conjugation through a saturated silicon atom (SC) 536 [G.E. *84*, 550 (1972)]
Estimation of spiro-interaction (spiroconjugation) in tetravinylsilane (SC) 537 [G.E. *84*, 551 (1972)]
Silicon as a carbanion substituent in ylides (CR) 944 [G.E. *84*, 957 (1972)]

Silicon dioxide, Graft reactions on ~ surfaces (CR) 337 [G.E. *84*, 359 (1972)]

Silicon β-effect, Nature of the "~" in allyltrimethylsilane (SC) 146 [G.E. *84*, 167 (1972)]

Silicon-nitrogen compounds, Two crystal structures of cyclic ~ with different disorder (SC) 58 [G.E. *84*, 27 (1972)]

Silver, Gmelins Handbuch der anorganischen Chemie (Book Review) 69

Silver compounds, Unusual oxidation states of metalloporphyrins: octaethylporphinatosilver(III) perchlorate (SC) 1014 [G.E. *84*, 1072 (1972)]

Silver ion, Catalysis of strained σ-bond rearrangements by ~ (CR) 328 [G.E. *84*, 310 (1972)]

1-Silylpyridyls, 1,4-Dihydro-~ – A new class of stable radicals (SC) 850 [G.E. *84*, 894 (1972)]

Single crystals, Chemical reactions on ~ of copolymers (CR) 340 [G.E. *84*, 363 (1972)]

Small ring carbocations, Insights into ~ provided by MO calculations (CR) 330 [G.E. *84*, 316 (1972)]

Small ring compounds, Bicyclic and tricyclic ~ (CR) 332 [G.E. *84*, 313 (1972)]

Small rings, International symposium on the chemistry of ~ (CR) 320 [G.E. *84*, 303 (1972)]

Solid compounds, Vibration-spectroscopic studies on ~ (FP) 26 [G.E. *84*, 8 (1972)]

Solid phase synthesis, Novel carrier for ~ of oligomers (SC) 713 [G.E. *84*, 712 (1972)]

Solid state, Mechanisms of reactions in the ~ (FP) 173 [G.E. *84*, 227 (1972)]
Nuclear magnetic resonance in ~ chemistry (FP) 607 [G.E. *84*, 498 (1972)]

Solvation complexes, Structure of ion pair ~ (FP) 112 [G.E. *84*, 127 (1972)]

Solvent molecules, How many ~ are nearest neighbors to a metal ion in solution? (LA) 65

Solvents, The chemistry of nonaqueous ~ (Book Review) 546

Spectroscopic methods, Spektroskopische Methoden in der organischen Chemie (Book Review) 650

Spectroscopy, Vibration-spectroscopic studies on solid compounds (FP) 26 [G.E. *84*, 8 (1972)]
X-ray spectroscopic investigation of chemical bonding in solids (FP) 34 [G.E. *84*, 51 (1972)]
Metal isotope effects on metal-ligand vibrations (FP) 666 [G.E. *84*, 755 (1972)]
Structure determinations of nitrogen compounds with the aid of NQR, NMR, and ESCA ~ (FP) 979 [G.E. *84*, 1037 (1972)]
Photochemical and spectroscopic properties of organic molecules in the adsorbed state (LA) 156

Spiroconjugation, Estimation of spiro- interaction (~) in tetravinylsilane (SC) 537 [G.E. *84*, 551 (1972)]

Spirodiene rearrangement (LA) 446

Spiroheptatrienes, Photofragmentation of spiropyrazoles. – Stable norcaradienes and ~ (SC) 224 [G.E. *84*, 215 (1972)]

Spiroheptatrienes by [1+2]-cycloaddition (SC) 225 [G.E. *84*, 215 (1972)]

Spiro[indene-1,7'-norcaradiene], 1-Diazoindene and ~ (SC) 44 [G.E. *84*, 31 (1972)]

Spiroisoindolines (LA) 735

Spirolactams, Rearrangements of ~ with synthetic cis- and trans-erythrinanes as example (CR) 240 [G.E. *84*, 220 (1972)]

Spirophosphoranes from acylhydrazines and phosphorus compounds (SC) 306 [G.E. *84*, 349 (1972)]

Spiropyrazoles, Photofragmentation of ~. – Stable norcaradienes and spiroheptatrienes (SC) 224 [G.E. *84*, 215 (1972)]

Squaric 1,3-diamides, New routes to ~ (SC) 431 [G.E. *84*, 480 (1972)]

Squaric diamidine, A ~ and an aza analog of biphenylene (SC) 433 [G.E. *84*, 481 (1972)]

Stability constants, Methods for calculation of ~ of metal complexes in solution (LA) 65

Steric effects, Influence of non-bonded H atom repulsions (LA) 66

Stereochemistry, Spatial requirements of pyridine N-oxide oxygen (SC) 727 [G.E. *84*, 770 (1972)]
~ of double bonds (LA) 855

Stilbenes, Biaryls, ~, benzo[c]cinnolines, and *dibenz[c,mn]*acridines from sulfonamides (SC) 826 [G.E. *84*, 822 (1972)]

L-Streptose, Synthesis of branched carbohydrates with aldehyde side-chains. – Simple synthesis of ~ and D-hamamelose (SC) 149 [G.E. *84*, 112 (1972)]

Structure determinations of nitrogen compounds with the aid of NQR, NMR, and ESCA spectroscopy (FP) 979 [G.E. *84*, 1037 (1972)]

Substituent effects, in 1,3-dipolar cycloadditions of phenyl azide (SC) 838 [G.E. *84*, 887 (1972)]
~ in Diels-Alder additions (SC) 840 [G.E. *84*, 888 (1972)]
Long-range ~ in acylation of thiophene-pyridine combinations (SC) 847 [G.E. *84*, 829 (1972)]

Substitutions, Structure and stereochemistry of the transition states and intermediates of heterolytic aromatic ~ (FP) 874 [G.E. *84*, 921 (1972)]
Ring ligand ~ of aromatic-metal complexes (LA) 945

Succinonitrile, Hydrogen cyanide chemistry: synthesis of diimino-~ (CR) 153 [G.E. *84*, 173 (1972)]

Sugars, Chemistry and biochemistry of branched-chain ~ (FP) 159 [G.E. *84*, 192 (1972)]

Sulfenyl halides, Oxidation, reduction, and addition reactions of ~ (LA) 244
Substitution and cyclization reactions (LA) 344

Sulfides, "Electron lone pairs" in organic ~ and disulfides (SC) 150 [G.E. *84*, 119 (1972)]

Sulfodiimides, Sequence of orbitals in sulfones and ~ (SC) 927 [G.E. *84*, 944 (1972)]

Sulfonamides, Biaryls, stilbenes, benzo[c]-cinnolines, and dibenz[c,mn]acridines from ~ (SC) 826 [G.E. *84*, 822 (1972)]

Sulfones, 1-Formylamino-1-arylsulfonyl alkenes from α-metalated isocyanomethyl aryl ~ and carbonyl compounds; conversion of a carbonyl compound into the next higher carboxylic acid (SC) 311 [G.E. *84*, 289 (1972)]
Sequence of orbitals in ~ and sulfodiimides (SC) 927 [G.E. *84*, 944 (1972)]

Sulfonium salts, Two unusual sulfur groups: Butadienyl-~ and sulfur diimides (CR) 1106 [G.E. *84*, 1154 (1972)]

C-Sulfonylthioformamides, Oxidative rearrangement (SC) 295 [G.E. *84*, 293 (1972)]

Sulfoxides, The "sulfoxide bond" (SC) 436 [G.E. *84*, 436 (1972)]
Free-radical alkylation with ~ and Fenton's reagent (CR) 241 [G.E. *84*, 222 (1972)]

Sulfur, Function in living organisms (LA) 157

Sulfur compounds, Preparation of cyclooctasulfur oxide, S_8O (SC) 302 [G.E. *84*, 344 (1972)]
$CH_3AsS_2N_2$, a five-membered arsenic-sulfur-nitrogen ring (SC) 529 [G.E. *84*, 585 (1972)]
X-ray structural analysis of N,N'-dimethyl-3,6-epitetrathio-2,5-piperazinedione (SC) 632 [G.E. *84*, 640 (1972)]
Synthesis of the first oxide of tetrasulfur tetranitride (SC) 918 [G.E. *84*, 946 (1972)]
Polymerization of vinyl- and related compounds in the presence of ~ (LA) 245
Recent developments in the synthetic organic chemistry of sulfur (LA) 732

Sulfur diimides, Two unusual sulfur groups: Butadienylsulfonium salts and ~ (CR) 1106 [G.E. *84*, 1154 (1972)]

Sulfur dioxide, Recent developments in the synthesis of organic compounds in liquid ~ (LA) 343

β-Sultones, Fluorinated ~ (FP) 583 [G.E. *84*, 623 (1972)]

Surfaces, Properties of clean metal ~ and reactions thereon (LA) 64
Physical ~ (Book Review) 549

Synthetic problems, Computer-assisted analysis of complex ~ (LA) 446

TACTICITIES, Mixtures of polymers having different ~ with a melting point maximum (CR) 335 [G.E. *84*, 357 (1972)]

Tetraacetylene, Preparation of pure triacetylene, ~, and pentaacetylene and investigation of their electronic spectra (SC) 438 [G.E. *84*, 483 (1972)]

Tetracyanoethylene, 1,4-Cycloaddition to methoxy- and phenoxy-cyclooctatetraene (SC) 716 [G.E. *84*, 766 (1972)]
Cycloaddition with cyclopropylethylenes (CR) 328 [G.E. *84*, 309 (1972)]

Tetracyclononane, cis,trans-Tetracyclo[6.1.-0.0^{2,4}.0^{5,7}]nonane, "trans-trishomobenzene" (SC) 310 [G.E. *84*, 346 (1972)]

Tetrahydropentalenes, Photoprocesses of phenyl-substituted ~ (SC) 719 [G.E. *84*, 719 (1972)]

Tetrasulfur tetranitride, Synthesis of the first oxide of ~ (SC) 918 [G.E. *84*, 946 (1972)]

Textbook, Lehrbuch der analytischen und präparativen anorganischen Chemie (Book Review) 547

Thermochemistry of the chemical bond (LA) 545

Thermolysis, Flach-vacuum ~ of p-benzoquinones (CR) 333 [G.E. *84*, 314 (1972)]

Thia[17]annulenes, Synthesis of stereoisomeric bisdehydro-~ and their dioxides (SC) 834 [G.E. *84*, 897 (1972)]

Thiatriazadiphosphorine, 1,3,3,5,5-Pentachloro-1λ^4,2,4,6,3λ^5,5λ^5-~ (SC) 642 [G.E. *84*, 685 (1972)]

N-Thienylalkyl-β-phenylethylamines, Anorectic ~ (LA) 736

Thiocarbamate, S-Benzyl N,N-di-sec-butyl-~ (PR) 946

Thioformamides, Oxidative rearrangement of C-sulfonyl-~ (SC) 295 [G.E. *84*, 293 (1972)]

Thioketones, Metal complexes of thio-β-diketones (LA) 157

Thiolactams, Conversion of cyclic nitrones into ~ by reaction with carbon disulfide (SC) 47 [G.E. *84*, 34 (1972)]

Thiophene, Long-range substituent effects in acylation of ~-pyridine combinations (SC) 847 [G.E. *84*, 829 (1972)]

Tin, Gmelins Handbuch der anorganischen Chemie (Book Review) 69

Tin compounds, Electron-impact induced rearrangements in dibenzoazastannines (SC) 521 [G.E. *84*, 542 (1972)]
Organotin compounds (Book Review) 1039

Titanium compounds, Bis(π-cyclopentadienyl)(1,2,3-triphenyltriphosphanato-P^1,P^3)-titanium and -zirconium (SC) 527 [G.E. *84*, 582 (1972)]

Titration, Titrationen in nichtwässrigen Medien (Book Review) 344

Toluene, Side-chain alkylation of ~ with ethylene (SC) 918 [G.E. *84*, 947 (1972)]

Toxins from marine invertebrates (LA) 244

Transannular interactions, Photoelectron spectroscopy and ~ – the question of transannular d-π interactions in 1-sila- and 1-germa-3-cyclopentenes (SC) 837 [G.E. *84*, 899 (1972)]

Transition metal compounds, Application of magnetic resonance methods in the elucidation of bonding properties of ~ (LA) 245
Theory of the magnetic properties of polynuclear ~ (LA) 545

Transition states as acids and bases (LA) 546

Triacetylene, Preparation of pure ~, tetraacetylene, and pentaacetylene and investigation of their electronic spectra (SC) 438 [G.E. *84*, 483 (1972)]

Triarenes of the type nucleophile-electrophile-nucleophile containing pyrimidine or s-triazine as central nucleus (SC) 848 [G.E. *84*, 830 (1972)]

s-Triazine, Triarenes of the type nucleophile-electrophile-nucleophile containing pyrimidine or ~ as central nucleus (SC) 848 [G.E. *84*, 830 (1972)]

v-Triazoles, Reaction of metalated nitrosamines with nitriles. New method for preparation of ~ (SC) 1102 [G.E. *84*, 1187 (1972)]

Tricyclo[5.1.0.0^{3,5}]octane-2,6-dione, Synthesis and X-ray structure analysis of anti-1-bromo-~ (anti-1-bromobishomoquinone) (SC) 236 [G.E. *84*, 170 (1972)]

Trifluoromethanesulfonic-carboxylic anhydrides, highly active acylating agents (SC) 299 [G.E. *84*, 294 (1972)]

Triketones, Geometry and n-ionization energies of alkyl-substituted ~ (SC) 220 [G.E. *84*, 210 (1972)]

1,4,7-Trioxacyclononatriene, Valence isomerization of syn-benzene trioxide to cis, cis,cis-~; anti-benzene trioxide (SC) 939 [G.E. *84*, 986 (1972)]

Trishomobarrelene, Bridgehead reactivities of ~ and trishomobullvalene (SC) 56 [G.E. *84*, 63 (1972)]

trans-Trishomobenzene, cis,trans-Tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane, "~" (SC) 310 [G.E. *84*, 346 (1972)]

Trishomobullvalene, Bridgehead reactivities of trishomobarrelene and ~ (SC) 56 [G.E. *84*, 63 (1972)]

Trithiatriazine, 4-(Difluorooxophosphoranyl)-1λ^4,3,5,2,4,6-~ (SC) 642 [G.E. *84*, 684 (1972)]

Tritium labeling, Exploration of biochemical mechanisms by ~ (LA) 734

Tropolone, 2-Hydroxy-4,9-methano[11]annulenone, a 10π-electron analog of ~ (SC) 218 [G.E. *84*, 208 (1972)]

Tungsten complexes, Optically active molybdenum complexes and ~ with tetragonal-pyramidal configuration (SC) 418 [G.E. *84*, 442 (1972)]

Tungsten compounds, Coordination compounds with silicon-molybdenum and silicon-tungsten bonds (SC) 516 [G.E. *84*, 538 (1972)]
Stereochemistry of the halocarbonylphosphanes and arsanes of molybdenum and tungsten (LA) 64

Turbidimetric titration of polymers (CR) 336 [G.E. *84*, 358 (1972)]

UMBELLIFERAE, Structural studies on constituents of ~ (CR) 239 [G.E. *84*, 219 (1972)]

Uroporphyrin III, Total synthesis of [α,γ-$^{14}C_2$]-~ (SC) 420 [G.E. *84*, 432 (1972)]

Uroporphyrinogen III, Biosynthesis of heme and vitamin B_{12} from [α,γ-$^{14}C_2$]-~ (SC) 421 [G.E. *84*, 433 (1972)]

UV spectroscopy, UV spectroscopic properties of simple compounds having N-N and N-O bonds (LA) 244

VALENCE tautomerism, Kinetics of the homotropilidene ~ (SC) 517 [G.E. *84*, 539 (1972)]

Vanadium compounds, Gmelins Handbuch der anorganischen Chemie (Book Review) 449

van der Waals molecules, Intermolecular interactions: ~ (FP) 486 [G.E. *84*, 570 (1972)]

Vibrational frequencies, Calculation of ~ and force constants (LA) 66

Vibrational spectroscopy of polymers (LA) 1034

N-Vinylcarbazole, Polymerization of ~ with metal salts (LA) 945

Vinyl cations, MO calculations on the insertion reactions of ~ (SC) 635 [G.E. *84*, 680 (1972)]
Formation and detection of ~ (CR) 544 [G.E. *84*, 592 (1972)]
Solvolysis of 1-cyclobutenyl nonafluorobutanesulfonate (SC) 714 [G.E. *84*, 714 (1972)]

Vinyl compounds, Polymerization of ~ and related compounds in presence of sulfur compounds (LA) 245

Vinyl chloride, Compositions containing block polymers of ~ (LA) 735

Vinylcyclopropanes, Reactions of strained C—C single bonds with transition metals–influence of geometrical factors on the reactivity of complex-bound vinylcyclopropane systems (SC) 522 [G.E. *84*, 583 (1972)]

Vinylogous fulvalene: synthesis and electrocyclic reaction (SC) 296 [G.E. *84*, 297 (1972)]

Vitamin B_{12}, Biosynthesis of heme and ~ from [α,γ-$^{14}C_2$]-uroporphyrinogen III (SC) 421 [G.E. *84*, 433 (1972)]

Vitamin B_{12} enzymes, Chemistry (LA) 1035

WALDEN inversion at an asymmetric molybdenum atom (SC) 923 [G.E. *84*, 955 (1972)]

Water, Kinetic data on ~ exchange between aquo complexes and solvent ~ (LA) 157
~ and ~ pollution (Book Review) 1109

Wittig reagents, Polymeric ~ (SC) 298 [G.E. *84*, 296 (1972)]

XENON compounds, Xenon bis(pentafluoroorthoselenate) and xenon fluoride pentafluoroorthoselenate (SC) 723 [G.E. *84*, 715 (1972)]

X-ray analysis, Automated X-ray structure determination as an analytical method (FP) 387 [G.E. *84*, 412 (1972)]
~ of a benzocyclopropene derivative (SC) 422 [G.E. *84*, 434 (1972)]
~ of 2,3,6-triphenylarsenin (SC) 630 [G.E. *84*, 679 (1972)]
~ of N,N'-dimethyl-3,6-epitetrathio-2,5-piperazinedione (SC) 632 [G.E. *84*, 640 (1972)]

X-ray spectroscopy, X-ray spectroscopic investigation of chemical bonding in solids (FP) 34 [G.E. *84*, 51 (1972)]

YLIDE complexes, Dimethylphosphane-(phenylmethoxy)methylenepentacarbonylchromium(0) – a route from carbene complexes to ~ (SC) 643 [G.E. *84*, 679 (1972)]

Ylides, Silicon as a carbanion substituent in ~ (CR) 944 [G.E. *84*, 957 (1972)]

Ynamines, 4-(Dialkylamino)quinolines and 3,3-disubstituted 4(3H)-quinolones from 4H-3,1-benzoxazinones and ~ (SC) 720 [G.E. *84*, 716 (1972)]

ZIEGLER-Natta catalysts, Characterization of the intermittently polymerization-active species of soluble ~ (CR) 336 [G.E. *84*, 359 (1972)]

Zirconium compounds, Bis(π-cyclopentadienyl)(1,2,3-triphenyltriphosphana to-P^1,P^3)-titanium and -zirconium (SC) 527 [G.E. *84*, 582 (1972)]